

PATENT SPECIFICATION (11)

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C2C 220 222 226 227 22Y 292 29X 29Y 30Y 311 313 314
 31Y 339 364 366 367 36Y 37X 43X 624 628 658 662
 697 699 AA BU

(54) 2-ARYL-PROPIONIC ACID PRECURSORS

(71) We, SYNTEX CORPORATION, of P.O. Box 7386, Panama 5, Republic of Panama, a Panamanian Corporation, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to the preparation of 2-aryl-propionic acids, and is divided out of our co-pending Patent Application No. 5673/78 (Serial No. 1581618) (herein referred to as the parent Specification).

The parent Specification discloses a direct coupling process whereby an aryl magnesium chloride or bromide, in which aryl is 6-methoxy-2-naphthyl, 4-fluoro-2-biphenyl or 4-alkylphenyl where alkyl has 1 to 4 carbon atoms, is coupled with a magnesium halide complex of alpha-bromo-propionic acid, and the reaction mixture acidified to produce the corresponding 2-aryl-propionic acid. The reaction mixture before acidification contains an alpha-aryl-propionic acid magnesium chloride or bromide complex. The parent Specification claims the starting alpha-bromo-propionic acid magnesium halide complex, a method for preparing it, and the method for using it to produce the 2-aryl-propionic acid and the alpha-aryl-propionic acid magnesium halide complex precursor thereof.

The present application is directed specifically to the complex precursors Aryl CH(CH₃)COOMgX and etherates thereof, wherein Aryl is as defined above and X is chloro or bromo. A preferred compound is that in which Aryl is 6-methoxy-2-naphthyl and X is chloro. The tetrahydrofuran mono-etherate is preferred.

The compounds hereof are prepared by contacting a solution of an alpha-bromo-propionic acid magnesium chloride or bromide complex with a solution of the aryl magnesium bromide, each solution being in an aprotic organic solvent medium comprising an ether. Suitable solvent media for the reaction include organic ethers and mixtures of organic ethers with aromatic hydrocarbons as

mentioned above for the complex formation step. A particularly preferred solvent medium for the coupling reaction is tetrahydrofuran. It is preferred that the aryl magnesium bromide solution be between 0.5 and 2 M, most preferably about 1.0 M. The reaction will take place under substantially anhydrous conditions.

The coupling process itself may be carried out over a temperature range of from about 0 to about +100°C, preferably between about 10 and 60°C. It is particularly preferred to allow the temperature to gradually rise during the addition stage up to about 40–60°C and then to return to ambient temperature until the desired degree of reaction has been attained.

Although the coupling reaction may be conducted utilizing the reagents in varying proportions to one another it is preferred that approximately equimolar amounts of the mixed magnesium halide complex and the aryl Grignard reagent be utilized. Preferred ratios are from about 0.9:1.1 to 1.1:0.9 complex: Grignard reagent.

The reactions may be performed by conveniently contacting the two reagents in the solvent medium in any manner conventional in the art. However, it is particularly preferred to add the mixed magnesium halide complex to the Grignard reagent and to keep these reagents in intimate admixture until the desired reaction is essentially complete.

The time necessary for performance of the desired reaction will, of course, be influenced by the particular choice of reagents, solvents and reaction temperature and will ordinarily be adjusted by the skilled practitioner to allow for the optimum production of the desired product. Generally however such reaction time will be in the range of from about 10 minutes to about 20 hours, usually being in the range of from about 1 to about 5 hours. The starting alpha-bromo-propionic acid magnesium halide complex can be produced by treatment of alpha-bromo-propionic acid with a suitable Grignard reagent, as described in the parent Specification. The parent

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Specification also provides specific examples of the preparation of the starting materials and their coupling together to produce the precursors of the present invention which are acidified *in situ* to produce 2-aryl propionic acids. As described in the parent Specification, if the preparation of the 2-aryl propionic acid is interrupted prior to acidification, and the solvent is removed *in vacuo*, the coupled magnesium halide complex Aryl CH(CH₃)COOMgX or etherate thereof may be isolated.

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- gX or an etherate thereof, wherein aryl is 6-methoxy-2-naphthyl, 4-fluoro-4-biphenyl or 4-alkylphenyl where alkyl has 1 to 4 carbon atoms, and X is bromo or chloro.
 2. The compound of claim 1 wherein aryl is 6-methoxy-2-naphthyl and X is chloro.
 3. The tetrahydrofuran monetherate of the compound of claim 1 or claim 2.

WHAT WE CLAIM IS:—

1. The compound Aryl CH(CH₃)COOM-

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- Specification also provides specific examples of the preparation of the starting materials and their coupling together to produce the precursors of the present invention which are acidified *in situ* to produce 2-aryl propionic acids. As described in the parent Specification, if the preparation of the 2-aryl propionic acid is interrupted prior to acidification, and the solvent is removed *in vacuo*, the coupled magnesium halide complex Aryl CH(CH₃)COOMgX or etherate thereof may be isolated.
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- gX or an etherate thereof, wherein aryl is 6-methoxy-2-naphthyl, 4-fluoro-4-biphenyl or 4-alkylphenyl where alkyl has 1 to 4 carbon atoms, and X is bromo or chloro.
2. The compound of claim 1 wherein aryl is 6-methoxy-2-naphthyl and X is chloro.
3. The tetrahydrofuran monetherate of the compound of claim 1 or claim 2.

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ERRATA

SPECIFICATION NO 1581619

Page 1, line 17, page 2, line 16, *for* 4¹ — fluoro *read* 4' — fluoro

Page 1, lines 22, 24, 27, 29, and 30, *for* proprionic *read* propionic

Page 1, line 26, *for* alph-bromo- *read* alpha-bromo-

Page 1, line 74, *for* reactions *read* reaction

Page 2, line 21, *for* monetherate *read* monoetherate

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