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(54) Title: PROCESS FOR PREPARING TRIORGANO BORATES WITH LOW ALCOHOL CONTENT

(57) Abstract: The present invention provides a process for preparing triorgano borates with low alcohol content.

Process for preparing triorgano borates with low alcohol content

Description

The present invention relates to a process for preparing triorgano borates with low alcohol content.

Triorgano borates such as trimethylborate, triisopropylborate or isopropylpinacol borate are known to contain small amounts (up to 2 wt%) of the corresponding alcohol from which they were made (Mehrotra, R. C.; Srivastava, G., Journal of the Chemical Society 1962, pages 3819 to 21). Low levels of alcohol come from the manufacturing process where typically an alcohol is reacted with boric oxide (B_2O_3) or another borate followed by a distillation process. Known methods to remove residual alcohol from borates include aceotropic distillation using benzene, toluene or hexanes (Hoffmann, R. W.; Metternich, R.; Lanz, J. W., Liebigs Annalen der Chemie 1987, Vol. 10, pages 881 to 887; Andersen, M.; Hildebrandt, B.; Koester, G.; Hoffmann, R. W., Chemische Berichte 1989, Vol. 122, pages1777 to 1782; Smoum, R.; Rubinstein, A.; Srebnik, M., Bioorganic Chemistry 2003, Vol. 31, pages 464 to 474; Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-N.; Liu, P.; Zhou, J., Organic Letters 2009, Vol. 11, pages 1999 to 2002). However, complete removal of the alcohol to below 0.05 wt% levels is difficult to achieve by aceotropic distillation.

Many solvents can be dried by distillation over alkali metals, and also alcohol impurities can be removed that way. However, tralkyl borates are known to react with metals like lithium (Bowie, R. A., Musgrave, O. C., Goldschmid, H. R., J. Chem. Coc. © 1970, pages 2228 to 2229), magnesium, calcium, strontium or barium (Wiberg, E. et al., Z. Naturforschung 1955, Vol. 10b, page 290).

Triorgano borates are typically used in borylation reactions and in reactions with organometallic compounds like Grignard compounds, alkyllithiums, etc. Borylation reactions are common in the synthesis of pharmaceutical drugs. The products of such reactions are typically used in Suzuki cross-coupling reactions to prepare complex intermediates for pharmaceutical products. Presence of alcohols in the borate raw material may impair the reaction of borates with organometallic compounds because they will decompose the organometallic species, thus resulting in side products or lower yield. Syntheses of pharmaceuticals may be very costly and any yield loss resulting from alcohol presence in borates is undesired.

It was therefore an object of the present invention to develop a process for preparing triorgano borates with low alcohol content.

Accordingly, a process for preparing triorgano borates with low alcohol content was found, comprising the step of bringing a triorgano borate into contact with at least one alkali metal at temperatures below 150 °C.

A preferred embodiment of the present invention is a process for preparing triorgano borates with low alcohol content, comprising the step of bringing a triorgano borate into contact with sodium-potassium-alloy at a temperature between 0 and 35 °C, most preferred at ambient temperature.

In a preferred embodiment of the present invention the triorgano borate is brought into contact with at least one alkali metal for a period of between 1 and 12 hours.

In another preferred embodiment of the present invention the triorgano borate is distilled off from the reaction mixture after it was in contact with the at least one alkali metal according to the invention.

Examples for alkali metals are lithium, sodium, potassium, rubidium and cesium.

As used in connection with the present invention, the term triorgano borate denotes a compound of the general formula

$$B(OR^1)(OR^2)(OR^3)$$

wherein R^1, R^2 and R^3 are the same or different organyl groups. Two of the groups R^1, R^2 and R^3 can also be connected to form a divalent organyl group (e. g. ortho-C_6H_4), that forms together with the BO_2 moiety, a cyclic structure.

Organyl groups as used herein are, for example, C_1 – C_{10} alkyl, C_3 – C_{10} cycloalkyl, C_6 – C_{14} aryl, C_7 – C_{16} aralkyl or C_7 – C_{16} alkaryl groups.

As used herein, the term "C_1 – C_{10} alkyl" denotes a branched or an unbranched saturated hydrocarbon group comprising between 1 and 10 carbon atoms. Examples are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, n-hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3- methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, n-heptyl, 5-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 2-ethylhexyl, n-octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, n-nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyloctyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, n-decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl and 1-,

2-, 3- or 4-propylheptyl. Preferred are the alkyl groups methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl and 1,1-dimethylpropyl, most preferred are isoamyl groups.

The term “isoamyl” denotes a branched methylbutyl group, preferably 3-methyl-2-butyl.

The term “C_3 – C_{10} cycloalkyl” denotes a saturated hydrocarbon group comprising between 3 and 10 carbon atoms including a mono- or polycyclic structural moiety. Examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl, dimethylcyclohexyl, cycloheptyl, cyclooctyl, norbornyl, isopinocampheyl, cyclononyl or cyclodecyl. Prefered are the cycloalkyl groups cyclopentyl, cyclohexyl, methylcyclohexyl and isopinocampheyl.

The term “isopinocampheyl” denotes all stereoisomers of a bicyclic hydrocarbon group obtainable via hydroboration of a-pinene.

The term "C_6 – C_{14} aryl" denotes an unsaturated hydrocarbon group comprising between 6 and 14 carbon atoms including at least one aromatic ring system like phenyl or naphthyl or any other aromatic ring system. ortho-C_6H_4 denotes a divalent aryl group occurring in catechol-type derivatives.

The term "C_7 – C_{16} aralkyl" denotes an aryl-substituted alkyl group comprising between 7 and 16 carbon atoms including for example a phenyl-, naphthyl- or alkyl-substituted phenyl- or alkyl-substituted naphthyl-group or any other aromatic ring system. Examples of aralkyl groups include benzyl, 1- or 2-phenylethyl, 1-, 2- or 3-phenylpropyl, mesityl and 2-, 3- or 4-methylbenzyl groups.

The term "C_7 – C_{16} alkaryl" denotes an alkyl-substituted aryl group comprising between 7 and 16 carbon atoms including for example a phenyl- or naphthyl- or alkyl-substituted phenyl- or alkyl-substituted naphthyl-group or any other aromatic ring system and an alkyl substituent as defined above. Examples for alkaryl groups are 2,- 3- or 4-methylphenyl, 2,- 3- or 4-ethylphenyl and 2,- 3-, 4-, 5-, 6-, 7- or 8-methyl-1-naphthyl groups.

The new process according to the invention allows for the preparation of triorgano borates with residual alcohol contents of below 0.1 wt%.

Therefore, another embodiment of the present invention is a triorgano borate with an alcohol content of below 0.1 wt%.

Example

3.5 g of sodium-potassium-alloy and 279 g isopropylpinacol borate (1.5 moles, containing 0.226 wt% of isopropanol) were stirred under nitrogen atmosphere at room temperature for 1 hour. Samples were taken and monitored by ^{11}B NMR spectroscopy. During a period of 3 hours an increase of the corresponding “ate” complex was noted (0.19 to 0.27%). The majority of the content was distilled into an oven dried clean distillation receiver (103 °C, 65 mmHg). The final product was analyzed by GC to find that the distillate only contained 0.057 wt% of isopropanol.

Claims

1. A process for preparing triorgano borates with low alcohol content, comprising the step of bringing a triorgano borate into contact with at least one alkali metal at temperatures below 150 °C.

2. A process according to claim 1, comprising the step of bringing a triorgano borate into contact with sodium-potassium-alloy at a temperature between 0 and 35 °C.

3. A process according to claim 1, comprising further the step of distilling out the triorgano borate.

4. A triorgano borate with an alcohol content of below 0.1 wt%.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/050635

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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: C07F 5

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 practicable, search terms used)

WPI, EPODOC, CNPAT, CNKI, CAPLUS, REG

BASF, borate, alcohol, boric, +oxyboron, ester, alkali, sodium, potassium, alloy, search according to the structure of triorgano borate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6100415 A (NIPPON PIONICS CO LTD), 08 Aug. 2000 (08.08.2000), see claims 1-4	4
A	the same as above	1-3
X	US 3024264 A (UNITED STATES BORAX CHEM), 06 March 1962 (06.03.1962), see examples I-IV	4
X	US 3005011 A (UNITED STATES BORAX CHEM), 17 Oct. 1961 (17.10.1961), see examples I-II and claims 1-6	4
X	US 3004058 A (CALLERY CHEMICAL CO), 10 Oct. 1961 (10.10.1961), see claims 1-17	4
A	DE 3126111 A1 (BASF AG), 20 Jan. 1983 (20.01.1983), see example 1	1-4

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 June 2011 (10.06.2011)	**14 Jul. 2011 (14.07.2011)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer CHANG, Xiaoyu Telephone No. (86-10)62084403

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2011/050635

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
US 6100415 A	08.08.2000	JP 11335310 A	07.12.1999
		JP 4287942 B2	01.07.2009
US 3024264 A	06.03.1962	none	
US 3005011 A	17.10.1961	GB 898325 A	06.06.1962
US 3004058 A	10.10.1961	none	
DE 3126111 A1	20.01.1983	NO 822258 A	24.01.1983
		FI 822292 A	28.02.1983

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both national classification and IPC：

C07F 5/04 (2006.01) i

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