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## FORMATION OF TETRAHYDROPYRIDINES FROM ARYLNITRILES WITH 2- AND 1-PROPENYL-METALS

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**Abstract:** Reaction of 4-chlorobenzonitrile or benzonitrile with 2-propenylgrignard or -lithium or with 1-propenyllithium yielded tetrahydropyridines 1 and 8.

One of the standard methods for the synthesis of ketones is the addition of organometals to nitriles.<sup>1</sup> However, when we reacted allylgrignard, prepared from 1-bromo-2-propene in diethylether with one equivalent of 4-chlorobenzonitrile at room temperature, we obtained, unexpectedly, the tetrahydropyridine<sup>2</sup> 1a instead of the desired ketone.



Tetrahydropyridines with the substitution pattern of 1a seem to be new and, surprisingly, very little has been published on the reaction of allylgrignard compounds with aromatic nitriles so far. We therefore studied the above reaction in more detail.

When allylgrignard was used in 100% excess, the amine 2a was obtained together with 1a. Formation of 2a resulting from a double addition of the organometal to the nitrile was not unexpected. It is interesting to note, however, that the yield of 1a remained almost unchanged. Inverting the order of addition of the reactants had no influence on the yield and the ratio of the two products. With unsubstituted benzonitrile we obtained the same results, except that the yield of the tetrahydropyridine 1b was lower as compared to that of 1a. Reaction of allyllithium with benzonitrile in diethylether at 0 to 5°C led to 1b in 45% yield. Again no aryl-2-propenyl-ketone could be detected.



In order to suppress the dimerisation reaction we repeated the experiment in tenfold dilution. The yield of 1b was indeed reduced, but instead of the expected ketone the enamine 3b was isolated. Evidently under these conditions the nitrile reacts faster with the primary addition product than with 2-propenyl-lithium or part of the latter is consumed by side reactions.

The formation of cyclodimerisation products in the reaction of allylmetals with nitriles has not been described previously. C.Bouchoule and P.Migniac studied the reaction of 2-pentenyl-metals with benzonitriles.<sup>3</sup> They obtained a mixture of the two ketones 4 and 5. The product ratio was



dependent on the metal used. Thus, whereas with the zinc-organic compound

ketone 4 was the main product, with the lithium- and the magnesium-derivatives ketone 5 was formed preferentially.

The formation of 1 in the reaction of benzonitriles with 2-propenylgrignard or -lithium could be explained by a mechanism involving cycloaddition of the two hypothetical intermediates  $\mathbf{A}$  and  $\mathbf{B}$ , which in turn could be formed from the primary addition product by a 1,3- and 1,5-sigmatropic H-shift. Coordination to the metal could assist the cycloaddition reaction.<sup>4</sup> A substituent at the neighbouring position to aryl, as in the product from the addition of 2-pentenyl-metals to benzonitrile, might prevent the H-shift through destabilisation of the required conformation.



Reaction of 1-alkenyl-metals with benzonitriles should lead directly to B-type structures. If the assumed 1,5-H-shift is reversible this could give rise to the same products as from the reaction of 2-alkenylmetals. J.Vekeman-Segers and H.Normant<sup>5</sup> reported the formation of dimeric products from the reaction of 1-propenyl-grignard with benzonitrile, to which they

$$6 \quad (X = NH) \quad 7 \quad (X = O)$$

assigned the structures 6 and 7. When we repeated this experiment we obtained in 37% yield a compound 8, whose structure was determined by  $^{1}$ H-NMR and MS to be again a tetrahydropyridine. The substitution patterns of 1 and 8, however, are different, because, in contrast to 1, 8 is the result of a head to tail cyclodimerisation of the primary addition product. The substituents in position 2,3 and 4 of 8 are in cis configuration. The 3,4-trans isomer 9 was also isolated as a minor byproduct.



8 2,3-cis, 3,4-cis 37% 9 2,3-tr., 3,4-cis 3%

Evidently, due to the high reactivity of the 1-azabutadiene system,<sup>6</sup> the addition of 1-propenyl-magnesium to the nitrile is followed by a rapid cyclodimerisation to give the tetrahydropyridine 8.

## References:

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- 2. The substituents in position 2 and 4 are in cis-configuration. The structure was determined by <sup>1</sup>H- and <sup>13</sup>C-NMR spectra and by MS. White crystals, m.p. 75-78°C. <sup>1</sup>H=NMR (CDCl<sub>3</sub>):  $\delta$  H<sub>A</sub> 3.51, H<sub>B</sub> 3.02, H<sub>C</sub> 4.21, H<sub>D</sub> 0.90, H<sub>E</sub> 2.0, H<sub>F</sub> 1.9, H<sub>G</sub> 2.79, H<sub>H</sub> 2.0, Me 1.06; J<sub>AB</sub> 16, J<sub>AC</sub> 6, J<sub>BC</sub> 7, J<sub>CD</sub> 12, J<sub>DE</sub> 12, J<sub>DF</sub> 12, J<sub>EF</sub> 6, J<sub>FMe</sub> 6.5, J<sub>FG</sub> 4, J<sub>FH</sub> 11, J<sub>GH</sub> 17, J<sub>GC</sub> 2, J<sub>HC</sub> 4 Hz; NOE H<sub>C</sub>-H<sub>F</sub>. <sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta$  198.1 (CO), 164.0 (CN), 139.1 + 137.6 + 135.8 + 135.5 + 129.6 + 128.6 + 128.1 + 127.4 (C-arom.), 57.3 (d, C-H<sub>C</sub>), 46.4 (t, H<sub>A</sub>-C-H<sub>B</sub>), 36.4 (t, H<sub>D</sub>-C-H<sub>E</sub>), 35.2 (t, H<sub>G</sub>-C-H<sub>H</sub>), 26.3 (d, C-H<sub>F</sub>) 21.9 (q, Me). MS: m/z 359 (M), <u>220</u> (M-ClC<sub>6</sub>H<sub>4</sub>CO), 139 (ClC<sub>6</sub>H<sub>4</sub>CO), 111 (ClC<sub>6</sub>H<sub>4</sub>C1).



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