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(54) Title: PROCESS FOR THE PREPARATION OF GRIGNARD COMPOUNDS

(57) Abstract: The invention relates to a process for the preparation of Grignard compounds using a continuous method which involves the reaction of an organic halide dissolved in an organic solvent with metallic magnesium which, together with the activator solution in an organic solvent, fills the flow reactor or optionally a system of flow reactors, and subsequently, the resulting reaction mixture is fed into the terminal flow reactor containing metallic magnesium in order to achieve complete conversion of the organic halide, whereby preferably the organic solvent is re-circulated to flow reactors in a form of vapour.



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Process for the preparation of Grignard compounds

The invention relates to a process for the preparation of a Grignard compound using a continuous method which leads to the preparation of the Grignard compound with high yield and with a low content of the consecutive reaction product between the Grignard compound and the organic halide.

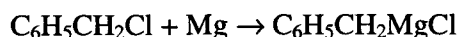
Organomagnesium compounds (Grignard reagents) are one of the best known and synthetically useful organometallic compounds. Applications of such compounds have been discussed in a number of monographs [Brilkina, T.G., Shushnov, V.A. *Reaction of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, NY 1969. Kharash, M.S., Reimuth, O. *Grignard Reaction of Nonmetallic Substances*, Prentise Hall, NY 1954.]

The formation of Grignard compounds is a heterogeneous reaction between organic halides and magnesium which occurs on the metal surface in the presence of solvating solvents. The reaction rate depends largely on the structure of the halide. In direct metalation, the relative reactivity of halides increases in the following order: organic fluoride, bromide and iodide. Alkyl halides react more readily than aryl halides. In general, reactivity increases in the following order: allyl halide, benzyl halide, primary alkyl halide, secondary alkyl halide, cycloalkyl halide, tertiary alkyl halide, aryl halide, vinyl halide. Its course depends to a large extent on the metal surface activity, type of solvent, water content in the reaction mixture and presence of oxygen. When halides react with magnesium very slowly, conversion rate and reaction yields are very low.

Ethers are usually used as solvents in Grignard reactions. Many Grignard compounds can be prepared with high yield when the reaction proceeds in diethyl ether. Tetrahydrofuran (THF) is another widely used solvent.

The weaker the carbon-halogen bond, the easier the Grignard compound forms. And the more reactive the Grignard compound, the more readily it undergoes homocondensation reaction.

In the case of highly reactive halides, such as allyl chloride or benzyl chloride, the Grignard compound being formed undergoes a consecutive reaction with the halide to yield a hydrocarbon.



One of the methods for reducing the consecutive reaction is to use diethyl ether, a solvent with a beneficial effect on surface reaction and consecutive reaction rates. The use of the ether as the solvent in industrial processes is, however, limited due to safety considerations, for diethyl ether is a volatile compound which forms an explosive mixture with oxygen.

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The reaction of organic chlorides with magnesium involves electron transfer from the metal surface to the chloride [Ashby, E.C. Reed, R., *J. Org. Chem.*, **1966**, *31*, 971. Oppolzer, W., Schneider, P. *Tetrahedron Lett.*, 1984, *25*, 3305. Freeman, P.K., Hutchinson, L.L., *J. Org. Chem.*, 1983, *48*, 879] which leads to the formation of organic radical R*. The formation of the carbon-magnesium bond occurs on the metal surface in the reaction of the radical formed. Recombination with the halide ion yields the organomagnesium compound. In a number of cases, the initial stage is controlled by diffusion; therefore, surface activity of the activated metal is in consequence a critical factor. Reactive magnesium powder can be obtained using the Rieke method [Ebert, G.W., Rieke, R.D., *J. Org. Chem.*, 1988, *53*, 4482] in which magnesium chloride is reduced *in situ* by metallic potassium. Highly dispersed magnesium powder is obtained, useful in reactions with reactive alkyl halides. Another option for the preparation of highly dispersed magnesium involves sublimation under reduced pressure and condensation at a temperature of -196°C. It has been proved that commercial magnesium can be obtained by sonication [Baker, K. V., Brown, J.M., Hughes, N., Skarnulis, A.J., *J. Org. Chem.* 1991, *56*, 698]. It has been argued that the role of ultrasounds is to disperse water bound with the metal surface and thus the first stage of Grignard compound formation is facilitated. The aforementioned processes for the manufacture of active magnesium are not employed in industrial practice due to their high cost.

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The analysis of the reaction mechanism leads to the conclusion that it is possible to obtain a high magnesium conversion rate in the reaction with reactive halides and to minimise halide consecutive reactions by using excess metal in the reaction mixture and treating the metal as appropriate. Highly developed surface
5 can be obtained by breaking up the metal mechanically in high-speed mixers. Such a solution is unsafe technology-wise due to the high reactivity of magnesium powder and explosion hazard in the presence of oxygen. The reaction conducted under the influence of ultrasounds, in turn, leads to the dispersion of the Grignard compound and metal surface activation, but it is difficult process-wise to
10 implement this on industrial scale.

Unexpectedly, it appeared that magnesium activation owing to which the Grignard reaction can be effectively carried out can be achieved by treating magnesium with a solution of an activator in ether employed as solvent in a column reactor.

15 In principle, manufacturing methods for Grignard compounds proceed in batch reactors. Such reactors are fraught with a number of inconvenient features:

- large volumes of tank-type reactors, which leads to:

- difficulties in the maintenance of physicochemical homogeneity of the whole medium, which in certain cases has an effect on the possibility of side
20 reactions,

- product impurities and the need to use separation procedures which are often complex, sequential, expensive and reduce total process yield,

- batch manufacture of a cyclic (periodic) type requires precise cleaning of the reactor, auxiliary equipment and the pipeline system along with fittings and
25 accessories, which leads to higher total manufacturing costs including also waste management expenses,

- the course of a batch process involves instability, and quite often this is caused by criteria of non-correlated nature which usually lead to chaotic conditions yielding out-of-specification products, especially if there is no process model or
30 interactive control,

- the periodic nature of synthesis also requires re-dimensioning of auxiliary equipment, in particular with respect to systems for the abatement of emissions of gaseous substances, vapours of liquids and solid waste, related to the nature of batch reaction kinetics.

5 A number of manufacturing facilities in pharmaceutical industry require special conditions subject to certain regulations (such as GMP), which leads to considerable design difficulties considering their large volume (customised, non-standard solutions) with respect to manufacturing organisation, which significantly increases investment cost.

10 Stoichiometric substrate quantities or slight excess of the alkyl halide fed into the reaction mixture are usually employed in batch processes. This means that in the terminal reaction stage, there is an unfavourable ratio of the alkyl halide to the Grignard compound, which increases the rate of the consecutive reaction which yields a hydrocarbon.

15 The specified characteristic elements of batch synthesis processes for pharmacological compounds, whose features largely contribute to difficulties in the manufacturing process, prove that it is appropriate to seek a correct solution involving a continuous process with universal features to as large extent as possible which could be applied in various areas of pharmaceutical technology.

20 The following advantages apply to continuous synthesis methods:

- the design of a flow reactor, usually of the pipe type, matches process kinetics and ensures quasi-homogeneous conditions of the reaction medium and complete, precise thermal control of the process which, combined, guarantee a high conversion rate with simultaneous minimisation of the presence of side products,

25 - the process occurs at stable thermodynamic parameters and significantly reduced streams compared to the batch reactor:

$$\dot{m} = \frac{V}{\tau} \text{ [kg/s]}$$

where: V [m^3] – volume of the batch reactor,

τ [s] – batch reaction time,

which leads to decreased demand for streams of electricity, heat energy and refrigerating and cooling media,

- pipe reactors, with varying design concepts, are devices with small volumes and small flow sections owing to which reaction plants can be constructed based on standard glass elements available in catalogues which ensure the highest corrosion resistance rates and constant process visualisation, while also facilitating periodic plant cleaning; the latter is, however, performed only when the manufacturing profile is changed, that is, sporadically rather than following each batch,
- it is much easier to ensure aseptic conditions considering the largely reduced volume of the plant,
- owing to continuous manufacturing at stable parameters, auxiliary equipment can be reduced and with stable process conditions, environmental protection and manufacturing organisation issues are also largely reduced.

The continuous work system requires, or allows for, the creation of a process model which is interactively coupled with the control system; this ensures precise process control and obtaining highest quality products.

When a continuous process is correctly programmed, the resulting Grignard compound leaves the reaction zone and it does not contact the reactive halide, which minimises the quantity of the hydrocarbon being formed.

The process of the invention involves passing a solution of an organic halide in an organic solvent through a system of flow reactors with magnesium, connected in series, which produces the metalation product with a very high yield and a small content of the hydrocarbon forming in the consecutive reaction. In the first stage, the halide solution is fed into a heterophase flow reactor with excess magnesium as the reaction initiation stage. The reactor is filled with magnesium strips and an organic solvent with an activator. In the case of organic halides with low reactivity, the solvent in the form of vapour is re-circulated into the reaction mixture.

The solvents may include ethers, such as THF, diethyl ether, di-*iso*-propyl ether, di-*n*-butyl ether, methyl-*tert*-butyl ether or mixtures thereof with hydrocarbon solvents, such as benzene or toluene.

The activators may include compounds, such as iodine, bromine, alkyl bromides, carbon tetrachloride, carbon tetrabromide.

The process for the preparation of the Grignard compound in the reaction between benzyl chloride and magnesium has been shown in the schematic diagram in Fig. 1.

In the first stage of the process, an activator solution in THF is fed into reactor 1 filled with magnesium strips. Subsequently, a solution of benzyl chloride in THF or in a THF-hydrocarbon mixture is passed in a continuous manner. Once the reaction has been initiated, the reaction mixture is cooled and temperature is maintained at 20-30°C. The resulting Grignard solution is fed into reactor 2 and followed by benzyl chloride. The reaction mixture is maintained in contact with excess magnesium. The hydrocarbon, 1,2-diphenylethane, practically does not form in such conditions. The process for the preparation of a Grignard compound can be carried out in a cascade reactor system, and the number of reactors depends on halide reactivity and magnesium surface activity. In the case of highly reactive halides, it is beneficial for the reaction to proceed in a system of three reactors connected in series. In order to obtain a saturated Grignard compound solution, the reaction mixture can be sent to an evaporator. After condensation, solvent vapours are fed to the reaction for the preparation of the Grignard compound. The resulting organomagnesium compound is subjected to the Grignard reaction, the ether from the reaction mixture is recovered by evaporation and ether vapours are re-circulated to the process. In the case of organic halides with low reactivity, the ether in the form of vapour is re-circulated into the second process stage. In reactor 2, the solvent is fed in a vapour form as a heating medium and also a factor which increases turbulence and facilitates mass exchange. When substrates are selected correctly in terms of their quantity, the process is a wasteless one.

The engineering scheme of the process for the preparation of the Grignard compound, benzylmagnesium chloride, is shown in Fig. 1. Reaction column 1 is filled with magnesium strips with a feature of cyclic and air-tight method for bed refill. The reactor is fitted with a cooling jacket supplied by a medium from the cooling system. The organic halide and the solvent are fed through a static mixer

onto the top of the column filled to 2/3 of its height. The reaction mixture flows gravitationally over the magnesium surface which causes the chloride to contact excess magnesium. At the reactor 1 outlet, the mixture passes through a lamellar separator at which the finely powdered highly reactive magnesium forming in the
5 reaction is sent back into the process and fed from a feeder onto column 1.

The reaction mixture and benzyl chloride are fed into reactor 2 fitted with a jacket which ensures that correct reaction temperature is maintained. Product quality stabilises in the reactor at a high conversion rate. Ether vapours can be charged into the bottom of the reactor in order to increase turbulence. The product
10 from reaction column 2 can be sent to the evaporator in which excess solvent is removed and a saturated organomagnesium compound solution is obtained. Ether vapours from the evaporator can be fed into reactor 2 and excess vapours are condensed and the solvent is re-circulated.

15 The invention is illustrated by the following examples which in no way restrict its scope:

Example 1.

Metallic magnesium in the form of chips (36.45 g) was fed into reactor 1 and
20 reactor 2 with a volume of 100 mL. Subsequently, the whole system was purged with argon heated to a temperature of 120°C. The columns were filled with 0.2% bromine solution in THF. After 30 minutes, column 1 was emptied to 2/3 of its height and charging a benzyl chloride solution (15%) in THF was started. After the reaction was initiated, proved by temperature increase to 30°C, the reactor
25 content was cooled and adding dropwise was controlled so as to maintain reaction mixture temperature in the range of 20-25°C. During the addition, the magnesium bed in reactor 1 was filled with the reaction mixture to 2/3 of its height. The reaction mixture was subsequently sent to reactor 2 and filled with benzyl chloride solution in THF (15%) so as the ratio of the mixture to the chloride was 10:1
30 (v/v). A temperature of 30-35°C was maintained in reactor 2. A Grignard compound solution was fed into the evaporator and concentrated and solvent vapours were fed partially into reactor 2 so as to achieve optimal process

temperature, condensed and fed back into the process. The resulting reaction mixture was dark-grey. The Grignard compound formed with a 98% yield. The product contained 2% of diphenylethane.

5 Example 2.

The reaction for the preparation of benzylmagnesium chloride was carried out as in Example 1.

Benzyl chloride was fed in a mixture of solvents: THF and methyl-tert-butyl ether (1:1; v/v) as a 10% solution. When the operation of the reaction system stabilised,
10 a solution of the Grignard compound was obtained with a 99% yield. The product did not contain diphenylethane.

Example 3.

The reaction for the preparation of benzylmagnesium chloride was carried out as
15 in Example 1.

Benzyl chloride was fed in a mixture of solvents: THF and toluene (10:1; v/v) as a 10% solution. When the operation of the reaction system stabilised, a solution of the Grignard compound was obtained with a 97% yield. The product contained
20 2% of diphenylethane.

Example 4.

The reaction between butyl bromide and magnesium was carried out as in Example 1. Butyl bromide was fed in a mixture of solvents: THF and methyl-tert-butyl ether (1:3; v/v) as a 15% solution. A temperature of 35°C was maintained in
25 reactor 1 and a temperature of 35°C to 40°C in reactor 2. When the operation of the reaction system stabilised, a solution of the Grignard compound was obtained with a 99% yield. The product did not contain octane hydrocarbon.

Example 5.

30 The reaction for the preparation of meta-chlorobenzylmagnesium chloride was carried out as in Example 1.

Meta-chlorobenzyl chloride was fed in a mixture of solvents: THF and methyl-tert-butyl ether (1:1; v/v) as a 10% solution. When the operation of the reaction system stabilised, a solution of the Grignard compound was obtained with a 99% yield. The product did not contain di-chlorophenylethane.

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Example 6.

The reaction for the preparation of para-chlorobenzylmagnesium chloride was carried out as in Example 1.

Para-chlorobenzyl chloride was added dropwise in a mixture of solvents: THF and methyl-tert-butyl ether (1:1; v/v) as a 10% solution. When the operation of the reaction system stabilised, a solution of the Grignard compound was obtained with a 98% yield. The product contained di-(p-chlorophenyl)ethane (1%).

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Example 7.

The process for the preparation of phenylmagnesium bromide was carried out in the apparatus as in Example 1.

Bromobenzene was fed as a 25% solution in a mixture of solvents: THF and methyl-tert-butyl ether (1:1; v/v). A temperature of 35°C was maintained in reactor 1 and a temperature of 35°C to 40°C in reactor 2. When the operation of the reaction system stabilised, a solution of the Grignard compound was obtained with a 98% yield.

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In order to compare the stationary and the continuous method for the preparation of Grignard compounds, synthesis of benzylmagnesium chloride in a flask fitted with a stirrer and a dropping funnel with pressure compensation was carried out. The synthesis was conducted in THF as the solvent using equimolar quantities of magnesium and benzyl chloride. The Grignard compound formed with a 90% yield. The product contained 6% of diphenylethane.

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Claims

1. A process for the preparation of Grignard compounds, characterised in that it employs a continuous method and involves the reaction of an organic halide
5 dissolved in an organic solvent with metallic magnesium which, together with the activator solution in an organic solvent, fills the flow reactor or optionally a system of flow reactors, and subsequently, the resulting reaction mixture is fed into the terminal flow reactor containing metallic magnesium in order to achieve complete conversion of the organic halide, whereby preferably the organic solvent
10 is re-circulated to flow reactors in a form of vapour.

2. Process for the preparation of a Grignard compound according to Claim 1, characterised in that the activator used in the process is bromine, iodine, alkyl bromide, carbon tetrachloride or carbon tetrabromide.
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3. Process for the preparation of a Grignard compound according to Claim 1, characterised in that the organic solvent used in the process is cyclic ether, symmetrical dialkyl ether, mixed dialkyl ether, a mixture of ethers or a mixture of ethers with a hydrocarbon.
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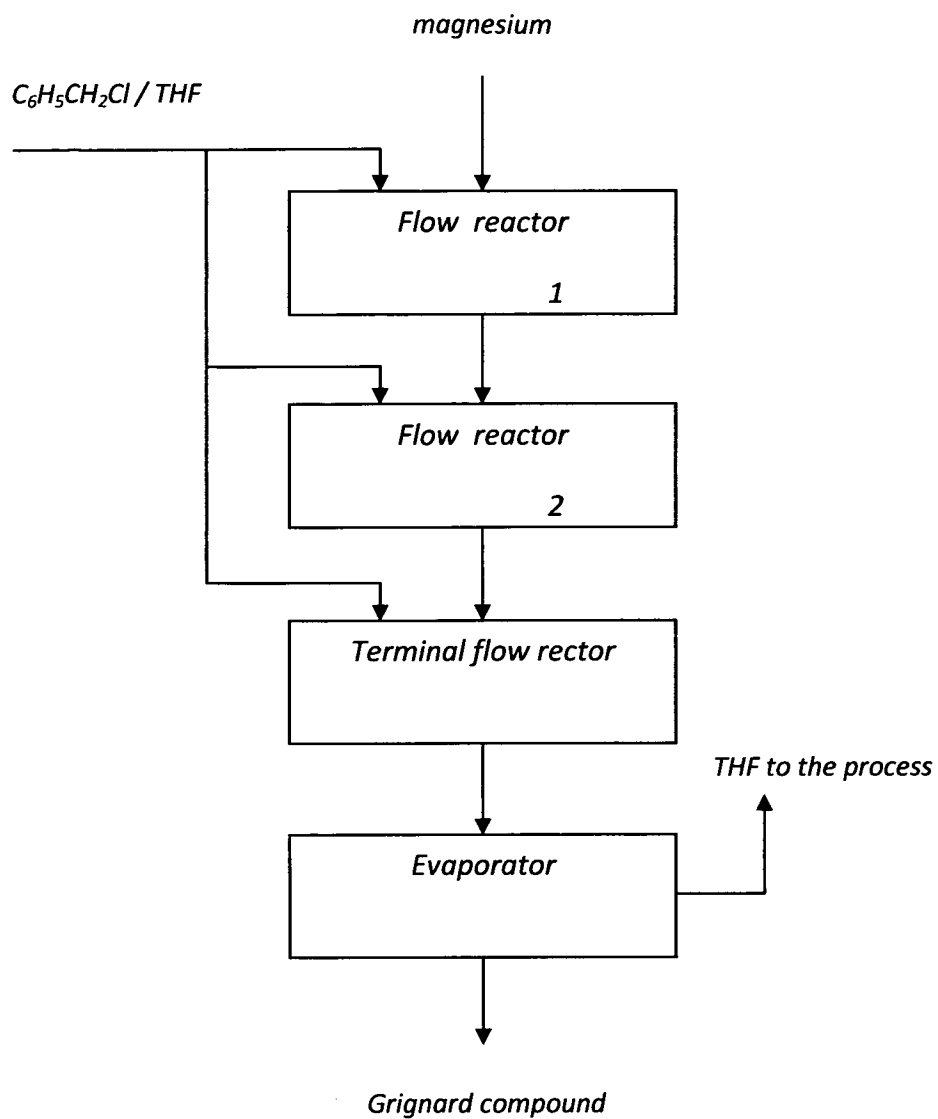


Fig.1. Diagram of the preparation of benzylmagnesium chloride using a continuous method.