

【SPECIFICATION】

【Invention Title】

METHOD FOR PREPARING COMPOUND BY NOVEL MICHAEL ADDITION REACTION USING WATER OR VARIOUS ACIDS AS ADDITIVE

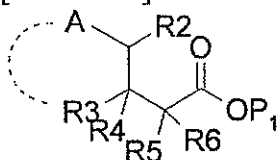
【Technical Field】

The present invention relates to a method for preparing a compound of Formula 1, which can be used as an intermediate of medicines, agricultural chemicals, electronic materials, liquid crystals and the like, through a novel Michael-addition reaction using water or a variety of acid as additive.

【Background Art】

Compound of Formula 1 has a variety of skeleton and biological activity, and thus it is widely used as an intermediate for synthesizing medicines, agricultural chemicals, electronic materials or liquid crystal materials, etc.

[Formula 1]



in which

A is R₁-C(=O)-, nitrile, substituted or unsubstituted C₁-C₁₀ alkylsulfonyl, or substituted or unsubstituted C₆-C₁₀ arylsulfonyl, where R₁ is selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₁₀ alkyl; substituted or unsubstituted C₃-C₁₀ cycloalkyl; substituted or unsubstituted C₆-C₁₀ aryl; substituted or unsubstituted 5-membered to 10-membered heteroaryl; and substituted or unsubstituted C₁-C₅ alkoxy; or when A is bonded to R₃, A and R₃ together with the carbon atoms to which they are attached form saturated or unsaturated C₆-C₁₀ cycloalkyl substituted with oxo(=O) group,

R₂, R₃ and R₄ are independently selected from the group consisting of hydrogen;

substituted or unsubstituted C₁-C₁₀ alkyl; substituted or unsubstituted C₃-C₁₀ cycloalkyl; substituted or unsubstituted C₆-C₁₀ aryl; substituted or unsubstituted 5-membered to 10-membered heteroaryl; substituted or unsubstituted C₁-C₅ alkoxy; nitrile; and substituted or unsubstituted C₁-C₁₀ alkylsulfonyl,

R₅ and R₆ are independently selected from the group consisting of hydrogen; halogen (i.e., F, Cl, Br, or I); and substituted or unsubstituted C₁-C₄ alkyl,

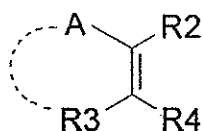
P₁ is selected from the group consisting of benzyl, methyl, ethyl, i-propyl and t-butyl.

A Compound of Formula 1 has an ester skeleton which can be easily substituted with other substrates and thus it is advantageously used in for synthesizing various organic compounds.. Therefore, methods for preparing compounds of Formula 1 have been studied widely, and various synthesis methods have been developed and reported in many literatures by organic synthesis chemists.

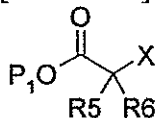
Among the compounds of Formula 1, those having organic fluorine derivatives are being studied actively, especially in Isumaro Kumadaki group (Setsunan University, Japan). However, there are many limitations in synthesizing such compounds having organic fluorine derivatives through Michael-addition reaction. It may be said that the first one of such limitations is excessive use of copper powder (6 equivalents or more), the second one is relatively long reaction time (1 to 7 hours), and the last one is relatively low yield (20 to 70%). Thus, there might be a problem in terms of cost, time and the like when synthesizing them in a large scale by using the conventional reactions [*Chem. Pharm. Bull.* **1999**, 47, 1023; *Chem. Pharm. Bull.* **2000**, 48, 1023; *J. Fluorine Chem.* **2003**, 121, 105; *J. Fluorine Chem.* **2004**, 125, 509].

An example which is known for synthesizing compound of Formula 1 is, a method of reacting a compound of Formula 2 with a compound of Formula 3 through Michael-addition reaction using copper powder.

[Formula 2]



[Formula 3]



In the above formulas, A, R2 to R6 and P₁ are the same as defined in Formula 1, and X is halogen (i.e., F, Cl, Br, or I).

However, conventional Michael-addition reactions simply using copper powder have shortcomings that a relatively long reaction time is needed and it is difficult to get a high yield due to generation of impurities.

【Detailed Description】

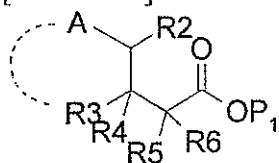
【Technical Purpose】

The purpose of the present invention is to provide a novel method for preparing a compound of Formula 1 with a high yield.

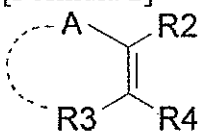
【Technical Solution】

Thus, the present invention provides a novel method for preparing a compound of Formula 1. According to the present invention, provided is a method for preparing a compound of Formula 1 wherein water or acid or a mixture thereof is added to a reaction mixture for preparing the compound of Formula 1 through Michael-addition reaction between a compound of Formula 2 and a compound of Formula 3 in the presence of copper powder:

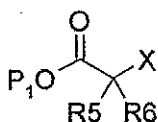
[Formula 1]



[Formula 2]



[Formula 3]



in which

A is R¹-C(=O)-, nitrile, substituted or unsubstituted C₁-C₁₀ alkylsulfonyl, or substituted or unsubstituted C₆-C₁₀ arylsulfonyl, where R¹ is selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₁₀ alkyl; substituted or unsubstituted C₃-C₁₀ cycloalkyl; substituted or unsubstituted C₆-C₁₀ aryl; substituted or unsubstituted 5-membered to 10-membered heteroaryl; and substituted or unsubstituted C₁-C₅ alkoxy; or when A is bonded to R³, A and R³ together with the carbon atoms to which they are attached form saturated or unsaturated C₆-C₁₀ cycloalkyl substituted with oxo(=O) group,

R², R³ and R⁴ are independently selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₁₀ alkyl; substituted or unsubstituted C₃-C₁₀ cycloalkyl; substituted or unsubstituted C₆-C₁₀ aryl; substituted or unsubstituted 5-membered to 10-membered heteroaryl; substituted or unsubstituted C₁-C₅ alkoxy; nitrile; and substituted or unsubstituted C₁-C₁₀ alkylsulfonyl,

R⁵ and R⁶ are independently selected from the group consisting of hydrogen; halogen (i.e., F, Cl, Br, or I); and substituted or unsubstituted C₁-C₄ alkyl,

P₁ is selected from the group consisting of benzyl, methyl, ethyl, i-propyl and t-butyl, and

X is halogen.

As used herein 'alkyl' refers to a linear or branched carbon chain having 1 to 10 (or 1 to 4) carbon atoms. Specifically, it may include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, neo-pentyl, hexyl, isohexyl and the like.

Also as used herein 'cycloalkyl' refers to a saturated or partially unsaturated mono- or poly-carbocyclic ring structure having 3 to 10 ring carbon atoms. Specifically, it may include cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl and the like.

Also as used herein 'aryl' refers to an aromatic mono- or poly-carbocyclic ring

structure having 6 to 10 ring carbon atoms. Specifically, it may include phenyl, naphthalenyl and the like.

Also as used herein 'heteroaryl' refers to an aromatic ring structure having 5 to 10 ring member atoms including 1 or 2 oxygens, nitrogens or sulfurs as a hetero atom(s). Specifically, it may include furan, pyran, isobenzofuran, chromene and the like.

Also as used herein 'alkoxy' refers to a linear or branched carbon chain having 1 to 5 carbon atoms to which a terminal oxygen is bound. Specifically, it may include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy, t-butoxy, pentoxy, neo-pentoxy and the like.

In the present invention, when A and R1 to R6 are substituted groups, it means they are substituted with one or more substituents selected from the group consisting of chloro, iodo, bromo, methyl, ethyl, n-propyl, isopropyl, butyl, methoxy, ethoxy, propoxy, butoxy, and acetyl.

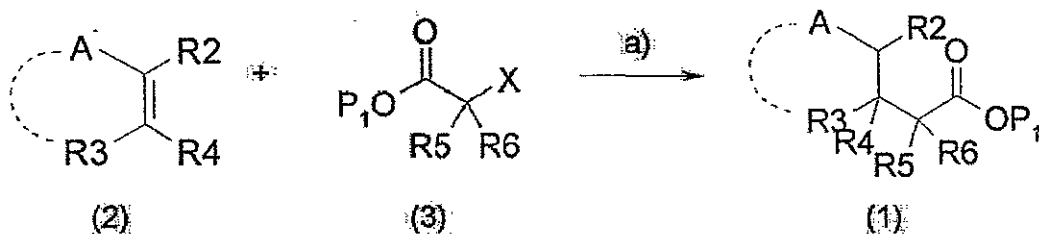
In an embodiment of the present invention, in the above Formulas 1 and 2, A is independently R1-C(=O)-, nitrile, substituted or unsubstituted C₁-C₁₀ alkylsulfonyl, or substituted or unsubstituted C₆-C₁₀ arylsulfonyl, where R1 is preferably selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₅ alkyl; substituted or unsubstituted C₃-C₆ cycloalkyl; substituted or unsubstituted C₆-C₈ aryl; substituted or unsubstituted 5-membered to 8-membered heteroaryl; and substituted or unsubstituted C₁-C₅ alkoxy; or when A is bonded to R3, A and R3 together with the carbon atoms to which they are attached form saturated or unsaturated C₆-C₁₀ cycloalkyl substituted with oxo(=O) group, and

more preferably R2, R3 and R4 are independently selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₅ alkyl; substituted or unsubstituted C₃-C₆ cycloalkyl; substituted or unsubstituted C₆-C₈ aryl; substituted or unsubstituted 5-membered to 8-membered heteroaryl; substituted or unsubstituted C₁-C₅ alkoxy; nitrile; and substituted or unsubstituted C₁-C₁₀ alkylsulfonyl.

The method for preparing a compound of Formula 1 of the present invention is

characterized in using water or a variety of acid as additive through Michael-addition reaction between a compound of Formula 2 and a compound of Formula 3 in the presence of copper powder,. In an embodiment of the present invention, for example, a compound of Formula 1 can be prepared according to the following Reaction Scheme 1.

[Reaction Scheme 1]



In the Reaction Scheme 1,

a is copper powder, additive(water or a variety of acid), amine compound and a solvent, and

A, R2, R3, R4, R5, R6, P₁ and X are the same as defined above.

In the method for preparing a compound of Formula 1 of the present invention, the amount of copper powder used is not especially limited. Considering some conditions, it is preferably used in an amount of 1.0 to 6.0 equivalents, more preferably 2.0 equivalents or more with respect to 1 mole of compound of Formula 2.

In the method for preparing a compound of Formula 1 of the present invention, water or a variety of acid or a mixture thereof is used as specific additive for the reaction. Acids available in the present invention may include inorganic acid selected from hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acid which is selected from formic acid, acetic acid, tartaric acid and the like, and the acid may be used alone or in combination of two or more. Especially, considering the reaction stability, convenience, etc., it is preferable to use water or acetic acid as the additive. In the present invention, the water or acid is preferably used in an amount of 0.1 to 6.0 equivalents, more preferably 0.1 to 1 equivalent, with respect to 1 mole of the compound of Formula 2.

The method for preparing a compound of Formula 1 of the present invention can be carried out in the presence of amine compound. In this case, amine compound such as

N,N,N',N'-tetramethylethylenediamine (TMEDA), *N,N,N',N'*-tetramethyl-1,3-propanediamine (TMPDA), *N,N,N',N',N'*-pentamethyldiethylenetriamine (PMDTA), 2-(dimethylamino)ethyl ether, *N,N*-dimethyl-2-(4-methyl-1-*piperazyl*)ethanamine and the like may be used, but it is not limited thereto. The amine compound is preferably used in an amount of 0.1 to 6.0 equivalents, more preferably 0.1 to 1 equivalent, with respect to 1 mole of the compound of Formula 2. In an embodiment of the present invention, TMEDA is used representatively.

Solvent used in the method for preparing a compound of Formula 1 of the present invention is a conventional organic solvent, and solvent such as acetonitrile, aliphatic nitriles, halogenated aliphatic hydrocarbons (for example, dichloromethane, dichloroethane, etc.) and cyclicethers (for example, tetrahydrofuran, 1,4-dioxane, etc.) may be used, but it is not limited thereto. In an embodiment of the present invention, tetrahydrofuran is used representatively.

Michael-addition reaction between a compound of Formula 2 and a compound of Formula 3 can be carried out at any temperature in a range of from 15 °C to the reflux temperature.

Although the reaction time of the present invention may vary according to reactants, type and amount of solvent, or the like, the present invention can curtail the reaction time in comparison with conventional methods under the same conditions. The reaction is terminated after confirming that all the compound of Formula 2, a starting material, are consumed by means of TLC, ¹H NMR, HPLC, GC, etc. If the reaction is terminated, the solvent is distilled under reduced pressure, and then the compound of Formula 1 can be separated and purified by means of conventional methods such as column chromatography, etc.

【Advantageous Effects】

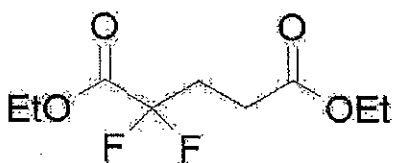
According to the present invention, a compound of Formula 1 can be prepared by using water or a variety of acid or a mixture thereof as additive, which has not been tried so far, and the reaction time can be curtailed and the yield can be improved remarkably in

comparison with conventional methods. Thus, a compound of Formula 1, which is useful as an intermediate of medicines, agricultural chemicals, electronic materials, liquid crystals and the like, can be produced in a commercial scale.

【Mode for Invention】

Hereinafter, the present invention will be described in more detail with reference to the following examples which are provided to facilitate understanding of the present invention. However, the scope of the present invention should not be construed to be limited thereby in any manner.

Example 1: Synthesis of diethyl 2,2-difluoropentanedioate

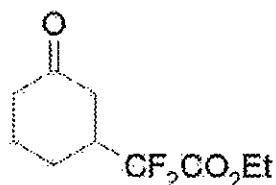


Copper powder (700 mg) and tetrahydrofuran (5.8 mL) were put in a reaction vessel and stirred at 50 °C, and ethyl acrylate (0.50 g) and ethyl bromodifluoroacetate (2.53 g) were added thereto, and then TMEDA (0.29 g) and acetic acid (0.27 g) were added dropwise thereto in this order. The reaction was conducted for 0.5 hour and then terminated. To the resulting mixture an aqueous solution of 10% ammonium chloride was added, and the resulting mixture was filtered by using celite pad to remove copper residue, and extracted with methyl t-butyl ether to obtain diethyl 2,2-difluoropentanedioate (1.09 g, yield: 97.4%).

In addition, excepting that water (0.10 g) was used instead of acetic acid, the same method as above was carried out to obtain diethyl 2,2-difluoropentanedioate (1.08 g, yield: 96.4%).

^1H NMR (400 MHz, CDCl_3) δ 1.26 (t, $J=7.2$ Hz, 3H), 1.37 (t, $J=7.2$ Hz, 3H), 2.37 – 2.49 (m, 2H), 2.55 (t, $J=7.2$ Hz, 2H), 4.16 (q, $J=7.2$ Hz, 2H), 4.29 (q, $J=7.2$ Hz, 2H).

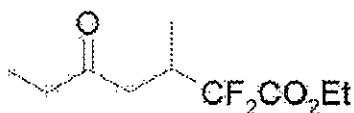
Example 2: Synthesis of ethyl 2,2-difluoro-2-(3-oxocyclohexyl)acetate



Copper powder (1.65 g) and tetrahydrofuran (7.60 mL) were put in a reaction vessel and stirred under a reflux condition, 2-cyclohexene-1-on (0.50 g) and ethyl bromodifluoroacetate (2.64 g) were added thereto, and then TMEDA (0.30 g) and acetic acid (0.28 g) were added dropwise thereto in this order. The reaction was conducted for 4 hours and then terminated. To the resulting mixture an aqueous solution of 10% ammonium chloride was added, and the resulting mixture was filtered by using celite pad to remove copper residue, and extracted with methyl t-butyl ether to obtain ethyl 2,2-difluoro-2-(3-oxocyclohexyl)acetate (1.12 g, yield: 97.8%).

^1H NMR (400 MHz, CDCl_3) δ 4.35 (q, $J=7.0$ Hz, 2H), 2.70 – 1.66 (m, 9H), 1.37 (t, $J=7.0$ Hz, 3H)

Example 3: Synthesis of ethyl 2,2-difluoro-3-methyl-5-oxoheptanoate



Copper powder (1.94 g) and tetrahydrofuran (7.4 mL) were put in a reaction vessel and stirred under a reflux condition, 4-hexene-3-on (0.50 g) and ethyl bromodifluoroacetate (2.59 g) were added thereto, and then TMEDA (0.30 g) and acetic acid (0.28 g) were added

dropwise thereto in this order. The reaction was conducted for 1 hour and then terminated. To the resulting mixture an aqueous solution of 10% ammonium chloride was added, and the resulting mixture was filtered by using celite pad to remove copper residue, and extracted with methyl t-butyl ether to obtain ethyl 2,2-difluoro-3-methyl-5-oxoheptanoate (1.04 g, yield: 91.9%).

^1H NMR (400 MHz, CDCl_3) δ 4.32 (q, $J=7.0$ Hz, 2H), 2.97 – 2.84 (m, 1H), 2.77 (dd, $J=17.7$, 4.0 Hz, 1H), 2.48 – 2.38 (m, 3H), 1.36 (t, $J=7.0$ Hz, 3H), 1.07 (t, $J=7.3$ Hz, 3H), 1.01 (d, $J=7.0$ Hz, 3H)

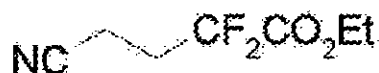
Example 4: Synthesis of ethyl-2,2-difluoro-5-oxohexanoate



Copper powder (0.48 g) and tetrahydrofuran (5.21 mL) were put in a reaction vessel and stirred at room temperature, methyl vinyl ketone (0.25 g) and ethyl bromodifluoroacetate (1.14 mL) were added thereto, and then TMEDA (0.21 g) and acetic acid (0.19 g) were added dropwise thereto in this order. The reaction was conducted for 1 hour and then terminated. To the resulting mixture an aqueous solution of 10% ammonium chloride was added, and the resulting mixture was filtered by using celite pad to remove copper residue, and extracted with methyl t-butyl ether to obtain ethyl-2,2-difluoro-5-oxohexanoate (0.63 g, yield: 91.0%).

^1H NMR (400 MHz, CDCl_3) δ 4.32 (q, $J=7.0$ Hz, 2H), 2.69 (t, $J=7.9$ Hz, 2H), 2.43 – 2.31 (m, 2H), 2.19 (s, 3H), 1.35 (t, $J=7.0$ Hz, 3H)

Example 5: Synthesis of ethyl-4-cyano-2,2-difluorobutanoate

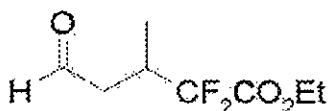


Copper powder (1.26 g) and tetrahydrofuran (13.8 mL) were put in a reaction vessel and stirred at room temperature, acrylonitrile (0.50 g) and ethyl bromodifluoroacetate (4.78 g) were added dropwise thereto, and then TMEDA (0.55 g) and acetic acid (0.51 g) were added thereto in this order. The reaction was conducted for 1 hour and then terminated. To the resulting mixture an aqueous solution of 10% ammonium chloride was added, and the resulting mixture was filtered by using celite pad to remove copper residue, and extracted with methyl t-butyl ether to obtain ethyl-4-cyano-2,2-difluorobutanoate (1.52 g, yield: 91.1%).

In addition, excepting that water (0.17 g) was used instead of acetic acid, the same method as above was carried out to obtain ethyl-4-cyano-2,2-difluorobutanoate (1.48 g, yield: 88.7%).

^1H NMR (400 MHz, CDCl_3) δ 4.37 (q, $J=7.0$ Hz, 2H), 2.62 (t, $J=7.6$ Hz, 2H), 2.48 (m, 2H), 1.38 (t, $J=7.0$ Hz, 3H)

Example 6: Synthesis of ethyl 2,2-difluoro-3-methyl-5-oxopentanoate



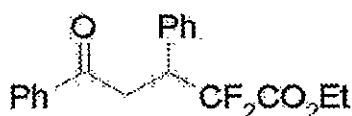
Copper powder (1.81 g) and tetrahydrofuran (10.40 mL) were put in a reaction vessel and stirred under a reflux condition, crotonaldehyde (0.50 g) and ethyl bromodifluoroacetate (3.62 g) were added dropwise thereto, and then TMEDA (0.41 g) and acetic acid (0.39 g) were added thereto in this order. The reaction was conducted for 1 hour and then terminated. To the resulting mixture an aqueous solution of 10% ammonium chloride was added, and the resulting mixture was filtered by using celite pad to remove copper residue, and extracted with methyl t-butyl ether to obtain ethyl 2,2-difluoro-3-methyl-5-oxopentanoate (0.79 g,

yield: 57.0%).

^1H NMR (400 MHz, CDCl_3) δ 9.77 (s, 1H), 4.34 (1, $J=7.0$ Hz, 2H), 3.02 – 2.87 (m, 1H), 2.84 (dd, $J=18.0, 4.0$ Hz, 1H), 2.46 (ddd, $J=18.0, 8.8, 2.6$ Hz, 1H), 1.36 (t, $J=7.0$ Hz, 3H), 1.08 (d, $J=7.0$ Hz, 3H)

In this example, 34% improvement in yield and 2 hours curtailment of reaction time were achieved in comparison with the yield (23%) and reaction time (3 hours) of a prior art (*J. Fluorine Chem.* **2003**, *121*, 105).

Example 7: Synthesis of ethyl 2,2-difluoro-5-exo-3-phenylhexanoate

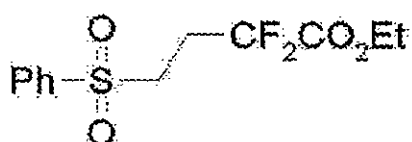


Copper powder (0.32 g) and tetrahydrofuran (10.4 mL) were put in a reaction vessel and stirred under a reflux condition, chalcone (0.50 g) and ethyl bromodifluoroacetate (1.22 g) were added dropwise thereto, and then TMEDA (0.14 g) and acetic acid (0.13 g) were added thereto in this order. The reaction was conducted for 1 hour and then terminated. To the resulting mixture an aqueous solution of 10% ammonium chloride was added, and the resulting mixture was filtered by using celite pad to remove copper residue, and extracted with methyl t-butyl ether to obtain ethyl 2,2-difluoro-5-exo-3-phenylhexanoate (833 mg, yield: 34.8%).

^1H NMR (400 MHz, CDCl_3) δ 7.94 – 7.92 (m, 2H), 7.57 – 7.53 (m, 1H), 7.46 – 7.43 (m, 2H), 7.37 – 7.35 (m, 2H), 7.29 – 7.23 (m, 2H), 4.36 – 4.24 (m, 1H), 4.14 (q, $J=7.0$ Hz, 2H), 3.67 (s, 1H), 3.65 (d, $J=2.4$ Hz, 1H), 1.14 (t, $J=7.0$ Hz, 3H)

In this example, 11.8% improvement in yield was achieved in comparison with the yield (23%) of a prior art (*J. Fluorine Chem.* **2003**, 121, 105). The reaction time of this example (1 hour) was the same as that of the prior art. However, the prior art needs a step of stirring the reactants for 1 hour and then adding TMEDA thereto, whereas the present invention does not need such a step, and thus the total reaction time could be further curtailed substantially.

Example 8: Synthesis of ethyl 2,2-difluoro-4-(phenylsulfonyl)butanoate



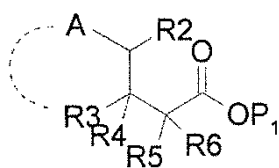
Copper powder (0.40 g) and tetrahydrofuran (4.40 mL) were put in a reaction vessel and stirred at 50 °C, phenyl vinyl sulfone (0.50 g) and ethyl bromodifluoroacetate (1.51 g) were added dropwise thereto, and then TMEDA (0.17 g) and acetic acid (0.16 g) were added thereto in this order. The reaction was conducted for 1 hour and then terminated. To the resulting mixture an aqueous solution of 10% ammonium chloride was added, and the resulting mixture was filtered by using celite pad to remove copper residue, and extracted with methyl t-butyl ether to obtain ethyl 2,2-difluoro-4-(phenylsulfonyl)butanoate (0.74 g, yield: 85.2%).

¹H NMR (400 MHz, DMSO) δ 7.98 – 9.96 (m, 2H), 7.80 (tt, *J*=7.4, 1.2 Hz, 1H), 7.72 – 7.65 (m, 2H), 4.27 (q, *J*=7.0 Hz, 2H), 3.57 – 3.48 (m, 2H), 2.50 – 2.40 (m, 2H), 1.24 (t, *J*=7.0 Hz, 3H)

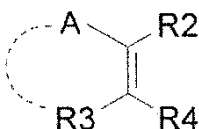
Claims

1. A method for preparing a compound of Formula 1 wherein water or acid or a mixture thereof is added to a reaction mixture for preparing the compound of Formula 1 through Michael-addition reaction between a compound of Formula 2 and a compound of Formula 3 in the presence of copper powder:

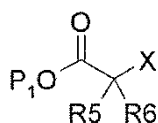
[Formula 1]



[Formula 2]



[Formula 3]



in which

A is R¹-C(=O)-, nitrile, substituted or unsubstituted C₁-C₁₀ alkylsulfonyl, or substituted or unsubstituted C₆-C₁₀ arylsulfonyl, where R¹ is selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₁₀ alkyl; substituted or unsubstituted C₃-C₁₀ cycloalkyl; substituted or unsubstituted C₆-C₁₀ aryl; substituted or unsubstituted 5-membered to 10-membered heteroaryl; and substituted or unsubstituted C₁-C₅ alkoxy; or when A is bonded to R³, A and R³ together with the carbon atoms to which they are attached form saturated or unsaturated C₆-C₁₀ cycloalkyl substituted with oxo (=O) group,

R², R³ and R⁴ are independently selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₁₀ alkyl; substituted or unsubstituted C₃-C₁₀ cycloalkyl; substituted or unsubstituted C₆-C₁₀ aryl; substituted or unsubstituted 5-membered to 10-membered heteroaryl; substituted or unsubstituted C₁-C₅ alkoxy; nitrile; and substituted or unsubstituted C₁-C₁₀ alkylsulfonyl,

R5 and R6 are independently selected from the group consisting of hydrogen; halogen (i.e., F, Cl, Br, or I); and substituted or unsubstituted C₁-C₄ alkyl,

P₁ is selected from the group consisting of benzyl, methyl, ethyl, i-propyl and t-butyl, and

X is halogen,

wherein, when A and R1 to R6 are substituted groups, they are substituted with one or more substituents selected from the group consisting of chloro, iodo, bromo, methyl, ethyl, n-propyl, isopropyl, butyl, methoxy, ethoxy, propoxy, butoxy, and acetyl.

2. The method according to claim 1, wherein

A is R1-C(=O)-, nitrile, substituted or unsubstituted C₁-C₁₀ alkylsulfonyl, or substituted or unsubstituted C₆-C₁₀ arylsulfonyl, where R1 is selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₅ alkyl; substituted or unsubstituted C₃-C₆ cycloalkyl; substituted or unsubstituted C₆-C₈ aryl; substituted or unsubstituted 5-membered to 8-membered heteroaryl; and substituted or unsubstituted C₁-C₅ alkoxy; or when A is bonded to R3, A and R3 together with the carbon atoms to which they are attached form saturated or unsaturated C₆-C₁₀ cycloalkyl substituted with oxo (=O) group,

R2, R3 and R4 are independently selected from the group consisting of hydrogen; substituted or unsubstituted C₁-C₅ alkyl; substituted or unsubstituted C₃-C₆ cycloalkyl; substituted or unsubstituted C₆-C₈ aryl; substituted or unsubstituted 5-membered to 8-membered heteroaryl; substituted or unsubstituted C₁-C₅ alkoxy; nitrile; and substituted or unsubstituted C₁-C₁₀ alkylsulfonyl, and

when A and R1 to R4 are substituted groups, they are substituted with one or more substituents selected from the group consisting of chloro, iodo, bromo, methyl, ethyl, n-propyl, isopropyl, butyl, methoxy, ethoxy, propoxy, butoxy, and acetyl.

3. The method according to claim 1, wherein the copper powder is used in an amount of 1.0 to 6.0 equivalents with respect to 1 mole of the compound of Formula 2.

4. The method according to claim 1, wherein the acid is inorganic acid selected from hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid; organic acid selected from formic acid, acetic acid and tartaric acid; or a mixture thereof.

5. The method according to claim 1, wherein the water or acid is used in an amount of 0.1 to 6 equivalents with respect to 1 mole of the compound of Formula 2.
6. The method according to any of claims 1 to 5, wherein amine compound is further added to the reaction mixture during the reaction of the compound of Formula 2 and the compound of Formula 3.
7. The method according to claim 6, wherein tetramethylethylenediamine is used in an amount of 0.1 to 6 equivalents with respect to 1 mole of the compound of Formula 2.