

PREPARATION OF SUBSTITUTED ACRYLATE COMPOUND

PRIORITY CLAIM

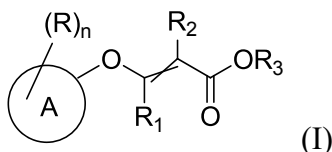
[0001] This application claims the priority of Chinese Invention Patent Application No. 202010856857.9, filed on August 24, 2020, the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present disclosure relates to a synthetic method of preparing substituted acrylate compounds of general formula (I).

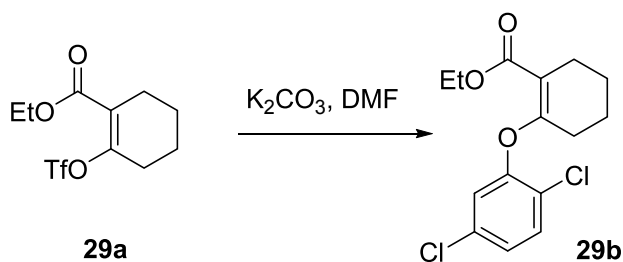
BACKGROUND OF THE INVENTION

[0003] The substituted acrylate compounds of general formula (I) are commonly used pharmaceutical intermediate compounds.



[0004] There are many methods of preparing the compound of general formula (I) in the prior art, but they generally suffer from low yields, need to use metal catalysts, poor safety, high prices of raw materials, and the like.

[0005] For example, WO2013096771A1 discloses the following reaction without using a metal catalyst, which comprises reacting compound 29a with 2,5-dichlorophenol, K_2CO_3 and DMF at 120°C for 2h, with a yield of 59% (See Example 29 on pages 120-121 of the PCT publication).



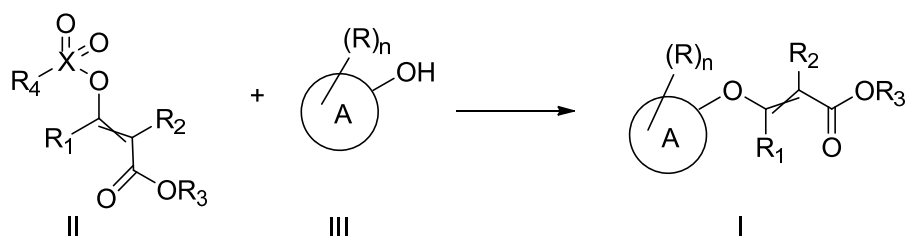
[0006] Therefore, there is still a general need for the preparation of substituted acrylate

compounds of general formula (I) in an economical, safe and effective manner.

SUMMARY OF THE INVENTION

[0007] After in-depth research, the inventors of the present invention have found a method suitable for industrial production of compounds of general formula (I), which does not use metal catalysts, can be implemented with cheap and readily available raw materials, and produces compounds of general formula (I) in high yields.

[0008] Specifically, in one aspect, the method comprises reacting a compound of general formula (II) with a compound of general formula (III), in the presence of a base:



[0009] wherein

[0010] ring A is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

[0011] X is S or P;

[0012] R₁ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, and 3- to 8-membered heterocyclyl;

[0013] R₂ is selected from H, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

[0014] R₃ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₀₋₆ alkylene-C₃₋₇ cycloalkyl, -C₀₋₆ alkylene-3- to 8-membered heterocyclyl, -C₀₋₆ alkylene-C₆₋₁₀ aryl, and -C₀₋₆ alkylene-5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m R' group(s);

[0015] R₄ is selected from C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -OR_a, -NR_aR_b, C₃₋₇ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m' R'' group(s);

[0016] R is selected from H, halogen, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

[0017] n is 0, 1, 2, 3, 4, or 5;

[0018] wherein R' and R'' are independently selected from halogen, -NO₂, -CN, -NR_aR_b, -NR_aC(O)R_b, C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, and phenyl;

[0019] m is 1, 2, 3, 4, or 5;

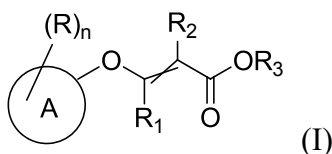
[0020] m' is 1, 2, 3, 4, or 5;

[0021] R_a and R_b are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl; or R_a and R_b, together with the nitrogen atom to which they are attached, form 3- to 8-membered heterocyclyl or 5- to 10-membered heteroaryl.

[0022] In another aspect, the method does not use metal catalysts.

[0023] In another aspect, the method does not use OTf, which is the most commonly used and most reactive leaving group in the art, and can increase the reaction yield compared with using OTf.

[0024] In another aspect, the present disclosure provides a compound of formula (I), prepared by the method described above:



[0025] wherein

[0026] ring A is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

[0027] R₁ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, and 3- to 8-membered heterocyclyl;

[0028] R₂ is selected from H, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

[0029] R₃ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₀₋₆ alkylene-C₃₋₇ cycloalkyl, -C₀₋₆ alkylene-3- to 8-membered heterocyclyl, -C₀₋₆ alkylene-C₆₋₁₀ aryl, and -C₀₋₆ alkylene-5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m R' group(s);

[0030] R is selected from H, halogen, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

[0031] n is 0, 1, 2, 3, 4, or 5;

[0032] wherein R' is selected from halogen, -NO₂, -CN, -NR_aR_b, -NR_aC(O)R_b, C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, and phenyl;

[0033] m is 1, 2, 3, 4, or 5;

[0034] R_a and R_b are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl,

3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl; or R_a and R_b, together with the nitrogen atom to which they are attached, form 3- to 8-membered heterocyclyl or 5- to 10-membered heteroaryl.

DETAILED DESCRIPTION OF THE INVENTION

[0035] Definition

[0036] Chemical definitions

[0037] Definitions of specific functional groups and chemical terms are described in more detail below.

[0038] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example “C₁₋₆ alkyl” is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅ and C₅₋₆ alkyl.

[0039] The term "about" means having a value that falls within the standard error of the accepted mean when considered by one of ordinary skill in the art. For example, "about" means $\pm 10\%$ of the indicated amount, or $\pm 5\%$ of the indicated amount.

[0040] “C₁₋₂₀ alkyl” refers to a radical of a straight or branched, saturated hydrocarbon group having 1 to 20 carbon atoms. In some embodiments, C₁₋₁₂ alkyl is alternative. In some embodiments, C₁₋₆ alkyl is alternative. In some embodiments, C₁₋₄ alkyl is alternative. Examples of C₁₋₆ alkyl include methyl (C₁), ethyl (C₂), n-propyl (C₃), iso-propyl (C₃), n-butyl (C₄), tert-butyl (C₄), sec-butyl (C₄), iso-butyl (C₄), n-pentyl (C₅), 3-pentyl (C₅), pentyl (C₅), neopentyl (C₅), 3-methyl-2-butyl (C₅), tert-pentyl (C₅) and n-hexyl (C₆). The term "C₁₋₆ alkyl" also includes heteroalkyl, wherein one or more (e.g., 1, 2, 3 or 4) carbon atoms are substituted with heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, phosphorus). Alkyl groups can be optionally substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent. Conventional abbreviations of alkyl include Me (-CH₃), Et (-CH₂CH₃), iPr (-CH(CH₃)₂), nPr (-CH₂CH₂CH₃), nBu (-CH₂CH₂CH₂CH₃) or iBu (-CH₂CH(CH₃)₂).

[0041] “C₂₋₆ alkenyl” refers to a radical of a straight or branched hydrocarbon group having 2 to 6 carbon atoms and at least one carbon-carbon double bond. In some embodiments, C₂₋₄ alkenyl is alternative. Examples of C₂₋₆ alkenyl include vinyl (C₂), 1-propenyl (C₃), 2-propenyl

(C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), etc. The term "C₂₋₆ alkenyl" also includes heteroalkenyl, wherein one or more (e.g., 1, 2, 3 or 4) carbon atoms are replaced by heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, phosphorus). The alkenyl groups can be optionally substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0042] "C₂₋₆ alkynyl" refers to a radical of a straight or branched hydrocarbon group having 2 to 6 carbon atoms, at least one carbon-carbon triple bond and optionally one or more carbon-carbon double bonds. In some embodiments, C₂₋₄ alkynyl is alternative. Examples of C₂₋₆ alkynyl include, but are not limited to, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), hexynyl (C₆), etc. The term "C₂₋₆ alkynyl" also includes heteroalkynyl, wherein one or more (e.g., 1, 2, 3 or 4) carbon atoms are replaced by heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, phosphorus). The alkynyl groups can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0043] "C₁₋₆ alkylene" refers to a divalent group of the "C₁₋₆ alkyl" as defined above, i.e., a divalent group formed by removing another hydrogen of the C₁₋₆ alkyl, and can be a substituted or unsubstituted alkylene. In some embodiments, C₁₋₄ alkylene is yet alternative. The unsubstituted alkylene groups include, but are not limited to, methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), butylene (-CH₂CH₂CH₂CH₂-), pentylene (-CH₂CH₂CH₂CH₂CH₂-), hexylene (-CH₂CH₂CH₂CH₂CH₂CH₂-), etc. Examples of substituted alkylene groups, such as those substituted with one or more alkyl (methyl) groups, include, but are not limited to, substituted methylene (-CH(CH₃)-, -C(CH₃)₂-), substituted ethylene (-CH(CH₃)CH₂-, -CH₂CH(CH₃)-, -C(CH₃)₂CH₂-, -CH₂C(CH₃)₂-), substituted propylene (-CH(CH₃)CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH₂CH(CH₃)-, -C(CH₃)₂CH₂CH₂-, -CH₂C(CH₃)₂CH₂-, -CH₂CH₂C(CH₃)₂-), etc.

[0044] "C₀₋₆ alkylene" refers to a chemical bond and "C₁₋₆ alkylene".

[0045] "Halo" or "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

[0046] Thus, "C₁₋₆ haloalkyl" refers to the above "C₁₋₆ alkyl", which is substituted by one or more halogens. In some embodiments, C₁₋₄ haloalkyl is yet alternative, and still alternatively C₁₋₂ haloalkyl. Exemplary haloalkyl groups include, but are not limited to, -CF₃, -CH₂F, -CHF₂,

-CHFCH₂F, -CH₂CHF₂, -CF₂CF₃, -CCl₃, -CH₂Cl, -CHCl₂, 2,2,2-trifluoro-1,1-dimethyl-ethyl, and the like. The haloalkyl can be substituted at any available point of attachment, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0047] “C₃₋₇ cycloalkyl” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 7 ring carbon atoms and zero heteroatom. In some embodiments, C₃₋₅ cycloalkyl is alternative. In other embodiments, C₃₋₆ cycloalkyl is alternative. In other embodiments, C₅₋₆ cycloalkyl is alternative. The cycloalkyl also includes a ring system in which the cycloalkyl described herein is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the cycloalkyl ring, and in such case, the number of carbon atoms continues to represent the number of carbon atoms in the cycloalkyl system. Exemplary cycloalkyl groups include, but are not limited to, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), etc. The cycloalkyl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0048] “3- to 8-membered heterocyclyl” refers to a radical of 3- to 8-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms. 3- to 6-membered heterocyclyl is alternative, which is a radical of 3- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms. 3- to 5-membered heterocyclyl is alternative, which is a radical of 3- to 5-membered non-aromatic ring system having ring carbon atoms and 1 to 2 ring heteroatoms. 4- to 8-membered heterocyclyl is alternative, which is a radical of 4- to 8-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms. 5- to 6-membered heterocyclyl is yet alternative, which is a radical of 5- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms. The heterocyclyl also includes a ring system wherein the heterocyclyl described above is fused with one or more cycloalkyl groups, wherein the point of attachment is on the cycloalkyl ring, or the heterocyclyl described above is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring; and in such cases, the number of ring members continues to represent the number of ring members in the heterocyclyl ring system. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, but

are not limited to, aziridinyl, oxiranyl and thiiranyl (thiorenyl). Exemplary 4-membered heterocyclyl groups containing one heteroatom include, but are not limited to, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, but are not limited to, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothienyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, but are not limited to, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, but are not limited to, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, but are not limited to, piperidyl, tetrahydropyranyl, dihydropyridyl and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, but are not limited to, piperazinyl, morpholinyl, dithianyl and dioxanyl. Exemplary 6-membered heterocyclyl groups containing three heteroatoms include, but are not limited to, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, but are not limited to, azepanyl, oxepanyl and thiepanyl. Exemplary 5-membered heterocyclyl groups fused with a C₆ aryl (also referred as 5,6-bicyclic heterocyclyl herein) include, but are not limited to, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, benzoxazolinonyl, etc. Exemplary 6-membered heterocyclyl groups fused with a C₆ aryl (also referred as 6,6-bicyclic heterocyclyl herein) include, but are not limited to, tetrahydroquinolinyl, tetrahydroisoquinolinyl, etc. The heterocyclyl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0049] “C₆₋₁₀ aryl” refers to a radical of monocyclic or polycyclic (e.g., bicyclic) 4n+2 aromatic ring system having 6-10 ring carbon atoms and zero heteroatom (e.g., having 6 or 10 shared π electrons in a cyclic array). In some embodiments, the aryl group has six ring carbon atoms (“C₆ aryl”; for example, phenyl). In some embodiments, the aryl group has ten ring carbon atoms (“C₁₀ aryl”; for example, naphthyl, e.g., 1-naphthyl and 2-naphthyl). The aryl group also includes a ring system in which the aryl ring described above is fused with one or more cycloalkyl or heterocyclyl groups, and the point of attachment is on the aryl ring, in which case the number of carbon atoms continues to represent the number of carbon atoms in

the aryl ring system. The aryl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0050] “5- to 10-membered heteroaryl” refers to a radical of 5- to 10-membered monocyclic or bicyclic $4n+2$ aromatic ring system (e.g., having 6 or 10 shared π electrons in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur. In the heteroaryl group containing one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom as long as the valence permits. Heteroaryl bicyclic systems may include one or more heteroatoms in one or two rings. Heteroaryl also includes ring systems wherein the heteroaryl ring described above is fused with one or more cycloalkyl or heterocyclyl groups, and the point of attachment is on the heteroaryl ring. In such case, the number the carbon atoms continues to represent the number of carbon atoms in the heteroaryl ring system. In some embodiments, 5- to 6-membered heteroaryl groups are yet alternative, which are radicals of 5- to 6-membered monocyclic or bicyclic $4n+2$ aromatic ring systems having ring carbon atoms and 1-4 ring heteroatoms. Exemplary 5-membered heteroaryl groups containing one heteroatom include, but are not limited to, pyrrolyl, furyl and thienyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, but are not limited to, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, but are not limited to, triazolyl, oxadiazolyl (such as, 1,2,4- oxadiazolyl), and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, but are not limited to, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, but are not limited to, pyridyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, but are not limited to, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, but are not limited to, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, but are not limited to, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, but are not limited to, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzoxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl, indolizinyl and purinyl. Exemplary

6,6-bicyclic heteroaryl groups include, but are not limited to, naphthyridinyl, pteridinyl, quinolyl, isoquinolyl, cinnolinyl, quinoxalinyl, phthalazinyl and quinazolinyl. The heteroaryl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0051] Specific examples of alternative heteroaryl groups include: pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, pyranyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, oxazolyl, isoxazolyl, oxazolyl (1,2,4-oxazolyl, 1,3,4-oxazolyl, 1,2,5-oxazolyl, thiazolyl, thiadiazolyl (1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl).

[0052] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl as defined herein are optionally substituted groups.

[0053] Exemplary substituents on carbon atoms include, but are not limited to, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{aa}, -ON(R^{bb})₂, -N(R^{bb})₂, -N(R^{bb})₃⁺X⁻, -N(OR^{cc})R^{bb}, -SH, -SR^{aa}, -SSR^{cc}, -C(=O)R^{aa}, -CO₂H, -CHO, -C(OR^{cc})₂, -CO₂R^{aa}, -OC(=O)R^{aa}, -OCO₂R^{aa}, -C(=O)N(R^{bb})₂, -OC(=O)N(R^{bb})₂, -NR^{bb}C(=O)R^{aa}, -NR^{bb}CO₂R^{aa}, -NR^{bb}C(=O)N(R^{bb})₂, -C(=NR^{bb})R^{aa}, -C(=NR^{bb})OR^{aa}, -OC(=NR^{bb})R^{aa}, -OC(=NR^{bb})OR^{aa}, -C(=NR^{bb})N(R^{bb})₂, -OC(=NR^{bb})N(R^{bb})₂, -NR^{bb}C(=NR^{bb})N(R^{bb})₂, -C(=O)NR^{bb}SO₂R^{aa}, -NR^{bb}SO₂R^{aa}, -SO₂N(R^{bb})₂, -SO₂R^{aa}, -SO₂OR^{aa}, -OSO₂R^{aa}, -S(=O)R^{aa}, -OS(=O)R^{aa}, -Si(R^{aa})₃, -OSi(R^{aa})₃, -C(=S)N(R^{bb})₂, -C(=O)SR^{aa}, -C(=S)SR^{aa}, -SC(=S)SR^{aa}, -SC(=O)SR^{aa}, -OC(=O)SR^{aa}, -SC(=O)OR^{aa}, -SC(=O)R^{aa}, -P(=O)₂R^{aa}, -OP(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -OP(=O)(R^{aa})₂, -OP(=O)(OR^{cc})₂, -P(=O)₂N(R^{bb})₂, -OP(=O)₂N(R^{bb})₂, -P(=O)(NR^{bb})₂, -OP(=O)(NR^{bb})₂, -NR^{bb}P(=O)(OR^{cc})₂, -NR^{bb}P(=O)(NR^{bb})₂, -P(R^{cc})₂, -P(R^{cc})₃, -OP(R^{cc})₂, -OP(R^{cc})₃, -B(R^{aa})₂, -B(OR^{cc})₂, -BR^{aa}(OR^{cc}), alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups;

[0054] or two geminal hydrogens on a carbon atom are replaced with =O, =S, =NN(R^{bb})₂, =NNR^{bb}C(=O)R^{aa}, =NNR^{bb}C(=O)OR^{aa}, =NNR^{bb}S(=O)₂R^{aa}, =NR^{bb} or =NOR^{cc} groups;

[0055] each of the R^{aa} is independently selected from alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl, or two of the R^{aa} groups are combined to form a

heterocyclyl or heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups;

[0056] each of the R^{bb} is independently selected from hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl, or two R^{bb} groups are combined to form a heterocyclyl or a heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups;

[0057] each of the R^{cc} is independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl, or two R^{cc} groups are combined to form a heterocyclyl or a heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups;

[0058] each of the R^{dd} is independently selected from halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{ee}, -ON(R^{ff})₂, -N(R^{ff})₂, -N(R^{ff})₃⁺X⁻, -N(OR^{ee})R^{ff}, -SH, -SR^{ee}, -SSR^{ee}, -C(=O)R^{ee}, -CO₂H, -CO₂R^{ee}, -OC(=O)R^{ee}, -OCO₂R^{ee}, -C(=O)N(R^{ff})₂, -OC(=O)N(R^{ff})₂, -NR^{ff}C(=O)R^{ee}, -NR^{ff}CO₂R^{ee}, -NR^{ff}C(=O)N(R^{ff})₂, -C(=NR^{ff})OR^{ee}, -OC(=NR^{ff})R^{ee}, -OC(=NR^{ff})OR^{ee}, -C(=NR^{ff})N(R^{ff})₂, -OC(=NR^{ff})N(R^{ff})₂, -NR^{ff}C(=NR^{ff})N(R^{ff})₂, -NR^{ff}SO₂R^{ee}, -SO₂N(R^{ff})₂, -SO₂R^{ee}, -SO₂OR^{ee}, -OSO₂R^{ee}, -S(=O)R^{ee}, -Si(R^{ee})₃, -OSi(R^{ee})₃, -C(=S)N(R^{ff})₂, -C(=O)SR^{ee}, -C(=S)SR^{ee}, -SC(=S)SR^{ee}, -P(=O)₂R^{ee}, -P(=O)(R^{ee})₂, -OP(=O)(R^{ee})₂, -OP(=O)(OR^{ee})₂, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{gg} groups, or two geminal R^{dd} substituents can be combined to form =O or =S;

[0059] each of the R^{ee} is independently selected from alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{gg} groups;

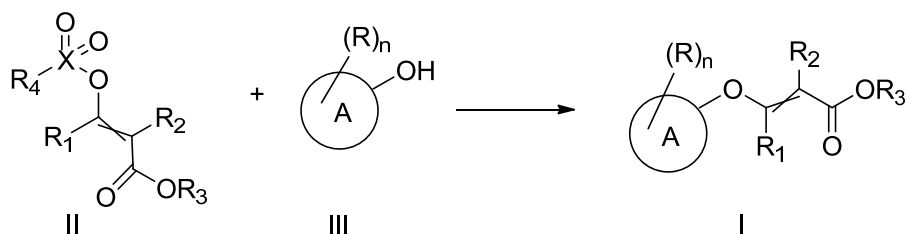
[0060] each of the R^{ff} is independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl, or two R^{ff} groups are combined to form

a heterocyclyl or a heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{gg} groups; **[0061]** each of the R^{gg} is independently selected from halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OC₁₋₆ alkyl, -ON(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₃⁺X⁻, -NH(C₁₋₆ alkyl)₂⁺X⁻, -NH₂(C₁₋₆ alkyl)⁺X⁻, -NH₃⁺X⁻, -N(OC₁₋₆ alkyl)(C₁₋₆ alkyl), -N(OH)(C₁₋₆ alkyl), -NH(OH), -SH, -SC₁₋₆ alkyl, -SS(C₁₋₆ alkyl), -C(=O)(C₁₋₆ alkyl), -CO₂H, -CO₂(C₁₋₆ alkyl), -OC(=O)(C₁₋₆ alkyl), -OCO₂(C₁₋₆ alkyl), -C(=O)NH₂, -C(=O)N(C₁₋₆ alkyl)₂, -OC(=O)NH(C₁₋₆ alkyl), -NHC(=O)(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), -NHCO₂(C₁₋₆ alkyl), -NHC(=O)N(C₁₋₆ alkyl)₂, -NHC(=O)NH(C₁₋₆ alkyl), -NHC(=O)NH₂, -C(=NH)O(C₁₋₆ alkyl), -OC(=NH)(C₁₋₆ alkyl), -OC(=NH)OC₁₋₆ alkyl, -C(=NH)N(C₁₋₆ alkyl)₂, -C(=NH)NH(C₁₋₆ alkyl), -C(=NH)NH₂, -OC(=NH)N(C₁₋₆ alkyl)₂, -OC(NH)NH(C₁₋₆ alkyl), -OC(NH)NH₂, -NHC(NH)N(C₁₋₆ alkyl)₂, -NHC(=NH)NH₂, -NHSO₂(C₁₋₆ alkyl), -SO₂N(C₁₋₆ alkyl)₂, -SO₂NH(C₁₋₆ alkyl), -SO₂NH₂, -SO₂C₁₋₆ alkyl, -SO₂OC₁₋₆ alkyl, -OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, -Si(C₁₋₆ alkyl)₃, -OSi(C₁₋₆ alkyl)₃, -C(=S)N(C₁₋₆ alkyl)₂, C(=S)NH(C₁₋₆ alkyl), C(=S)NH₂, -C(=O)S(C₁₋₆ alkyl), -C(=S)SC₁₋₆ alkyl, -SC(=S)SC₁₋₆ alkyl, -P(=O)₂(C₁₋₆ alkyl), -P(=O)(C₁₋₆ alkyl)₂, -OP(=O)(C₁₋₆ alkyl)₂, -OP(=O)(OC₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ carbocyclyl, C₆-C₁₀ aryl, C₃-C₇ heterocyclyl, C₅-C₁₀ heteroaryl; or two geminal R^{gg} substituents may combine to form =O or =S; wherein X⁻ is a counter-ion.

[0062] Exemplary substituents on nitrogen atoms include, but are not limited to, hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{bb})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, alkyl, haloalkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl, or two R^{cc} groups attached to a nitrogen atom combine to form a heterocyclyl or a heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is independently substituted with 0, 1, 2, 3, 4 or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as described herein.

SPECIFIC EMBODIMENTS

[0063] In one embodiment, the present disclosure relates to a method of preparing a compound of general formula (I), comprising reacting a compound of general formula (II) with a compound of general formula (III), in the presence of a base:



[0064] wherein

[0065] ring A is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

[0066] X is S or P;

[0067] R₁ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, and 3- to 8-membered heterocyclyl;

[0068] R₂ is selected from H, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

[0069] R₃ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₀₋₆ alkylene-C₃₋₇ cycloalkyl, -C₀₋₆ alkylene-3- to 8-membered heterocyclyl, -C₀₋₆ alkylene-C₆₋₁₀ aryl, and -C₀₋₆ alkylene-5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m R' group(s);

[0070] R₄ is selected from C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -OR_a, -NR_aR_b, C₃₋₇ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m' R'' group(s);

[0071] R is selected from H, halogen, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

[0072] n is 0, 1, 2, 3, 4, or 5;

[0073] wherein R' and R'' are independently selected from halogen, -NO₂, -CN, -NR_aR_b, -NR_aC(O)R_b, C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, and phenyl;

[0074] m is 1, 2, 3, 4, or 5;

[0075] m' is 1, 2, 3, 4, or 5;

[0076] R_a and R_b are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl; or R_a and R_b, together with the nitrogen atom to which they are attached, form 3- to 8-membered heterocyclyl or 5- to 10-membered heteroaryl.

[0077] Ring A

[0078] In a specific embodiment, ring A is C₆₋₁₀ aryl; in another specific embodiment, ring A is 5- to 10-membered heteroaryl; in another specific embodiment, ring A is phenyl; in another specific embodiment, ring A is naphthyl; in another specific embodiment, ring A is 5- to 6-membered heteroaryl; in another specific embodiment, ring A is thienyl.

[0079] X

[0080] In a specific embodiment, X is S; in another specific embodiment, X is P.

[0081] R₁

[0082] In a specific embodiment, R₁ is H; in another specific embodiment, R₁ is C₁₋₆ alkyl; in another specific embodiment, R₁ is methyl; in another specific embodiment, R₁ is C₁₋₆ haloalkyl; in another specific embodiment, R₁ is C₃₋₇ cycloalkyl; in another specific embodiment, R₁ is 3- to 8-membered heterocyclyl.

[0083] R₂

[0084] In a specific embodiment, R₂ is H; in another specific embodiment, R₂ is C₁₋₆ alkyl; in another specific embodiment, R₂ is C₁₋₆ haloalkyl.

[0085] R₃

[0086] In a specific embodiment, R₃ is H; in another specific embodiment, R₃ is C₁₋₆ alkyl; in another specific embodiment, R₃ is ethyl; in another specific embodiment, R₃ is t-butyl; in another specific embodiment, R₃ is C₁₋₆ haloalkyl; in another specific embodiment, R₃ is C₂₋₆ alkenyl; in another specific embodiment, R₃ is C₂₋₆ alkynyl; in another specific embodiment, R₃ is -C₀₋₆ alkylene-C₃₋₇ cycloalkyl; in another specific embodiment, R₃ is -C₀₋₆ alkylene-3- to 8-membered heterocyclyl; in another specific embodiment, R₃ is -C₀₋₆ alkylene-C₆₋₁₀ aryl; in another specific embodiment, R₃ is -C₀₋₆ alkylene-5- to 10-membered heteroaryl; in another specific embodiment, R₃ is benzyl. In the above specific embodiments, the groups are unsubstituted or independently substituted with m R' group(s).

[0087] R_4

[0088] In a specific embodiment, R_4 is C_{1-20} alkyl; in another specific embodiment, R_4 is C_{1-12} alkyl; in another specific embodiment, R_4 is C_{1-6} alkyl; in another specific embodiment, R_4 is C_{1-6} haloalkyl; in another specific embodiment, R_4 is $-OR_a$; in another specific embodiment, R_4 is methyl; in another specific embodiment, R_4 is $-NR_aR_b$; in another specific embodiment, R_4 is C_{3-7} cycloalkyl; in another specific embodiment, R_4 is 3- to 8-membered heterocyclcyl; in another specific embodiment, R_4 is C_{6-10} aryl; in another specific embodiment, R_4 is phenyl; in another specific embodiment, R_4 is 5- to 10-membered heteroaryl. In the above specific embodiments, the groups are unsubstituted or independently substituted with m' R'' group(s).

[0089] R' and R''

[0090] In a specific embodiment, R' is halogen; in another specific embodiment, R' is chloro; in another specific embodiment, R' is $-NO_2$; in another specific embodiment, R' is $-CN$; in another specific embodiment, R' is $-NR_aR_b$; in another specific embodiment, R' is $-NR_aC(O)R_b$; in another specific embodiment, R' is C_{1-20} alkyl; in another specific embodiment, R' is C_{1-12} alkyl; in another specific embodiment, R' is C_{1-6} alkyl; in another specific embodiment, R' is methyl; in another specific embodiment, R' is C_{1-6} haloalkyl; in another specific embodiment, R' is $-O-C_{1-6}$ alkyl; in another specific embodiment, R' is phenyl.

[0091] In a specific embodiment, R'' is halogen; in another specific embodiment, R'' is chloro; in another specific embodiment, R'' is $-NO_2$; in another specific embodiment, R'' is $-CN$; in another specific embodiment, R'' is $-NR_aR_b$; in another specific embodiment, R'' is $-NR_aC(O)R_b$; in another specific embodiment, R'' is C_{1-20} alkyl; in another specific embodiment, R'' is C_{1-12} alkyl; in another specific embodiment, R'' is C_{1-6} alkyl; in another specific embodiment, R'' is methyl; in another specific embodiment, R'' is C_{1-6} haloalkyl; in another specific embodiment, R'' is $-O-C_{1-6}$ alkyl; in another specific embodiment, R'' is phenyl.

[0092] In the above specific embodiments, R_a and R_b are independently selected from H, C_{1-6} alkyl and C_{1-6} haloalkyl.

[0093] m

[0094] In a specific embodiment, m is 0; in another specific embodiment, m is 1; in another specific embodiment, m is 2; in another specific embodiment, m is 3; in another specific embodiment, m is 4; in another specific embodiment, m is 5.

[0095] m'

[0096] In a specific embodiment, m' is 0; in another specific embodiment, m' is 1; in another specific embodiment, m' is 2; in another specific embodiment, m' is 3; in another specific embodiment, m' is 4; in another specific embodiment, m' is 5.

[0097] R

[0098] In a specific embodiment, R is H; in another specific embodiment, R is halogen; in another specific embodiment, R is chloro; in another specific embodiment, R is -O-C₁₋₆ alkyl; in another specific embodiment, R is C₁₋₆ alkyl; in another specific embodiment, R is C₁₋₆ haloalkyl.

[0099] n

[00100] In a specific embodiment, n is 0; in another specific embodiment, n is 1; in another specific embodiment, n is 2; in another specific embodiment, n is 3; in another specific embodiment, n is 4; in another specific embodiment, n is 5.

[00101] Any technical solution or any combination thereof in any one of the above specific embodiments may be combined with any technical solution or any combination thereof in other specific embodiments. For example, any technical solution or any combination thereof of X may be combined with any technical solution or any combination thereof of ring A, R₁-R₄, R, R', R'', m, m', n, and the like. The present disclosure is intended to include all the combinations of such technical solutions, which are not exhaustively listed here to save space.

[00102] In a more specific embodiment, the present disclosure provides the above method, wherein X is S.

[00103] In a more specific embodiment, the present disclosure provides the above method, wherein R_4 is C_{6-10} aryl or 5- to 10-membered heteroaryl, which is unsubstituted or independently substituted with m' R'' group(s).

[00104] In a more specific embodiment, the present disclosure provides the above method, wherein R_4 is selected from phenyl, 1-naphthyl, 2-naphthyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-dichlorophenyl, 2,4-difluorophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-nitrophenyl, 4-nitrophenyl, 2-methylphenyl, 4-methylphenyl, 4-propylphenyl, 4-*t*-butylphenyl, 2,5-dimethylphenyl, mesityl, 2,4,6-triisopropylphenyl, 2-dodecylphenyl, 3-dodecylphenyl, 4-dodecylphenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 4-methoxyphenyl, *N,N*-dimethylaminophenyl, 4-acetylaminophenyl, 4-biphenyl, thienyl and 5-bromothieryl; alternatively, R_4 is selected from phenyl, 1-naphthyl, 2-naphthyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-nitrophenyl, 2-methylphenyl, 4-propylphenyl, 4-*t*-butylphenyl, 2,5-dimethylphenyl, 2,4,6-triisopropylphenyl, 2-dodecylphenyl, 3-dodecylphenyl, 4-dodecylphenyl, 4-methoxyphenyl, 4-acetylaminophenyl, 4-methylphenyl and mesityl; yet alternatively, R_4 is selected from phenyl, 4-chlorophenyl, 4-methylphenyl and mesityl.

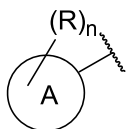
[00105] In a more specific embodiment, the present disclosure provides the above method, wherein R_4 is C_{1-12} alkyl, $-OR_a$, $-NR_aR_b$, C_{3-7} cycloalkyl, or 3- to 8-membered heterocyclyl, which is unsubstituted or independently substituted with m' R'' group(s).

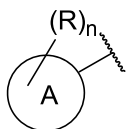
[00106] In a more specific embodiment, the present disclosure provides the above method, wherein R_4 is selected from *N,N*-dimethylamino, methyl, ethyl, butyl, dodecyl, methoxy, ethoxy, and cyclopropyl.

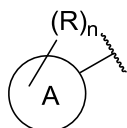
[00107] In a more specific embodiment, the present disclosure provides the above method, wherein ring A is substituted or unsubstituted phenyl, naphthyl or thienyl; alternatively substituted or unsubstituted phenyl.

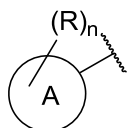
[00108] In a more specific embodiment, the present disclosure provides the above method, wherein R is H, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl; alternatively, R is H or halogen.

[00109] In a more specific embodiment, the present disclosure provides the above method,



wherein  is selected from phenyl, naphthalene-1-yl, naphthalene-2-yl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3,5-trichlorophenyl, 4-isopropylphenyl and 4-t-butylphenyl;



alternatively,  is 2-chlorophenyl.

[00110] In a more specific embodiment, the present disclosure provides the above method, wherein R_1 is selected from C_{1-6} alkyl, such as methyl.

[00111] In a more specific embodiment, the present disclosure provides the above method, wherein R_2 is H.

[00112] In a more specific embodiment, the present disclosure provides the above method, wherein R_3 is H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH_2CH_2CH_3$, phenyl or $-CH_2$ -phenyl; alternatively, R_3 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$ or $-CH_2$ -phenyl.

[00113] In a more specific embodiment, the present disclosure provides the above method, wherein the base is selected from inorganic bases and organic bases; alternatively, the inorganic base is selected from carbonates, bicarbonates, phosphates, hydrogenphosphates, dihydrogenphosphates, hydroxides and hydrides of alkali metals and alkaline earth metals, for example, LiOH, NaOH, KOH, Li_2CO_3 , Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , Na_3PO_4 , K_3PO_4 , K_2HPO_4 , KH_2PO_4 and NaH; alternatively, the organic base is selected from alkoxides of alkali metals and alkaline earth metals, and organic amines, such as NaOMe, KOMe, NaOEt, KOEt, NaOtBu, KOtBu, triethylamine, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DIPEA (N,N-diisopropylethylamine), DABCO (1,4-diazabicyclo[2.2.2]octane) and DMAP (4-dimethylaminopyridine).

[00114] In a more specific embodiment, the present disclosure provides the above method, wherein the reaction is performed in the presence of a solvent selected from water, alkanes, ethers, esters, alcohols, halogenated hydrocarbons, ketones, amides, sulfones, sulfoxides, nitriles, and mixtures thereof, such as water, n-heptane, toluene, THF (tetrahydrofuran), MTBE

(methyl tert-butyl ether), methyltetrahydrofuran, ethyl acetate, isopropyl acetate, butyl acetate, methanol, ethanol, isopropanol, tert-butanol, tert-amyl alcohol, dichloromethane, 1,2-dichloroethane, chlorobenzene, acetone, 2-butanone, DMF (N,N-dimethylformamide), DMA (N,N-dimethylacetamide), NMP (N-methylpyrrolidone), DMSO (dimethyl sulfoxide) and acetonitrile.

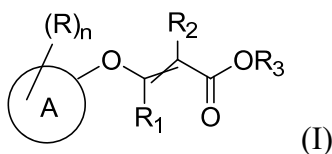
[00115] In a more specific embodiment, the present disclosure provides the above method, wherein the reaction temperature is from room temperature to the reflux temperature of the solvent, alternatively 40-90°C; yet alternatively 50-80°C.

[00116] In a more specific embodiment, the present disclosure provides the above method, wherein the molar ratio of the compound of the general formula (II) to the compound of the general formula (III) is 1:(0.7-3), alternatively 1:(0.7-1.5), yet alternatively 1:(1-1.2), still alternatively 1:1, 1:1.05, 1:1.1, 1:1.15, or 1:1.2.

[00117] In a more specific embodiment, the present disclosure provides the above method, wherein the molar ratio of the compound of the general formula (II) to the base is 1:(1-5), alternatively 1:(2-4), yet alternatively 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, 1:2, 1:2.1, 1:2.2, 1:2.3, 1:2.4, 1:2.5, 1:2.6, 1:2.7, 1:2.8, 1:2.9, or 1:3.

[00118] In a more specific embodiment, the method of the present disclosure is implemented on an industrial scale.

[00119] The present disclosure also provides a compound of formula (I), prepared by the method described above:



[00120] wherein

[00121] ring A is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

[00122] R₁ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, and 3- to 8-membered heterocyclyl;

[00123] R₂ is selected from H, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

[00124] R₃ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₀₋₆

alkylene-C₃₋₇ cycloalkyl, -C₀₋₆ alkylene-3- to 8-membered heterocyclyl, -C₀₋₆ alkylene-C₆₋₁₀ aryl, and -C₀₋₆ alkylene-5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m R' group(s);

[00125] R is selected from H, halogen, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

[00126] n is 0, 1, 2, 3, 4, or 5;

[00127] wherein R' is selected from halogen, -NO₂, -CN, -NR_aR_b, -NR_aC(O)R_b, C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, and phenyl;

[00128] m is 1, 2, 3, 4, or 5;

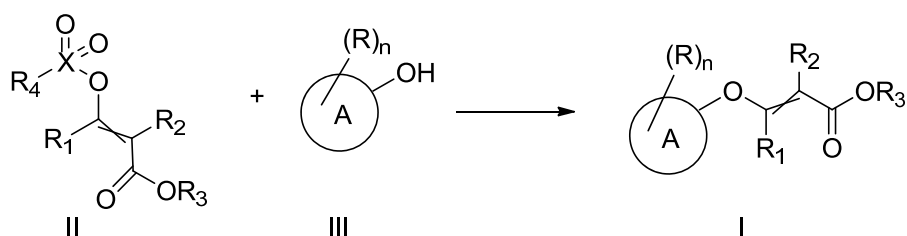
[00129] R_a and R_b are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl; or R_a and R_b, together with the nitrogen atom to which they are attached, form 3- to 8-membered heterocyclyl or 5- to 10-membered heteroaryl.

Examples

[00130] Materials or reagents used herein are either commercially available or prepared by synthetic methods generally known in the art. The following reaction scheme exemplarily illustrates the practice of the method for the compound of the present disclosure.

[00131] General operation

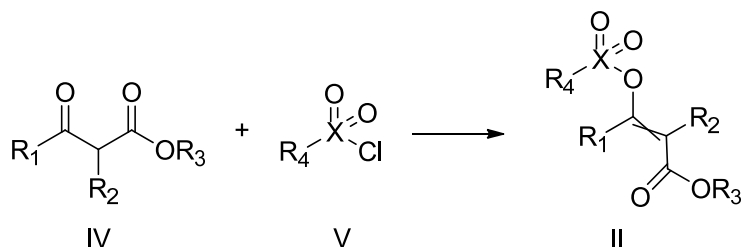
[00132] The reaction scheme and typical operation of preparing the compound of general formula (I) are as follows:



[00133] To a reactor are added the compound of general formula (III), a base, the compound of general formula (II), and an optional solvent, and the temperature is maintained at room temperature to reflux temperature of the solvent. The mixture is stirred until the reaction is completed, during which the progress of the reaction is monitored. After completion of the reaction, the reaction solution is cooled down to room temperature. The organic phase is

separated and purified to give the compound of general formula (I).

[00134] The compound of general formula (II) is commercially available, or is prepared by a method known in the art. For example, the following route can be used:

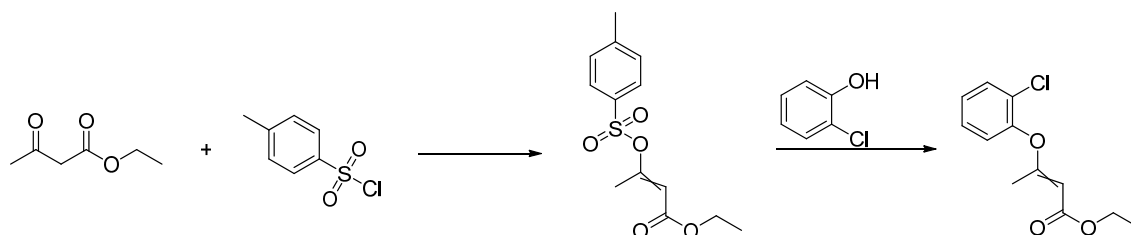


[00135] To a reactor are added the compound of general formula (IV), the compound of general formula (V), a base and a solvent. The mixture is stirred at a certain temperature until the reaction is completed, during which the progress of the reaction is monitored. After completion of the reaction, the organic phase is separated. The organic phase can be directly used for the next reaction step, or evaporated to dryness for later use, or purified by rectification or column chromatography.

[00136] Alternatively, the compound of general formula (V) can be converted into an acid anhydride before reacted with the compound of general formula (IV) as described above.

Example 1

[00137] Preparation of ethyl 3-(2-chlorophenoxy)-2-butenolate



[00138] (1) Ethyl acetoacetate (50.0 g, 384 mmol, 1.0 eq), triethylamine (38.8 g, 384 mmol, 1 eq), DABCO (17.2 g, 154 mmol, 0.4 eq), and 250 mL of isopropyl acetate were added to a reactor, and then a solution of p-toluenesulfonyl chloride (87.8 g, 460.8 mmol, 1.2 eq) in isopropyl acetate (250 mL) was added dropwise at 0-10 °C over 1-2 h. After the addition was completed, the mixture was reacted with stirring at 10-20 °C for 3 h. After the reaction was completed, 250 mL of water was added to quench the reaction. The organic phase was separated and washed respectively with 250 mL of 5% p-toluenesulfonic acid solution and 250 mL of 8% sodium bicarbonate solution to give a solution of ethyl

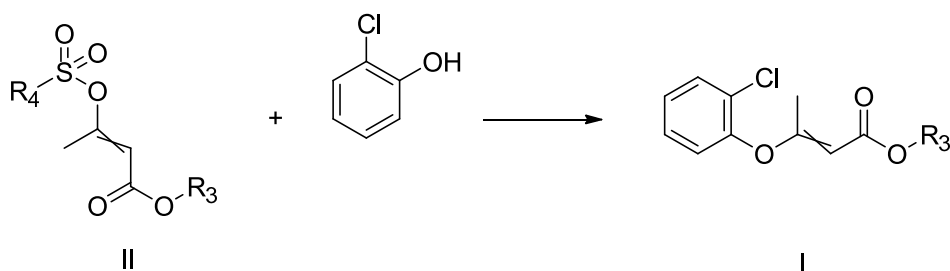
3-(p-toluenesulfonyloxy)-2-butenolate in isopropyl acetate (98.7% yield (external standard method)), which was used after evaporation to dryness (99.2% purity) or directly for the next reaction.

[00139] (2) Potassium carbonate (150 g, 1.09 mol, 2.8 eq), 350 mL of isopropyl acetate, and the solution of ethyl 3-(p-toluenesulfonyloxy)-2-butenolate in isopropyl acetate from step (1) were added to a reactor. The mixture was heated to 70-80 °C, and then a solution of 2-chlorophenol (50 g, 0.389 mol, 1.0 eq) in isopropyl acetate (400 mL) was added dropwise at 70-80 °C over 2-3 h. After the addition was completed, the mixture was reacted with stirring at 70-80 °C for another 19 h. The reaction mixture was cooled down to room temperature and quenched by adding water. The organic phase was separated as a solution of ethyl 3-(2-chlorophenoxy)-2-butenolate in isopropyl acetate with a purity of 94.9%. The above solution of ethyl 3-(2-chlorophenoxy)-2-butenolate in isopropyl acetate was concentrated to give 99.7 g of crude product (containing 85.4% product), with a total yield of 92.1% over two steps.

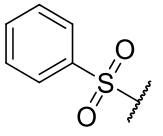
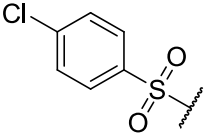
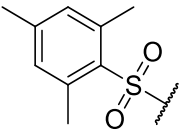
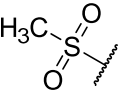
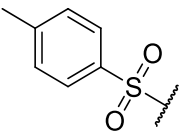
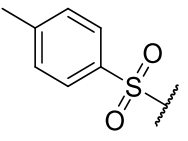
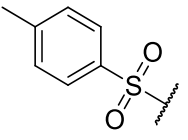
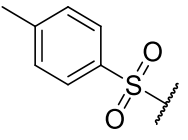
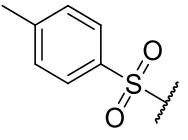
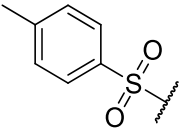
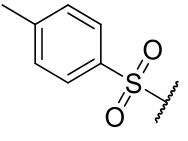
[00140] ¹H-NMR (CDCl₃, 400 MHz): δ 7.46-7.48(m, 1H), 7.29-7.33(m, 1H), 7.21-7.23(m, 1H), 7.10-7.11(m, 1H), 4.78(s, 1H), 4.11(q, 2H, J = 4.2), 2.54(s, 3H), 1.23(t, 3H, J = 4.2).

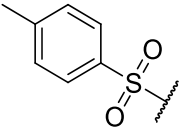
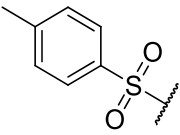
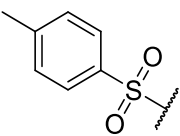
Examples 2-15

[00141] The corresponding compounds were prepared according to the method of Example 1, using the reagents or groups in the table below.



Example	Structure of	R ₃	Base	Solvent	Temperature and time	Yield

2		Et	K ₂ CO ₃ , 1.9 eq	IPrOAc + DMF = 2:1	70-80 °C, 16 h	94.3%
3		Et	K ₂ CO ₃ , 1.9 eq	IPrOAc + DMF = 2:1	70-80 °C, 16 h	73.7% over two steps
4		Et	K ₂ CO ₃ , 1.9 eq	IPrOAc + DMF = 2:1	70-80 °C, 16 h	96.3%
5		Et	K ₂ CO ₃ , 2.0 eq	IPrOAc + DMF = 2:1	60-70 °C, 16 h	73.6%
6		Bn	K ₂ CO ₃ , 2.0 eq	IPrOAc	70-80 °C, 16 h	89.3%
7		Et	K ₃ PO ₄ ·3H ₂ O, 2.0 eq	IPrOAc	50-60 °C, 20 h	82.3%
8		Et	NaOH, 2.0 eq	IPrOAc	50-60 °C, 16 h	88.9%
9		Et	K ₃ PO ₄ , 2.0 eq	IPrOAc	50-60 °C, 16 h	91.6%
10		Et	DABCO, 2.0 eq	IPrOAc	50-60 °C, 42 h	90.2%
11		Et	K ₂ CO ₃ , 2.0 eq	n-Hep	60-70 °C, 16 h	70.7%
12		Et	K ₂ CO ₃ , 2.0 eq	Me-THF	60-70 °C, 16 h	97.3%

13		Et	K ₂ CO ₃ , 1.9 eq	DMF	70-80 °C, 15 h	90.5%
14		Et	K ₂ CO ₃ , 3.0 eq	tert-Amyl alcohol	80 °C, 16 h	85.5%
15		Et	K ₂ CO ₃ , 1.9 eq	2-Butanone	60-70 °C, 16 h	97.6%

[00142] Notes:

IPrOAc: isopropyl acetate; DMF: N,N-dimethylformamide; Bn: benzyl; DABCO: 1,4-diazabicyclo[2.2.2]octane; n-Hep: n-heptane; Me-THF: 2-methyltetrahydrofuran.

[00143] Example 6: tert-Butyl 3-(2-chlorophenoxy)-2-butenate, ¹H-NMR (CDCl₃, 400 MHz): δ7.36-7.38(m, 1H), 7.19-7.21(m, 1H), 7.10-7.11(m, 1H), 7.01-7.03(m, 1H), 4.61(s, 1H), 2.46(s, 3H), 1.35(s, 9H).

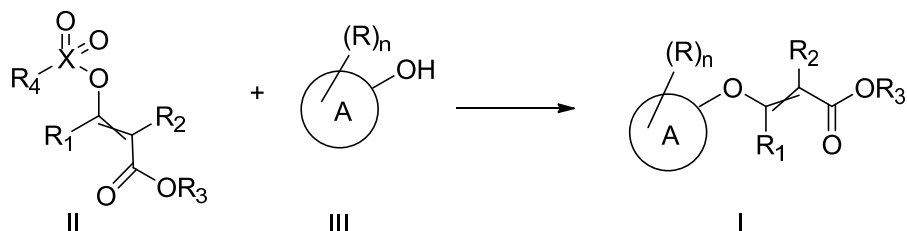
[00144] Example 7: Benzyl 3-(2-chlorophenoxy)-2-butenate, ¹H-NMR (CDCl₃, 400 MHz): δ7.33-7.35(m, 1H), 7.20-7.32(m, 6H), 7.17-7.21(m, 1H), 7.00-7.10(m, 1H), 4.99(s, 2H), 4.72(s, 1H), 2.46(s, 3H).

[00145] The above is a further detailed description of the present disclosure in connection with the specific alternative embodiments, and the specific embodiments of the present disclosure are not limited to the description. It will be apparent to those skilled in the art that the present disclosure may be practiced by making various simple deduction and replacement, without departing from the spirit and scope of the present invention.

CLAIMS

What is claimed is:

1. A method of preparing a compound of general formula (I), comprising reacting a compound of general formula (II) with a compound of general formula (III), in the presence of a base:



wherein

ring A is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

X is S or P;

R₁ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, and 3- to 8-membered heterocyclyl;

R₂ is selected from H, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R₃ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₀₋₆ alkylene-C₃₋₇ cycloalkyl, -C₀₋₆ alkylene-3- to 8-membered heterocyclyl, -C₀₋₆ alkylene-C₆₋₁₀ aryl, and -C₀₋₆ alkylene-5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m R' group(s);

R₄ is selected from C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -OR_a, -NR_aR_b, C₃₋₇ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m' R'' group(s);

R is selected from H, halogen, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

n is 0, 1, 2, 3, 4, or 5;

wherein R' and R'' are independently selected from halogen, -NO₂, -CN, -NR_aR_b, -NR_aC(O)R_b, C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, and phenyl;

m is 1, 2, 3, 4, or 5;

m' is 1, 2, 3, 4, or 5;

R_a and R_b are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl; or R_a and R_b,

together with the nitrogen atom to which they are attached, form 3- to 8-membered heterocyclyl or 5- to 10-membered heteroaryl.

2. The method of claim 1, wherein X is S.

3. The method of claim 1 or 2, wherein R₄ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is unsubstituted or independently substituted with m' R'' group(s).

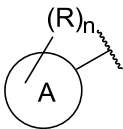
4. The method of claim 3, wherein R₄ is selected from phenyl, 1-naphthyl, 2-naphthyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-dichlorophenyl, 2,4-difluorophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-nitrophenyl, 4-nitrophenyl, 2-methylphenyl, 4-methylphenyl, 4-propylphenyl, 4-t-butylphenyl, 2,5-dimethylphenyl, mesityl, 2,4,6-triisopropylphenyl, 2-dodecylphenyl, 3-dodecylphenyl, 4-dodecylphenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 4-methoxyphenyl, N,N-dimethylaminophenyl, 4-acetylaminophenyl, 4-biphenyl, thienyl and 5-bromothieryl; alternatively, R₄ is selected from phenyl, 1-naphthyl, 2-naphthyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-nitrophenyl, 2-methylphenyl, 4-propylphenyl, 4-t-butylphenyl, 2,5-dimethylphenyl, 2,4,6-triisopropylphenyl, 2-dodecylphenyl, 3-dodecylphenyl, 4-dodecylphenyl, 4-methoxyphenyl, 4-acetylaminophenyl, 4-methylphenyl and mesityl; yet alternatively, R₄ is selected from phenyl, 4-chlorophenyl, 4-methylphenyl and mesityl.

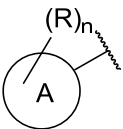
5. The method of claim 1 or 2, wherein R₄ is C₁₋₁₂ alkyl, -OR_a, -NR_aR_b, C₃₋₇ cycloalkyl, or 3- to 8-membered heterocyclyl, which is unsubstituted or independently substituted with m' R'' group(s).

6. The method of claim 5, wherein R₄ is selected from N,N-dimethylamino, methyl, ethyl, butyl, dodecyl, methoxy, ethoxy, and cyclopropyl.

7. The method of any one of claims 1-6, wherein ring A is substituted or unsubstituted phenyl, naphthyl or thienyl; alternatively substituted or unsubstituted phenyl.

8. The method of any one of claims 1-7, wherein R is H, halogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; alternatively, R is H or halogen.

9. The method of any one of claims 1-8, wherein  is selected from phenyl, naphthalene-1-yl, naphthalene-2-yl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3,5-trichlorophenyl, 4-isopropylphenyl and

4-t-butylphenyl; alternatively,  is 2-chlorophenyl.

10. The method of any one of claims 1-9, wherein R₁ is selected from C₁₋₆ alkyl, such as methyl.

11. The method of any one of claims 1-10, wherein R₂ is H.

12. The method of any one of claims 1-11, wherein R₃ is H, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -C(CH₃)₃, -CH₂CH₂CH₂CH₃, phenyl or -CH₂-phenyl; alternatively, R₃ is -CH₃, -CH₂CH₃, -C(CH₃)₃ or -CH₂-phenyl.

13. The method of any one of claims 1-12, wherein the base is selected from inorganic bases and organic bases; alternatively, the inorganic base is selected from carbonates, bicarbonates, phosphates, hydrogenphosphates, dihydrogenphosphates, hydroxides and hydrides of alkali metals and alkaline earth metals, for example, LiOH, NaOH, KOH, Li₂CO₃, Na₂CO₃, K₂CO₃, Cs₂CO₃, Na₃PO₄, K₃PO₄, K₂HPO₄, KH₂PO₄ and NaH; alternatively, the organic base is

selected from alkoxides of alkali metals and alkaline earth metals and organic amines, such as NaOMe, KOMe, NaOEt, KOEt, NaOtBu, KOtBu, triethylamine, DBU, DIPEA, DABCO and DMAP.

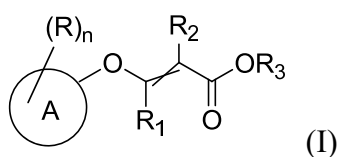
14. The method of any one of claims 1-13, wherein the reaction is performed in the presence of a solvent selected from water, alkanes, ethers, esters, alcohols, halogenated hydrocarbons, ketones, amides, sulfones, sulfoxides, nitriles, and mixtures thereof, such as water, n-heptane, toluene, THF, MTBE, methyltetrahydrofuran, ethyl acetate, isopropyl acetate, butyl acetate, methanol, ethanol, isopropanol, tert-butanol, tert-amyl alcohol, dichloromethane, 1,2-dichloroethane, chlorobenzene, acetone, 2-butanone, DMF, DMA, NMP, DMSO and acetonitrile.

15. The method of any one of claims 1-14, wherein the reaction temperature is from room temperature to the reflux temperature of the solvent, alternatively 40-90°C; yet alternatively 50-80°C.

16. The method of any one of claims 1-15, wherein the molar ratio of the compound of the general formula (II) to the compound of the general formula (III) is 1:(0.7-3), alternatively 1:(0.7-1.5), yet alternatively 1:(1-1.2), still alternatively 1:1, 1:1.05, 1:1.1, 1:1.15 or 1:1.2.

17. The method of any one of claims 1-16, wherein the molar ratio of the compound of the general formula (II) to the base is 1:(1-5), alternatively 1:(2-4), yet alternatively 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, 1:2, 1:2.1, 1:2.2, 1:2.3, 1:2.4, 1:2.5, 1:2.6, 1:2.7, 1:2.8, 1:2.9 or 1:3.

18. A compound of formula (I), which is prepared by the method described in any one of claims 1-17:



wherein

ring A is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R₁ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, and 3- to 8-membered heterocyclyl;

R₂ is selected from H, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R₃ is selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -C₀₋₆ alkylene-C₃₋₇ cycloalkyl, -C₀₋₆ alkylene-3- to 8-membered heterocyclyl, -C₀₋₆ alkylene-C₆₋₁₀ aryl, and -C₀₋₆ alkylene-5- to 10-membered heteroaryl, wherein the groups are unsubstituted or independently substituted with m R' group(s);

R is selected from H, halogen, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

n is 0, 1, 2, 3, 4, or 5;

wherein R' is selected from halogen, -NO₂, -CN, -NR_aR_b, -NR_aC(O)R_b, C₁₋₂₀ alkyl, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, and phenyl;

m is 1, 2, 3, 4, or 5;

R_a and R_b are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, and 5- to 10-membered heteroaryl; or R_a and R_b, together with the nitrogen atom to which they are attached, form 3- to 8-membered heterocyclyl or 5- to 10-membered heteroaryl.