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(54) **SYNTHESE D'ACIDES ARYLE BORONIQUES**
(54) **SYNTHESIS OF ARYL BORONIC ACIDS**

(57) L'invention concerne un procédé servant à effectuer la synthèse d'acides aryle boroniques.

(57) A method for synthesis of aryl boronic acids is disclosed.

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(54) Title: SYNTHESIS OF ARYL BORONIC ACIDS

(57) Abstract

A method for synthesis of aryl boronic acids is disclosed.

SYNTHESIS OF ARYL BORONIC ACIDS

This application is a continuation of United States application Serial No. 09/094,511 filed 10 June 1998.

FIELD OF THE INVENTION

This invention relates to the synthesis of aryl boronic acids.

BACKGROUND OF THE INVENTION

The use and effectiveness of Grignard reagents in ethereal solvents to alkylate or arylate non-metal compounds was established in the first half of the Twentieth Century. See, Kharasch, M.S., Reinmuth, O., "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, New York (1954).

Known aryl boronic acid synthesis typically entails concurrent or dual addition of substantially equimolar amounts of a trialkyl borate ester and an aromatic Grignard reagent to a reaction vessel at a temperature of less than -60°C, wherein a reaction mixture containing an aryl boronic acid ester is produced in a 30% to 50% yield. The ester is separated and hydrolyzed to provide the desired aryl boronic acid.

Aryl boronic acids are now in substantial commercial use to synthesize biaryl compounds by the palladium catalyzed cross-coupling "Suzuki" reaction. See, e.g., A. Suzuki, et al., Syn.Commun. (1981) 513-

519; Y. Young, et al., Acta Chem.Scand. (1939) 47:221-230; G.B. Smith, et al., J.Org.Chem. (1994) 598:8151-8156; S. Sengupta, et al., J.Org.Chem. (1997) 62:3405-3406. Accordingly, there is a need for an improved aryl boronic acid synthesis.

SUMMARY OF THE INVENTION

It has been found, contrary to the prior art, that neither temperatures below -60°C nor control of reactant mole ratio is necessary during the synthesis of the aryl borate alkyl diesters. Pursuant to this invention, the synthesis of aryl borate diesters is accomplished at a temperature of from about -10° to 0°C by direct addition of the Grignard to the trialkyl borate or conversely in any desired mole ratio. Hydrolysis of the aryl borate diesters may be accomplished in situ in synthesis reaction mixture with an aqueous mineral, preferably, aqueous sulfuric acid, in known manner. This invention typically provides aryl boronic yields approximately 20-40% greater than those achieved by the prior art. More specifically, the invention may provide aryl boronic acid yields of from about 50% to about 70% based on the trialkyl borate reactant.

DETAILED DESCRIPTION OF THE INVENTION

The invention may, but need not be, practiced as a one pot method. A Grignard reagent is prepared in known manner in an appropriate ethereal solvent, preferably at the greatest concentration resulting in a

solution. Any ethereal solvent compatible with Grignard formation may be used. Useful solvents may be ethers which are cyclic, e.g., tetrahydrofuran, or which have the formula ROR, in which R is an alkyl group preferably having 2 to 6 carbon atoms.

Pursuant to the invention, an aryl boronic acid triester is synthesized at a temperature of -10°C to 0°C as illustrated by equation 1:

$$ArMgX + B(OR)_3 \xrightarrow{T\ -10^{\circ}C\ \text{to}\ 0^{\circ}C} ArB(OR)_2 + ROMgX \quad (1)$$

Yield = 50-70%.

The Grignard aryl (Ar) groups may be substituted at one, some, or all available positions by any halogen (chlorine, bromine, fluorine or iodine), or by any straight or branched chain, substituted or unsubstituted alkyl group, or by any functional group compatible with or protected by standard methods to be compatible with the Grignard function. Phenyl, 4-fluorophenyl and naphthyl groups are typical Grignard aryl groups.

The alkyl borate reactant ($B(OR_3)$) is preferably used in an amount greater than stoichiometric with respect to the ArMgX reagent. For example, from about 1.1 to 2.0, preferably about 1.5 moles, of $B(OR_3)$ may be used for each mole of ArMgX.

Each of the R groups may be any alkyl group. Appropriate R groups have one to ten carbon atoms. R is preferably methyl.

The hydrolysis of the aryl boronic acid diester (equation 2) may be performed in known manner, e.g., by combining a mineral acid, preferably aqueous H_2SO_4, directly with the Grignard reaction mixture:

$$ArB(OR)_2 + H_2SO_{4(aq)} \longrightarrow ArB(OH)_2 + 2ROH \qquad (2)$$

EXAMPLE 1

(General Example)

The Grignard reagent is prepared in known manner in an appropriate ethereal solvent, preferably at the greatest concentration resulting in a solution.

A flask of appropriate size to accommodate the reaction volume as well as the volume of the aqueous acid hydrolysis solution is set up under a sweep of inert atmosphere and equipped for reflux and cooling. Trialkyl borate, e.g., trimethyl borate diluted with an equal weight of an ethereal solvent, preferably THF, is charged to the flask in an amount to provide a mole ratio of $ArMgX:B(OCH_3)_3$ of 1:1.5. The flask is cooled with dry ice:acetone to -10°C and addition of Grignard reagent begun, wherein a reaction mixture containing an aryl borate dialkyl ester is produced.

Upon completion of the Grignard addition, the reaction mixture is stirred to room temperature (1-2 hours). The dialkyl ester is hydrolyzed <u>in situ</u> by directly adding a 10% w/v H_2SO_4 aqueous solution in an amount equal to 2 mole H_2SO_4 with vigorous stirring for 30 minutes. The reaction mixture is then allowed to settle for 30 minutes. The hydrolysis reaction mixture

forms an upper organic layer and a lower aqueous layer. The organic layer is separated, and then dried over sodium sulfate. Solvent is distilled until solids begin to precipitate. Hexanes are added, and the precipitated product collected by filtration.

The method described by this general example has yielded the results reported in Table 1.

TABLE 1

Grignard Name	Grignard Concen-tration	Solvent	Product Name(s)	Quantity Reacted (Mole)	Yield of Product (Mole)	% Yield
Phenyl MgCl	2M	THF	Phenyl boronic acid; Benzene boronic acid	5	2	67
Phenyl MgBr	3M	Ether	Phenyl boronic acid; Benzene boronic acid	3	1.9	65

4-Fluoro phenyl MgBr	1.5M	THF	4-Fluoro phenyl boronic acid; 4-Fluoro-benzene boronic acid	3	1.65	55
4-Fluoro phenyl MgBr	2M	Ether	4-Fluoro phenyl acid; 4-Fluoro-benzene boronic acid	3	1.71	57
4-Methyl phenyl MgCl	2M	THF	4-Methyl phenyl boronic acid; 4-Methyl benzene boronic acid	3	1.65	55
4-Methyl phenyl MgBr	2M	Ether	4-Methyl phenyl boronic acid; 4-Methyl benzene boronic acid	3	1.62	54

Naphthyl MgBr	1M	THF	1-Naphthyl boronic acid	28.9	14.7	51
4-Chloro phenyl MgBr	2M	Ether	4-Chloro phenyl boronic acid; 4-Chloro-benzene boronic acid	2	1.24	62
4-Bromo phenyl MgBr	2M	Ether	4-Bromo phenyl boronic acid; 4-Bromo-benzene boronic acid	2	1.12	56
4-Methoxy phenyl MgBr	1.2M	THF	4-Methoxy benzene boronic acid	3	1.65	55
4-Methoxy phenyl MgBr	2M	Ether	4-Methoxy benzene boronic acid	3	1.8	60

The results reported in Table 1 were obtained in the laboratory with the exception that the synthesis of 1-naphthyl boronic acid was achieved in a pilot plant.

EXAMPLE 2

(Phenyl Boronic Acid)

A reaction flask was charged with trimethyl borate (1.5 moles, 155.7g) and tetrahydrofuran (300g). The mixture was cooled to a temperature of -5°C to 0°C.

One mole of phenyl magnesium bromide was added slowly with maintenance of the temperature between -5°C and 0°C. The reaction mixture was stirred for thirty minutes.

Ten percent (10%) aqueous sulfuric acid was directly added to the Grignard reaction mixture which contained the methyl ester of phenyl boronic acid. The resulting hydrolysis reaction mixture was stirred for thirty minutes and then allowed to settle for thirty minutes. The mixture separated into an upper layer and a lower layer. The upper layer was separated, dried over sodium sulfate (10g), and filtered. The volume of the filtrate was reduced by distillation of THF, 300 ml of hexane was added, and the distillation continued until most of the THF was removed. The remainder of the reaction mixture was cooled and filtered to recover solids which dried in vacuum. Yield—65% to 70% phenyl boronic acid.

WE CLAIM:

1. A process for producing an aryl boronic acid which comprises:

(i) directly combining an aryl Grignard reagent with a trialkyl borate at a temperature of -10°C to 0°C in a reaction vessel,

wherein the mole ratio of said trialkyl borate to said aryl Grignard reagent is from 1.1 to 2.0, and

wherein a reaction mixture containing an aryl boronic acid alkyl diester is produced; and

(ii) subjecting said reaction mixture in said reaction vessel to conditions effective to hydrolyze said aryl boronic acid alkyl diester contained in said reaction mixture,

wherein said hydrolysis yields said aryl boronic acid.

2. The claim 1 process, wherein said aryl boronic acid is phenyl boronic acid, or 4-fluorophenyl boronic acid.

3. The claim 1 or claim 2 method, wherein said trialkyl borate of step (i) is trimethyl borate.

4. A process for producing an aryl boronic acid which comprises:

(i) providing a solution of a boronic acid alkyl triester in a non-interfering solvent;

(ii) directly combining an aryl magnesium halide with said step (i) solution

wherein said boronic acid alkyl triester in said step (i) solution reacts with said aryl magnesium halide of step (ii) to produce a first, Grignard reaction mixture comprising an aryl boronic acid alkyl diester in solution in said non-interfering solvent;

wherein said directly combining step (ii) is conducted at a temperature of -10°C to 0°C; and

wherein the mole ratio of said boronic acid alkyl triester to said aryl magnesium halide in said directly combining step (ii) is from 1.1 to 2.0;

(iii) subjecting said first, Grignard reaction mixture produced in step (ii) to conditions effective to hydrolyze said aryl boronic acid alkyl diester,

wherein a second reaction mixture containing said aryl boronic acid is produced; and

(iv) separating said aryl boronic acid from said second reaction mixture.

5. The claim 4 process wherein said non-interfering solvent in step (i) is tetrahydrofuran.

6. The claim 4 process wherein said boronic acid alkyl diester in step (i) is methyl borate.

7. The claim 4 process wherein said aryl magnesium halide is phenyl magnesium bromide, or naphthyl magnesium bromide, or 4-fluorophenyl magnesium bromide, or 4-chlorophenyl magnesium bromide, or methoxy phenyl magnesium bromide.

8. The claim 4 process wherein said step (iii) conditions are produced by 10% aqueous sulfuric acid.

9. A process for producing an aryl boronic acid which comprises:

(i) directly combining an aryl Grignard reagent with a trialkyl borate at a temperature of -10°C to 0°C in a reaction vessel,

wherein the mole ratio of trialkyl borate to said aryl Grignard reagent is about 1.5,

wherein a reaction mixture containing an aryl boronic acid alkyl diester is produced; and

(ii) subjecting said reaction mixture in said reaction vessel to conditions effective to hydrolyze said aryl boronic acid alkyl diester contained in said reaction mixture,

wherein said hydrolysis yields said aryl boronic acid.

10. The claim 9 process, wherein said step (i) is accomplished at a temperature of -5°C to 0°C.

11. A process for producing an aryl boronic acid which comprises:

(i) providing a reaction vessel containing a non-interfering solvent solution of a trialkyl borate;

(ii) adjusting the temperature of said step (i) reaction vessel and its contents to a range of -10°C to 0°C°;

(iii) combining the contents of said reaction vessel at a temperature of -10°C to 0°C with an aryl Grignard reagent,

wherein said combining provides a mole ratio of said aryl Grignard reagent to said trialkyl borate which is greater than stoichiometric,

wherein a first reaction mixture containing an aryl borate diester is produced in said reaction vessel;

(iv) hydrolyzing said step (i) aryl borate diester in situ in said step (i) reaction vessel,

wherein a second reaction mixture is produced in said reaction vessel,

wherein said second reaction mixture contains an aryl boronic acid; and

(v) recovering said aryl boronic acid from said second hydrolysis reaction mixture.

12. The claim 11 process wherein the step (i) mole ratio of said trialkyl borate to said aryl Grignard reagent is from about 1.1 to about 2.0.

13. The claim 11 or claim 12 process wherein said hydrolyzing step (iv) is accomplished by combining aqueous sulfuric acid with step (iii) aryl borate diester wherein said second hydrolysis reaction mixture forms an upper organic layer and a lower aqueous layer, and wherein said claim 11 or claim 12 process further comprises a step (iv)(a):

(iv)(a) separating said upper organic layer from said lower aqueous layer of said hydrolysis reaction mixture.