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THE BARBIER REACTION: NO ORGANOMETALLIC PATHWAY IN A ONE-STEP ALTERNATIVE GRIGNARD REACTION.

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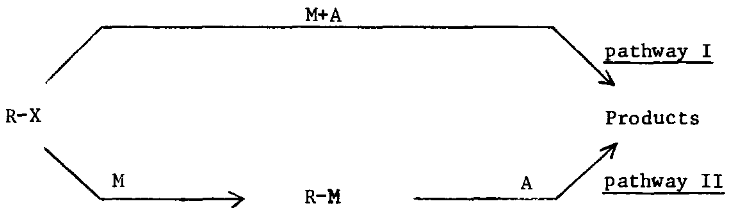
From the synthesis standpoint, there is renewed interest in the Barbier reaction (I), i.e. condensation between a reagent, A, and a halogenated derivative, RX, in the presence of a metal (magnesium or lithium), M,[1-5] due to the very high yields observed in certain cases. Furthermore, the difference in yields between this reaction and the Grignard reaction (II) calls for re-examination of the reaction mechanisms in question.



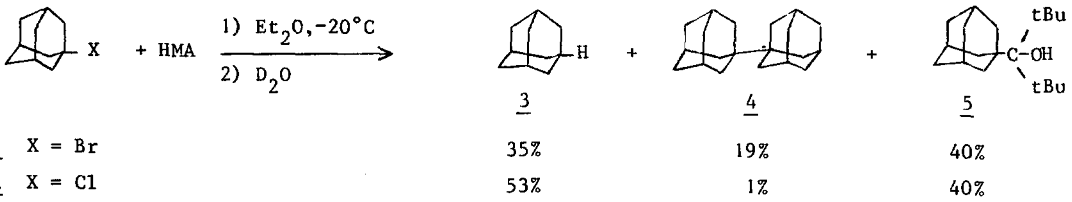
Indeed, although it is generally accepted that the Barbier reaction proceeds via an organometallic compound generated in situ, the presence of the latter has never been clearly demonstrated.[4-6] Even recent CIDNP studies by Blomberg et al.[2] are inconclusive; however, these authors do not exclude the possibility that the Barbier reaction might occur via a radical pathway.

In the course of our work on organomagnesium and organolithium derivatives of adamantane we envisaged so as to account for their formation, a radical mechanism[7] whose active intermediates initially appear on the metal surface. The ascertained difference in yields between reactions I and II led us to believe that, in the case of the Barbier reaction I, certain intermediates, precursors of the organometallic compound, could be attacked by reagent A prior to formation of the organometallic compound.

Since kinetic control of this is more easily demonstrated when limit cases are available, we sought a reaction model that would simplify interpretation of the results and, therefore, chose a Barbier reaction where a two-step mechanism (pathway II), although possible, is in fact excluded under the experimental conditions adopted. These conditions are obtained by seeking a totally hindered Grignard reaction at low temperature, i.e. at -20°C in ether, the usual conditions for the Barbier reaction (pathway I).

Since 1-adamantyl lithium, which we recently succeeded in synthesizing and which condenses at 25°C on hexamethylacetone (HMA) in a 30% yield,[8] is, as far as we know, one of the rare tertiary organolithium compounds that are stable in ether at -20°C, we chose it for our study. Therefore 1-adamantyl lithium was synthesized, in ether at -20°C, from either 1-bromo adamantane, 1, or 1-chloro adamantane, 2, by the previously described working method.[8] In both cases deuterolysis shows a 75% presence[9] of 1-adamantyl lithium, whereas there is 20-22% non-deuterated adamantane, 3, 1-2% biadamantane, 4, and 2-3% 1-adamantanol. At -20°C, a stoichiometric amount (0.15 M) of hexamethylacetone (HMA) in ether is added to the thus obtained lithium solution (reaction II). Two hours later there is no trace of condensation alcohol, 5, and deuterolysis of the reaction medium shows a 70% presence[10] of deuterated adamantane. The ketone is entirely recuperated at the end of the reaction, thereby indicating that, under these conditions, 1-adamantyl lithium does not reaction with HMA.

In contrast, the addition of stoichiometric amounts of 1-bromo adamantane, 1, and of HMA to a slight excess of lithium powder (reaction I) in the presence of ether at -20°C yields, after 45 mins., to 40% ditertiobutyl adamantyl carbinol, 5,[11] and 60% carbides (35% of 3 and 19% of 4)

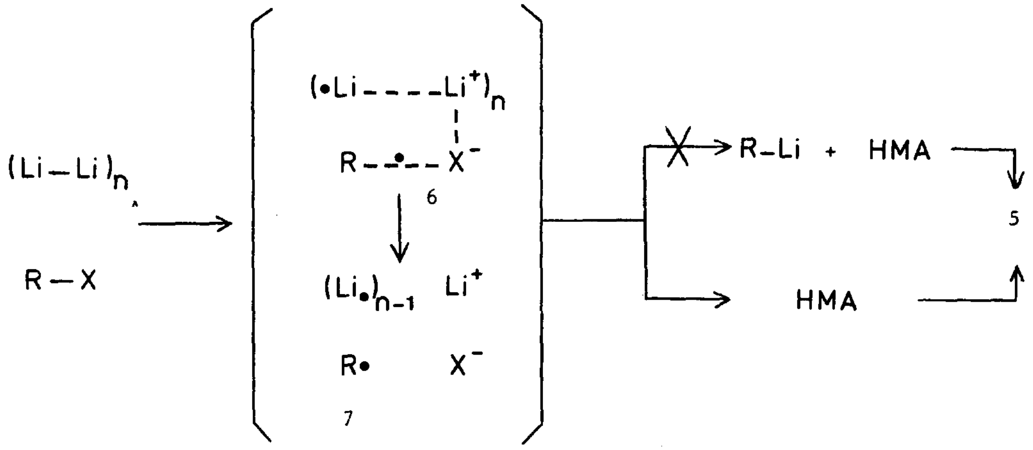


Scheme 1

Use of 1-chloro adamantane, 2, leads to comparable results: 40% of 5, 53% of 3, and 1% of 4. Deuterolyses carried out during these reactions show no trace of deuterated adamantane and thereby confirm the absence of organolithium compound in the medium.

Thus, in contrast to generally accepted hypotheses, these results indicate that formation of an organometallic compound does not occur during this Barbier reaction. However, the presence of carbides, notably 4, suggests the validity of the hypothesis that the Barbier reaction might occur via a radical pathway.

By analogy with the mechanisms proposed to explain the formation of organomagnesium[7,12] and organolithium[13] compounds, it can, at this stage of our study, be supposed that, in the case of the Barbier reaction, either anion radical 6, or radical $R^{\bullet}$, 7, resulting from 6, reacts with the ketone before formation of the organometallic compound (Scheme 2).



Scheme 2

These ascertainments account more satisfactorily for the fact that, for certain Barbier reactions, yields are generally greater than for the Grignard reaction.[14]

Although past work[4-6] on the Barbier reaction supposes the intermediate formation of a Grignard reagent (pathway II), we succeed in demonstrating, in this work, the existence of pathway I. This enables us to envisage a general mechanism which groups reaction pathways I and II. However, at this stage of our studies and on the sole basis of overly sparse and uncertain literature data, we cannot determine whether competition between these two pathways indeed exists, nor by which factors it is influenced. Therefore, additional work is under way in order to test these hypotheses and to determine the extent to which the choice of a working method can enhance a given synthesis.

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9. Yield determined by mass spectroscopy after deuterolysis of the medium.
10. The deviation in percentage of organolithium compound before and after addition of the ketone corresponds to a slight attack by the solvent on 1-adamantyl lithium.
11. This previously obtained alcohol[8] was isolated and characterized by NMR, IR and mass spectroscopy.
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