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(54) Title: PROCESS FOR THE PREPARATION 3,5-BIS(TRIFLUOROMETHYL)BENZYLALCOHOL

(57) Abstract: The present invention concerns a process for preparing 3,5bis(trifluoromethyl)benzylalcohol by formylation in a solvent of an appropriate organo-magnesium derivative with solid paraformaldehyde and optionally its conversion into a 3,5-bis(trifluoromethyl)benzyl halide.

"Process for the preparation 3,5-bis(trifluoromethyl)benzylalcohol".

BACKGROUND OF THE INVENTION

This invention concerns a new process for preparing 1,3-
5 bis(trifluoromethyl)benzene derivatives. In particular, the invention concerns a
process for preparing 3,5-bis(trifluoromethyl)benzyl alcohol by formylation of 3,5-
bis(trifluoromethyl)phenyl-magnesium halide with paraformaldehyde.

3,5-bis(trifluoromethyl)benzylalcohol is also a very useful intermediate in the
preparation of 3,5-bis(trifluoromethyl)halo-benzyls, for example 3,5-
10 bis(trifluoromethyl)benzylbromide or benzylchloride.

The United States patent US 3,625,970 describes the preparation of 3,5-
bis(trifluoromethyl)benzylalcohol by reaction of 3,5-bis(trifluoromethyl)-phenyl
magnesium halides with gaseous formaldehyde produced by thermal decomposition
of paraformaldehyde according to the description given in Organic Synthesis, Vol I,
15 pages 188-190. In particular the latter article describes the formylation of halides of
cyclohexyl-magnesium in diethyl ether, a solvent conventionally used for these
formylation reactions, and it is specifically indicated that the use of
paraformaldehyde leads to low yields, of 40-50%.

Though gaseous formaldehyde is a first choice reagent according to the known
20 technique, it is nevertheless highly undesirable due to its toxicity and the critical
conditions of handling.

BRIEF DESCRIPTION OF THE INVENTION

It has now been surprisingly found that the formylation reaction of organo-magnesium 1,3-bis(trifluoromethyl)benzene derivatives with solid paraformaldehyde may be carried out with ease and allows to obtain on this substratum yields in 3,5-bis(trifluoromethyl)benzylalcohol comparable to those obtained with gaseous formaldehyde.

DETAILED DESCRIPTION OF THE INVENTION

So, according to one of its aspects, the invention concerns a process for preparing 3,5-bis(trifluoromethyl)benzyl alcohol which comprises reacting a 3,5-bis(trifluoromethyl)-phenylmagnesium halide with solid paraformaldehyde in a solvent.

According to the present invention, appropriate solvents are aliphatic ethers such as, for example, tetrahydrofuran (THF), alone or, preferably, in admixture with aromatic hydrocarbons. For example, mixtures of diethyl ether, THF, methyl-THF, isobutyl-ether, dimethoxyethane (DME), diethoxyethane, diglyme, butyl-diglyme, ethyl-diglyme, triglyme with toluene, o,m,p-xylenes, o,m,p-hexafluoroxylenes for example 1,3-bis(trifluoromethyl)benzene, and similar may be used.

According to a preferred aspect, a mixture of THF and an aromatic hydrocarbon is used, for example toluene or 1,3-bis(trifluoromethyl)benzene, advantageously a mixture which comprises from 20 to 60% p/p of THF.

According to the invention the tetrahydrofuran is substantially anhydrous.

The starting 3,5-bis(trifluoromethyl)-phenylmagnesium halide according to the invention may be obtained from the corresponding 3,5-bis(trifluoromethyl)-1-

halobenzene by treatment with magnesium according to the conventional techniques well known to the skilled in the art.

For example the preparation of the 3,5-bis(trifluoromethyl)-phenylmagnesium halide may be carried out in any of the conditions known in the art for preparing
5 organo-magnesium adducts (as described for example in Organic Synthesis, vol. 1, page 550; Chem. Ber. 1996, 129:233-235 and related references); the reaction is advantageously carried out in an anhydrous environment to avoid the hydrolysis of the organo-magnesium adduct, at a temperature between room temperature and the reflux temperature of the mixture of solvents. An excess of magnesium is generally
10 used. It is not usually necessary to activate the reaction, since the addition for example of 3,5-bis(trifluoromethyl)-1-bromobenzene to the reaction mixture provokes self-starting; However, if necessary or desired, it is possible to add a usual activator, such as bromine, iodine, 1,2-dibromoethane or Vitride®, in order to accelerate the starting of the reaction. Generally after 2-5 hours all the reagent is used
15 up; the progress of the reaction may be controlled by means of the usual gaschromatographic analytical controls or with thin layer liquid chromatography.

For example, the preparation between the starting 3,5-bis(trifluoromethyl)-phenylmagnesium halide from 3,5-bis(trifluoromethyl)-1-halobenzene may be carried out in one of the solvents indicated above for the preparation of 3,5-
20 bis(trifluoromethyl)benzylalcohol. In this way it is possible to proceed with the synthesis of the 3,5-bis(trifluoromethyl)benzylalcohol according to the present invention without isolating the 3,5-bis(trifluoromethyl)-phenylmagnesium halide.

3,5-bis(trifluoromethyl)-1-bromobenzene and the starting 3,5-bis(trifluoromethyl)-1-chlorobenzene are known products, available on the market.

In practice, after having prepared the organo-magnesium derivative according to the known techniques as indicated above, powdered paraformaldehyde is added to the reaction mass, advantageously in portions, and it is left to react for a period of
5 between 1 and 5 hours, preferably at a temperature between 30 and 90°C.

According to the process of the invention, the amount of solid paraformaldehyde necessary to obtain the best yields is generally equimolar or slightly in excess with respect to the starting organo-magnesium derivative, for
10 example an excess of not more than 5%. In fact it was noted with surprise that a great excess of this reagent, contrary to what is normally remarked in organic chemical reactions, does not lead to an improvement of yields, but rather leads to a decrease of the same and to a more difficult processing of the final reaction mixture.

When the reaction is ended (which can be checked by the techniques known to
15 the skilled in the art, for example by gas-chromatography), the adduct formed is hydrolysed with an aqueous solution of a mineral acid, such as sulphuric acid or hydrochloric acid, and the desired product, 3,5-bis(trifluoromethyl)benzylalcohol, is obtained, which may be isolated and purified with the usual techniques, for example by crystallising or distilling, or used as it is for further chemical transformations.

20 In fact 3,5-bis(trifluoromethyl)benzylalcohol, isolated and purified or as a crude reaction product, can in turn be used as the starting product for the preparation

of halogenated derivatives such as 3,5-bis(trifluoromethyl)benzyl halides, 3,5-bis(trifluoromethyl)benzyl bromide or 3,5-bis(trifluoromethyl)benzyl chloride.

To do this it is sufficient to submit the 3,5-bis(trifluoromethyl)benzylalcohol to a halogenation reaction, for example with aqueous hydrochloric acid or hydrobromic acid, optionally in the presence of sulphuric acid.

Thus, according to another of its aspects, the invention concerns a process for preparing 3,5-bis(trifluoromethyl)benzyl halides, which comprises:

- (a) forming a 3,5-bis(trifluoromethyl)-phenyl magnesium halide from a 3,5-bis(trifluoromethyl)-halo-benzene in a solvent selected from the aliphatic ethers and a mixture of aliphatic ethers and aromatic hydrocarbons.
- (b) adding solid paraformaldehyde to the reaction mixture thus obtained;
- (c) submitting the 3,5-bis(trifluoromethyl)benzylalcohol thus obtained to a halogenation reaction with HX where X is a halide, optionally in the presence of sulphuric acid;
- (d) isolating the 3,5-bis(trifluoromethyl)benzyl halide thus obtained.

The starting halogenated derivative of step (a) and the HX acid of step (c) need not necessarily contain the same halogen.

According to a preferred embodiment, in step (a) 3,5-bis(trifluoromethyl)-phenylmagnesium bromide is used or 3,5-bis(trifluoromethyl)-phenylmagnesium chloride, the bromine derivative being particularly preferred.

According to another preferred embodiment, in step (c) X is selected from bromide, chloride and iodide, bromide being a preferred halide.

The reaction in step (c) may also be carried out according to any appropriate technique for the halogenation of benzylalcohols, for example with phosphorous tribromide (PBr₃) or NaBr and sulphuric acid, by heating.

Some preferred embodiments of the invention are given in the following
5 experimental part.

The following example is given purely as illustration and is not limiting in any way.

EXPERIMENTAL PART

EXAMPLE 1

10 (i) Preparation of 3,5-bis(trifluoromethyl)-phenyl magnesium bromide

In a 4-neck flask with capacity 5 L equipped with mechanical stirrer, thermometer, bubble condenser and 250 ml filling filter, at room temperature 5.9 g of Mg (1.8881 moles); 310.0 g of anhydrous THF; 50.0 g of 3,5-bis(trifluoromethyl)-1-bromo-benzene (0.1706 moles) are loaded. Stirring
15 vigorously, wait for the starting of the reaction (10 minutes approx.). A temperature increase is noted and a variation in the colour of the reaction mass from colourless to dark brown. A temperature increase up to about 60°C is noted. The exothermic reaction is allowed to abate and, as soon as a fall in the internal temperature is noted, 826 g of anhydrous 1,3-
20 bis(trifluoromethyl)benzene are loaded in the flask. The remaining: 451.0 g of 3,5-bis(trifluoromethyl)-1-bromo-benzene (1.539 moles) are metered,

regulating the pouring rate so as to maintain the temperature at 45°C (pouring duration 4.5 h). Once pouring is finished, 45°C are maintained for 1-3 h.

(ii)-Preparation of 3,5-bis(trifluoromethyl)-benzylalcohol

53.8 g of solid paraformaldehyde (1,7933 moles) are added to the reaction mixture obtained in the previous step (i), dosing it in two portions of about 27g. The reaction is exothermic. It is left to react at 45°C for 6 hours and then the organo-magnesium adduct is hydrolysed with 1002.3 g of H₂SO₄ at 20%, cooling the system by means of an ice/water bath (T_{max}=37°C), after which it is kept stirring vigorously for another hour. the mixture is left to settle, the two phases are separated and the solvents are eliminated from the organic phase; it is then distilled in a vacuum (20 mbar) collecting 318.6 g of evaporated crude alcohol (tit. > 92%).

EXAMPLE 2

Preparation of 3,5-bis(trifluoromethyl)-benzyl bromide

In a 4-neck flask with capacity 1000 ml equipped with mechanical agitator, thermometer, bubble condenser and 100 ml loading funnel , 262.2 g of the product of Example 1 (ii) at 92.8% (0.988 moles), 550,2 g HBr 48% (3.2645 moles) are loaded; this is heated at 50°C so as to melt the alcohol, then one starts to dose 113 g of concentrated H₂SO₄ (1.153 moles). Pouring is accomplished in 30 minutes, noting an increase of the internal temperature. This is heated to 100-105°C and left to react for 8 hours. The reaction is completed by reflux heating for per 1.5 hours. the mixture is left to settle and

the phases are separated; the solvents are removed from the organic phase and the product in the title is obtained with a yield of 99.1%.

CLAIMS

1. Process for preparing 3,5-bis(trifluoromethyl)benzylalcohol which comprises reacting a 3,5-bis(trifluoromethyl)-phenylmagnesium halide with solid paraformaldehyde in a solvent.
- 5 2. Process according to claim 1, characterised in that said solvent is an aliphatic ether.
3. Process according to claim 2, characterised in that said aliphatic ether is tetrahydrofuran (THF).
4. Process according to claim 1, characterised in that said solvent is a mixture of
10 aliphatic ethers and aromatic hydrocarbons .
5. Process according to claim 4, characterised in that the aliphatic ether is selected from diethyl ether, THF, methyl-THF, isobutyl-ether, dimethoxyethane (DME), diethoxyethane, diglyme, butyl-diglyme, ethyl-diglyme and triglyme.
- 15 6. Process according to claim 4, characterised in that the aromatic hydrocarbon is selected from toluene, o,m,p-xylenes, o,m,p-esafuoroxylenes and 1,3-bis(trifluoromethyl)benzene.
7. Process according to claim 4, characterised in that the reaction solvent is a mixture of THF and an aromatic hydrocarbon.
- 20 8. Process according to claim 7, characterised in that the reaction solvent is a mixture of THF and an aromatic hydrocarbon selected from toluene and 1,3-bis(trifluoromethyl)benzene.

9. Process according to claim 7 or 8, characterised in that said mixture comprises from 20 to 60% p/p of THF.
10. Process according to any one of the previous claims, characterised in that the 3,5-bis(trifluoromethyl)-phenylmagnesium halide is selected from 3,5-bis(trifluoromethyl)-phenylmagnesium bromide and 3,5-bis(trifluoromethyl)-phenylmagnesium chloride.
11. Process according to any one of the previous claims, characterised in that the solid paraformaldehyde is used in an approximately equimolar amount or slightly in excess with respect to the 3,5-bis(trifluoromethyl)-phenylmagnesium halide.
12. Process according to claim 11 characterised in that the molar excess of paraformaldehyde is less than or equal to 5% with respect to the halide or 3,5-bis(trifluoromethyl)phenyl-magnesium.
13. Process according to any one of the previous claims, characterised in that the reaction temperature is between 30 and 90°C.
14. Process according to any one of the previous claims, characterised in that at the end of the reaction the adduct is hydrolysed with an aqueous solution of a mineral acid.
15. Process according to claim 14, characterised in that said mineral acid is selected from hydrochloric acid and sulphuric acid.

16. Process according to any one of the previous claims, characterised in that the
3,5-bis(trifluoromethyl)benzylalcohol is isolated by distillation or
crystallisation.
17. Process according to any one of the previous claims, characterised in that the
5 3,5-bis(trifluoromethyl)benzylalcohol obtained is used as a reagent to obtain
a 3,5-bis(trifluoromethyl)benzyl halide.
18. Process according to any one of the previous claims, characterised in that said
3,5-bis(trifluoromethyl)-phenyl-magnesium halide is obtained starting from
the corresponding 3,5-bis(trifluoromethyl)-1-halobenzene by treatment with
10 magnesium in a solvent selected from the solvents quoted in claims 2 to 9.
19. Process according to claims 17 and 18, characterised in that :
- (a) a 3,5-bis(trifluoromethyl)-phenyl magnesium halide is formed from a
3,5-bis(trifluoromethyl)-halobenzene in a solvent selected from the
aliphatic ethers and a mixture of aliphatic ethers and aromatic
15 hydrocarbons;
 - (b) solid paraformaldehyde is added to the reaction mixture thus obtained;
 - (c) the 3,5-bis(trifluoromethyl)benzylalcohol thus obtained is submitted
to a halogenation reaction with HX where X is a halide, optionally in
the presence of sulphuric acid;
 - 20 (d) the 3,5-bis(trifluoromethyl)benzyl halide thus obtained is isolated.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 03/00616

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07C29/40 C07C33/46 C07C17/16 C07C22/08 C07F3/02				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED				
Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BEILSTEIN Data, WPI Data, PAJ				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	US 3 625 970 A (AMBRUS LASZLO) 7 December 1971 (1971-12-07) cited in the application column 4, line 46 - line 70 -----	1, 2, 10, 13-19		
Y	WO 02/088058 A (ISHIHARA SANGYO KAISHA LTD) 7 November 2002 (2002-11-07) abstract -----	1, 2, 10, 13-19		
Y	EP 0 491 326 A (DONEGANI GUIDO IST) 24 June 1992 (1992-06-24) claims; example 2 -----	1, 2, 10, 13-19		
<input type="checkbox"/> Further documents are listed in the continuation of box C.				
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° Special categories of cited documents :				
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Information on patent family members

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