Pergamon

Tetrahedron Letters, Vol. 35, No. 32, pp. 5857-5860, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01191-5

New Perspectives in the Formation of the Grignard Reagent

Eric Péralez, Jean-Claude Négrel*, Michel Chanon

Laboratoire AM3, associé au CNRS (URA 1411), Faculté des Sciences de St Jérôme
Université d'Aix-Marseille III, 13013 Marseille (France)

Abstract: Inhibitors, in very low concentration, inhibit the reaction between 1-bromo-3-methyl-butane and magnesium obtained by vaporization of metal. For such a magnesium derivative, the inhibitors cannot play the role of "killers" for active sites. A chain reaction for the formation of the Grignard reagent is proposed.

The general agreement for intermediacy alkyl radicals[1-3] during Grignard reagent formation (Scheme 1) is founded on the alkyl group isomerization observed in the reaction of magnesium metal with alkyl halides in diethylether and on CIDNP studies[4].

$$RX + Mg \longrightarrow R^{\cdot} + MgX^{\cdot}$$
$$R^{\cdot} + MgX^{\cdot} \longrightarrow RMgX \qquad \textbf{Scheme 1}$$

There is disagreement, however, concerning the mobility of these radicals during the reaction. The question of whether these radicals are adsorbed on the magnesium surface[5] or diffuse freely in solution[6] has currently been discussed.

Two classes of mechanisms for the Grignard reagent formation are proposed: D-(Diffusion)[7] and A-(Adsorption) models[5].

The first mechanism[8-10] follows from a mathematical model based on a kinetic analysis of the product distribution. This model supposes that "all the radicals leave the surface and diffuse freely in solution", because it uses the existing kinetic data in the literature[11] obtained under homogeneous solution conditions. The second mechanism is based on experimental product distributions and stereochemistries observed during the formation of Grignard reagent. This model supposes that the intermediate radical interacts with the surface of magnesium to explain why the radicals generated from optically active alkyl halides partially maintain their configuration[5, 12-17]. A strongest support for the A-model comes from the using of a perdeuterated ether solvent or a radical trap deuterated dicyclohexylphosphine. In all cases, only a small percentage of the radicals leave the surface of magnesium to yield the deuterioalkane[12].

We now wish to report further results of our study designed to suggest steps which will account for the formation of RMgX from the radical R·. These steps are in agreement with the A-model. *However, once adsorbed, these radicals will produce an intermediate RMg(I) that could be a better reducing agent than the magnesium surface. Therefore a radical chain process is proposed in place of the stoichiometric one described in model A.* This mechanism is based on the following evidence:

- The reaction between organic halides and magnesium often shows an induction period which can be shortened by the use of "activators"[1]. This period of initiation[18,19] is characterized by the formation of isolated corrosion pits while the solution become turbid. When the reaction proceeds, the turbidity disappears and the corrosion pits grow in size. This observation might suggest a step of chain propagation.
- A low concentration of inhibitors inhibits the Grignard reagent formation[1].

The aim of our work is to carry out the Grignard reaction with catalytic quantities of inhibitors. Indeed, the radical chain inhibition can be used as a diagnostic test for reactions which involve radicals or radical-anions[20]. We used an active magnesium obtained by vaporization of metal in a rotary metal atom reactor[21], at -110 °C in THF. This method allows the formation of clean, alkali halide free, and extremely reactive magnesium. This clean magnesium excludes the presence of MgO which could poison the active sites and the important number of active sites excludes the possibility that small quantities of inhibitors might inhibit all the sites.

The first piece of evidence (**Table 1**) consists in a test of reactivity of 1-bromo-3-methylbutane and magnesium. Experiments give identical yields (100%) of 2-methylbutane (RH).

Table 1. Reactivities of 1-Bromo-3-methylbutane and Mg[a]

Reaction	T, °C	Reaction times / min[b]	Yields RH, %[c]
1	20	90	100
2	- 40	90	100
3	- 80	90	100
4	20	<1	100

[a] Magnesium activated by vaporization; [b] addition + stirring + hydrolysis
[c] % determinated by CG with internal standard.

The reactions 1-3 are carried out under the same experimental conditions as the one later used for the reaction with the inhibitors. A complete reaction occurs, whatever the temperature of experiment. Reaction 4 is carried out with a minimum time of addition of the alkyl halide and quenched immediately after this addition. The reaction is also complete. These results permit to exclude the hypothesis that a poor reactivity of alkyl halide and magnesium could be the cause of the later studies concerning the inhibition of Grignard reagent formation.

Table 2 summarizes the effect of inhibitors on the reaction between the activated magnesium and 1-bromo-3-methylbutane. The reactions were carried out by standard Schlenk techniques, in THF, at -80° C and under purified Ar. The values gathered in Table 2 correspond to a threshold determined by 5-6 different experiments with adding decreasing quantities of inhibitors to the reactive magnesium-alkyl halide mixture. The

consequences of adding these inhibitors are striking. Indeed, in all cases, the inhibition of the Grignard reagent formation is shown by the total absence of consumption of the alkyl halide.

Table 2. The Effect of Inhibitors on the Reaction between RBr[a] and Mg[b]

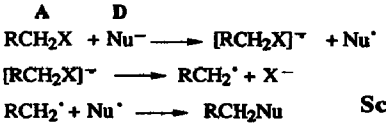
Inhibitors	mmoles of inhibitors / mmoles of RBr	Yields, %	
		RH[c]	RBr[a]
None		100	0
Benzonitrile	$1.40 \cdot 10^{-3}$	0	100
m-Dinitrobenzene	$1.23 \cdot 10^{-2}$	0	100
CCl_4	$2.00 \cdot 10^{-4}$	0	100
$CuCl_2$	$1.20 \cdot 10^{-3}$	0	100

[a] 1-Bromo-3-methylbutane; [b] Magnesium activated by vaporization
[c] 2-Methylbutane.

The m-dinitrobenzene concentration is 1/100 in comparison with the concentration used by Kornblum[22] in the famed electron transfer induced substitution reaction. A concentration 25 times more important was used by Tanner[20]. Recently, this author proposed an electron transfer chain process for the reduction of α-bromocamphor with amines[23], following the inhibition of the reaction with 4% of p-dinitrobenzene. Though these inhibitors are present in very low concentration, they are able to suppress the radical or / and radical-anion reaction. The reaction between the 1-bromo-3-methylbutane and the magnesium is probably a chain process.

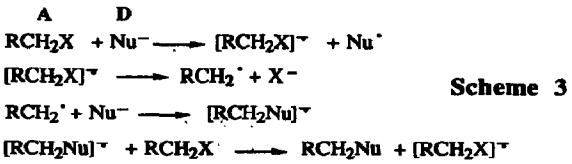
The metallic surface would play the role of a generalized base or nucleophile[24]. This process could permit a generalization of mechanisms worked out by Kornblum[22,25-27] and Russell[28].

Indeed, in 1964, Kornblum proposed (**Scheme 2**) that carbon alkylation was a radical-anion process for the reaction between the lithium salt of 2-nitropropane and the nitrobenzyl halides[25].



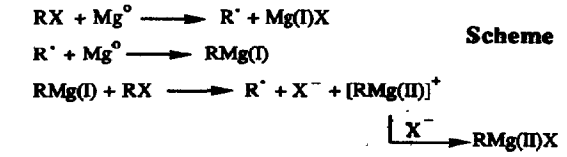
Scheme 2

The nucleophile (the anion derived from 2-nitropropane) plays the role of electron donor D whereas the alkyl halide, the role of electron acceptor A. This mechanism parallels the one generally accepted for the Grignard reagent formation (**Scheme 1**). It was shown in 1966 to be incomplete and a chain reaction was introduced to explain all the observed facts[27] (**Scheme 3**).



Scheme 3

Our experimental results point to the possibility that the mechanism of the Grignard reagent formation can operate by a completely analogous chain process (**Scheme 4**).



Scheme 4

We proposed earlier such a chain mechanism, without direct experimental evidence, in a review[24] by comparison with the scheme proposed by Hush and Oldham[29] for the alkyl mercuric halides formation. We prefer this chain mechanism to the one proposed on the basis of kinetic studies by Hòrak[30], but we have no compelling evidence to discard the latter.

References:

1. Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall: New-York, 1954, pp 1-91.
2. Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1927**, *49*, 236-257.
3. Bryce-Smith, D.; Cox, G. F. *J. Chem. Soc.* **1958**, 1050-1053.
4. Bodewitz, H. W. H. J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron Lett.* **1975**, *24*, 2003-2006 and references cited therein.
5. Hamdouchi, C.; Topolski, M.; Goedken, V.; Walborsky, H. M. *J. Org. Chem.* **1993**, *58*, 3148-3155.
6. Garst, J. F.; Ungváry, F.; Batlaw, R.; Lawrence, K. E. *J. Am. Chem. Soc.* **1991**, *113*, 5392-5397.
7. Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95-97.
8. Garst, J. F.; Swift, B. L. *J. Am. Chem. Soc.* **1989**, *111*, 241-250.
9. Root, K. S.; Hill, C. L.; Lawrence, L. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 5405-5412.
10. Walling, C. *Acc. Chem. Res.* **1991**, *24*, 255-256.
11. Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317-323.
12. Walborsky, H. M.; Zimmermann, C. *J. Am. Chem. Soc.* **1992**, *114*, 4996-5000.
13. Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286-293.
14. Fostein, P.; Pommier, J.-C. *J. Organometal. Chem.* **1978**, *150*, 187-201.
15. Walborsky, H. M.; Banks, B. *Bull. Soc. Chim. Belg.* **1980**, *89*, 849-868.
16. Dubois, J.-E.; Molle, G.; Tourillon, G.; Bauer, P. *Tetrahedron Lett.* **1979**, *52*, 5069-5072.
17. Lawrence, L. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 2493-2494.
18. Hill, C. L.; Vander Sande, J. B.; Whitesides, G. M. *J. Org. Chem.* **1980**, *45*, 1020-1028.
19. Koon, S. E.; Oyler, C. E.; Hill, J. H. M.; Bowyer, W. J. *J. Org. Chem.* **1993**, *58*, 3225-3226.
20. Tanner, D. D.; Blackburn, E. V.; Diaz, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 1557-1559.
21. Négrel, J.-C.; Gony, M.; Chanon, M.; Lai, R. *Inorg Chim Acta* **1993**, *207*, 59-63 and references cited therein.
22. Kerber, R. C.; Urry, G. W.; Kornblum, N. *J. Am. Chem. Soc.* **1965**, *87*, 4520-4528.
23. Chen, J. J.; Tanner, D. D. *Can. J. Chem.* **1992**, *70*, 173-176.
24. Chanon, M. *Bull. Soc. Chim. Fr.* **1982**, *7-8*, 197-238.
25. Kerber, R. C.; Urry, G. W.; Kornblum, N. *J. Am. Chem. Soc.* **1964**, *86*, 3904-3905.
26. Kornblum, N.; Michel, R. E.; Kerber, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 5660-5662.
27. Kornblum, N.; Michel, R. E.; Kerber, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 5662-5663.
28. Russell, G. A.; Danen, W. C. *J. Am. Chem. Soc.* **1966**, *88*, 5663-5665.
29. Hush, N. S.; Oldham, K. M. *J. Electroanal. Chem.* **1963**, *6*, 34.
30. Hòrak, M.; Palm, V.; Soogenbits, U. *Reakts. Sposobn. Organ. Soedin.* **1975**, 709-719. Idem, *Chem. Abstr.*, **1976**, *84*, ref. 73330b

(*Received in France* 26 *April* 1994; *accepted* 15 *June* 1994)