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A NOVEL THREE CARBON-AMINO GRIGNARD REAGENT: ITS USE IN AN EFFICIENT PYRROLIDINE SYNTHESIS

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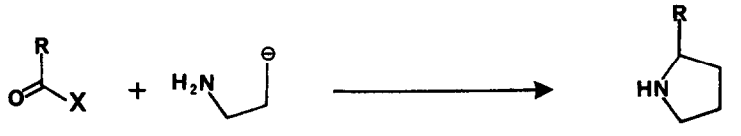
SUMMARY: A novel primary amino protected Grignard reagent has been developed; 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-propyl magnesium bromide **1a**. Its usefulness is illustrated in the synthesis of 2-substituted pyrrolidines.

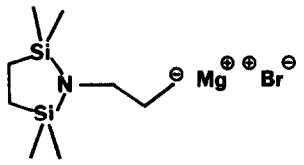
Grignard reagents are widely utilized in organic syntheses and those bearing other reactive functionalities in protected forms are especially valuable.[1] However, there are no primary amino protected Grignard reagents that can be easily formed, are stable to Grignard conditions, and allow easy removal of the protecting group after the reaction.

We required a short synthesis of 2-substituted pyrrolidines and envisioned a sequence in which the reaction between a suitable acid derivative and a primary amino protected Grignard, followed by reduction, would afford the desired products (Equation 1).



Equation 1

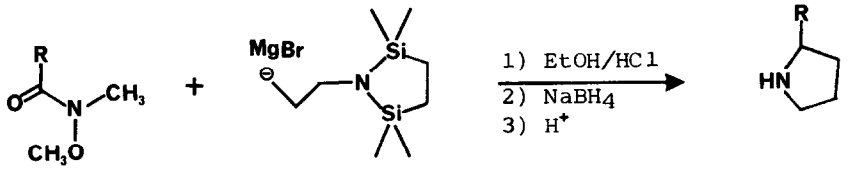
We investigated the possibility of preparing a primary amino protected Grignard using tetramethyldisilylazacyclopentane, developed by Magnus,[2] as the protecting group and 3-amino propyl bromide. In this communication, we wish to report on the formation of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-propyl magnesium bromide (**Ia**), its reaction with a carboxylic acid derivative, cyclization and reduction of the imine product to give a number of pyrrolidines.



Ia

The Grignard reagent can be prepared in a normal manner from the corresponding amino-protected propyl bromide[3] and magnesium activated with I_2 in diethyl ether. The labile N-Si bond remains intact during this operation.

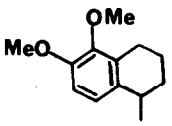
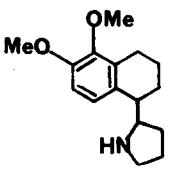
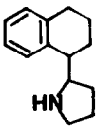
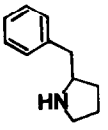
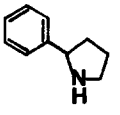
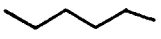
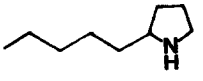
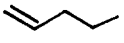
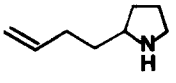
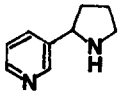
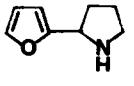
The carboxylic acid derivatives that we chose to react with the Grignard **Ia** were N-methoxy-N-methyl amides (Equation II), which are readily available from the corresponding acid chloride. In the presence of a large excess of organometallic reagent these amides provide only the desired ketones with no trace of the tertiary alcohols.[4] In the present cases, the ketonic intermediates were not isolated. It was found to be important to allow the reaction of the ketones with ethanolic hydrochloric acid to proceed for at least 3 h at ambient temperature to allow cleavage of the nitrogen silicon bond and concomitant cyclization to the imine.



Equation II

As shown in Table 1, this application of the new Grignard reagent **Ia** affords a simple and short synthesis to pyrrolidines which are otherwise obtainable only by longer routes.[5] Utilizing the same methodology and a corresponding stabase protected butyl Grignard we anticipate that piperidines can be prepared in a similar one pot reaction, and these could find useful applications in organic syntheses.

Table 1 - Conversion of N-methoxy-N-methyl Amide to 2-Substituted Pyrrolidines - Equation II

	Starting Material	Products	Isolated Yield %[a]
	R		
1.			~55%
2.			50%
3.			48%
4.			70%*
5.			62%
6.			65%
7.			60%*
8.			71%*

[a] No attempts were made to optimize yields.

* Quantitative yield was obtained when the Schiff base was isolated then subjected to $NaBH_4$ reduction.

Representative Procedure for Pyrrolidine Synthesis

To a solution of 1 mmol N-methoxy-N-methyl amide in 10 ml of dry THF was added an excess of the organometallic reagent Ia (>3 eq.) at 0°C. The reaction mixture was stirred overnight at room temperature. Then, 10% HCl in EtOH was added slowly at 0°C followed by stirring for 3 h at room temperature. The reaction was cooled to 0° then treated with an excess of either $NaBH_4$ or $NaCNBH_3$ and the mixture stirred at RT for 3 h. The solvent was stripped in vacuo and the residue partitioned between ether and H_2O. The acidic aqueous layer was made basic then extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and evaporated in vacuo and the product purified by either conversion to the HCl salt or by distillation.

Acknowledgements: We thank Professor Peter Beak at the University of Illinois Champaign-Urbana for helpful discussions during the course of this work.

References and Notes

1. Cases include OH, SH, CO_2H or $\geq$ O for example see a) B.A. Tromiov and S.E. Korostova; Russ. Chem. Rev. (Eng. Transl.), 44, 41 (1975), b) H. Normant; Bull. Soc Chim. Fr., 2161 (1972), and c) R. Luckenbach and K. Lorenz; Z. naturforsch, Teil B., 32, 1038 (1977).

2. S. Diuric, J. Venit and P. Magnus; Tett. Lett., 1787 (1981).

3. Prepared by adding a solution of 1,1,4,4-tetramethyl-1,4-dichlorodisilethylene (0.1 mol) (Petrarch System) in 100 ml dry methylene chloride to a mixture of 3-bromopropylamino HBr (0.1 mol) and Et_3N (0.3 mol) in 300 ml methylene chloride. The mixture was stirred for 3 h at ambient temperature under N_2. The solvent was evaporated in vacuo and the residue triturated with hexane, filtered and evaporated. The product distilled at 85-90°/ 1-2 mm Hg. This bromide is not stable at ambient temperature for long periods of time. However, it can be stored under N_2 at -78°C.

   The Grignard reagent was treated with benzaldehyde which afforded the corresponding amino-alcohol in 50% yield, suggesting the molarity of the Grignard to be ~0.5 M.

4. S. Nahm and S.M. Weinreb; Tett. Lett. 3815 (1981).

5. a) S.P. Gaur, C.P. Jain and N. Anand; Indian J. Chem. Sect. B. 21B(1), 46-51 (1982).
   b) M. Malmerg and K. Nybers; Acta. Chem. Scand. Ser. B. B35(6), 411-17 (1981).
   c) E. Schmitz, H. Sonnenschern and C. Gruendemann; J. Prakt. Chem. 322, 261 (1980).
   d) G.F. Alberici, J. Andrieux, G. Adam and M.M. Plat; Tett. Lett. 24, 1937 (1983).

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