(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 000 633**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **04.11.81**

(51) Int. Cl.³: **C 07 D 333/24**

(21) Application number: **78300140.7**

(22) Date of filing: **12.07.78**

(54) **Process for the preparation of alpha-substituted-thien-3-ylacetic acid and derivatives thereof.**

(30) Priority: **23.07.77 GB 3100877**

(43) Date of publication of application:
07.02.79 Bulletin 79/3

(45) Publication of the grant of the European patent:
04.11.81 Bulletin 81/44

(84) Designated Contracting States:
BE CH DE FR GB NL SE

(56) References cited:
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Courier Press, Leamington Spa, England.

EP 0 000 633 B1

Process for the preparation of alpha-substituted-thien-3-yl-acetic acid and derivatives thereof

This invention relates to a chemical process for the preparation of 3-substituted thiophenes, which are useful as intermediates in the production of penicillins and cephalosporins.

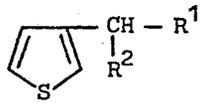
A number of important penicillins and cephalosporins having a 3-thienyl group in the side-chain are well known. For example our British Patent No: 1,004,670 describes the penicillin 'ticarcillin' viz α-carboxy-3-thienylmethyl-penicillin, whilst esters of that compound are disclosed in our British Patent Nos. 1,125,557 and 1,133,886. The 6α-methoxy substituted derivative of tricarcillin is disclosed in W. German Offenlegungsschrift No. 2,600,866.

α-Carboxy-3-thienylmethylcephalosporin is disclosed as an antibacterial agent in U.K. Patent No. 1,193,302.

The most widely used method of preparation of this type of penicillin and cephalosporin is the process disclosed in British Patent No. 1,125,557 wherein the penicillins are prepared from a 3-thienylmalonic ester itself synthesised from 3-thienylacetonitrile. The 3-thienylacetonitrile was prepared from 3-methylthiophene by the method of Campaigne *et al* (J. Amer. Chem. Soc. 1948, *70* 1553) which involves reaction with N-bromo-succinimide and treatment of the resulting 3-bromo-methylthiophene with sodium cyanide. However, this bromination gives the desired bromo-derivative in low yield and the 3-methylthiophene starting material is unduly expensive, with the result that the final penicillin or cephalosporin is considerably more expensive than other penicillin and cephalosporin derivatives.

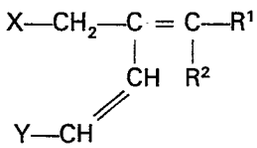
We have now devised a process for the preparation of 3-substituted thiophenes which involves cyclisation of a novel intermediate to form the thiophene moiety. The process is applicable to a wide variety of 3-substituents.

Accordingly the present invention provides a process for the preparation of a thiophene of formula (I):



(I)

wherein R^1 represents a carboxylic acid group or an ester or amide derivative thereof or a nitrile (—CN) group; and R^2 represents hydrogen, a hydrocarbon or heterocyclic group, a carboxylic acid group or an ester or amide derivative thereof, or an acyl, nitrile, isonitrile (—NC) or optionally substituted imine group of formula —CH=NZ or —N=CHZ (where Z represents hydrogen, alkyl or aryl), or SO_2R^a —SR^a, —SO.R^a or —SO_2OR^a group wherein R^a represents C_{1-6} alkyl, or aryl, which process comprises treating a compound of formula (II):

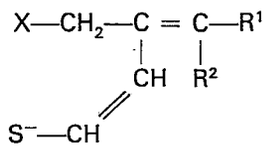


(II)

wherein R^1 and R^2 are as defined with respect to formula (I) above; X represents a halogen atom, a hydroxyl group or a functionalised hydroxyl group; and Y represents a halogen atom or a hydroxyl or alkoxy group; with a source of nucleophilic sulphur under basic conditions.

This cyclisation process may be carried out in a wide range of solvents subject to the solubility of the source of nucleophilic sulphur. It is often convenient to use a polar solvent, preferably a water—miscible solvent such as, for example, tetrahydrofuran, acetone, dimethylformamide, dimethylsulphoxide, hexamethylphosphoramide, acetonitrile, dimethoxyethane, dioxan, or an alcohol such as methanol, ethanol, propanol, butanol, in particular ethanol. Preferred solvents include tetrahydrofuran and acetone. An organic solvent such as methylene dichloride may also be employed. The reaction may be carried out at ambient to elevated temperature depending on the particular reagents used and the values of X, Y, R^1 and R^2. For example suitable temperatures for the process are from −20°C to 100°C, preferably 10° to 50°C.

It is necessary to use a source of nucleophilic sulphur in the process of this invention. It is thought that the initial step in the process is nucleophilic displacement of the group Y in compound (II) by a sulphur moiety, and the ability to displace a group Y is the criterion for choosing a compound suitable for providing the source of nucleophilic sulphur for the process of this invention. Basic conditions are required for the subsequent step, which is thought likely to be formation of an intermediate of formula (III):



(III)

which then undergoes displacement of the group X by internal nucleophilic attack by the sulphide, S^-, in structure (III), an hence cyclisation to give compound (I).

Although it is usually most convenient to have the reaction under basic conditions when the source of nucleophilic sulphur is added to the compound (II), it is also possible to carry out the reaction in two steps, that is by firstly treating compound (II) with a source of nucleophilic sulphur and then subsequently completing the cyclisation reaction by addition of a base.

One suitable source of nucleophilic sulphur is for example the bisulphide ion, HS^-

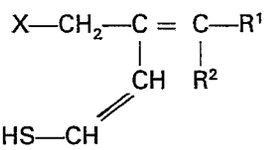
The bisulphide ion for the process of this invention may be provided by using a salt of this ion, preferably an alkali metal salt for example sodium bisulphide NaSH, which may be prepared, optionally *in situ* in the reaction, from sodium sulphide Na_2S and sodium bicarbonate. An alternative, and preferred, source of the bisulphide ion comprises hydrogen sulphide and a base, which again produces HS^- *in situ*.

This combination of reagents has the advantage that the base employed can be the same as that used for the cyclisation process itself.

Suitable bases which may be employed to provide the basic conditions for the process of this invention include inorganic bases, such as alkali metal hydroxides, preferably potassium hydroxide, and alkali metal bicarbonates preferably sodium bicarbonate and organic basis such as substituted amines for example tri(C_{1-6})alkylamines such as trimethylamine or triethylamine.

The bisulphide ion may also be generated *in situ* from sulphurated sodium borohydride, $NaBH_2S_3$.

In some cases it is possible to employ a compound for providing the source of nucleophilic sulphur, which compound is also capable of providing the basic conditions for the cyclisation step. Alkali metal bisulphides, especially sodium bisulphide, are suitable such compounds. Thus reaction of compound (II) with an alkali metal bisulphide produces an intermediate of formula (IV):



(IV)

Addition of further bisulphide (or presence of excess initially) removes a proton to give structure (III) above which then cyclises.

Another way of providing the basic conditions required for the process is to produce the intermediate ion of formula (III) directly which can then act as its own base for cyclisation. This may be achieved for example by treating compound (II) with an alkali metal sulphide, in particular sodium sulphide Na_2S. Because the sulphur ion in such a compound has a double negative charge, S^{2-}, the intermediate formed after nucleophilic attack on compound (II), is structure (III) rather than structure (IV). No further base need then be present to complete the cyclisation. This reaction is still under basic conditions by virtue of the presence of the ion (III) itself, or excess of the alkali metal sulphide; if the reaction medium became neutral or acidic, the sulphide ion in structure (III) would be protonated and the cyclisation would not proceed.

The compounds of formula (II) are novel compounds and are the subject matter of copending European Patent Application No. 80105285.3, which is a divisional of the present application.

In formula (II) the group X should be readily displaced by nucleophilic attack by sulphide ions. Such groups include chloride, bromine, hydroxyl, arylsulphonyloxy such as benzenesulphonyloxy, p-toluenesulphonyloxy, or p-nitrosulphonyloxy, alkylsulphonyloxy such as methanesulphonyloxy or C_{1-6} alkanoyloxy such as acetoxy, propionoxy or butyroxy.

The group Y may be, for example, chlorine, bromine, hydroxy or C_{1-6} alkoxy such as methoxy, ethoxy, or propoxy. Preferably both X and Y are halogen, especially chlorine.

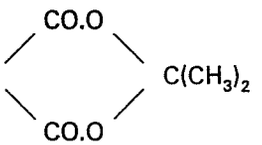
The radicals R^1 and R^2 in compound (II) are chosen according to the requirements of the compound (I). For the preparation of penicillin and cephalosporin derivatives the group R^1 should be carboxylic acid group or a group which may be converted to a carboxylic acid group or a functional derivative thereof for acylation the amino group of the penicillin or cephalosporin nucleus. The R^2 group is chosen to provide the required α-substituent, or a precursor thereof, for the side chain of a penicillin or cephalosporin.

The radical R^1 may be an ester group $—CO_2R^3$ wherein R^3 is an alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heterocyclic group, any of which may be substituted. Suitable such R^3 groups include:

(a) alkyl especially C_{1-6} alkyl such as methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl, and pentyl;
(b) substituted C_{1-6} alkyl wherin the substituent is at least one of: chloro, bromo, fluoro, nitro, carbo (C_{1-6} alkoxy), C_{1-6} alkanoyl, C_{1-6} alkoxy, cyano, C_{1-6} alkylmercapto, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulphonyl, 1-indanyl, 2-indanyl, furyl, pyridyl, 4-imidazolyl, phthalimido, 1-azetidinyl, 1-aziridinyl, 1-pyrrolidinyl, piperidino, morpholino, thiomorpholino, 4-(C_{1-6} alkyl)-1-piperazinyl, 1-pyrrolyl, 1-imidazolyl, 2-imidazolin-1-yl, 2,5-dimethyl-1-pyrrolidinyl, 1,4,5,6-tetrahydro-1-pyrimidinyl, 4-methylpiperidino, 2,6-dimethylpiperidino, alkylamino, dialkylamino, alkanoylamino, N-alkylanilino, or substituted N-alkylanilino wherein the substituent in the benzene moiety is chloro, bromo, C_{1-6} alkyl or C_{1-6} alkoxy;
(c) cycloalkyl and (C_{1-6} alkyl) substituted cycloalkyl having from 3 to 7 carbon atoms in the cycloalkyl moiety;
(d) alkenyl having up to 8 carbon atoms;
(e) alkynyl having up to 8 carbon atoms;
(f) phenyl and substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, C_{1-6} alkoxy, C_{1-6} alkanoyl, carbo-(C_{1-6}) alkoxy, nitro, or di(C_{1-6}) alkyl amino;
(g) benzyl or substituted benzyl wherein the substituent in the benzene moiety is chloro, bromo, fluoro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, carbo-(C_{1-6})-alkoxy, nitro, or di(C_{1-6}-alkyl) amino;
(h) a 5- or 6- membered hereocyclic group containing one or more sulphur and/or nitrogen and/or oxygen atoms in the ring optionally fused to a second 5- and 6-membered hydrocarbyl or heterocyclic ring and which may be substituted with an alkyl group having 1 to 3 carbon atoms, for example thienyl, furyl quinolyl, methyl-substituted quinolyl, phenazinyl, pyridyl, methylpyridyl, phthalidyl, indanyl.

Preferred groups for R^3 include C_{1-6} alkyl, benzyl, phthalidyl, indanyl, phenyl, mono- di-, and tri-(C_{1-6})-alkyl substituted phenyl such as *o*-, m or p methylphenyl, ethylphenyl, *n*- or *iso*-propylphenyl, *n*-, *sec*-, *iso*- or butylphenyl.

Suitable groups R^2 include hydrogen, C_{1-6} alkyl, such as methyl, ethyl, propyl, or butyl, benzyl, phenyl, alkylphenyl, napthyl, a 5- or 6- membered heterocyclic group containing one or more sulphur and/or nitrogen and/or oxygen atoms in the ring and which may be substituted by an alkyl group having from 1 to 3 carbon atoms, for example thienyl, imidazolyl, thiadiazolyl, isoxazolyl, methylisoxazolyl, tetrazolyl, methyltetrazolyl, pyrimidinyl, pyridyl, pyrazinyl, pyrrolidyl, piperidyl, morpholinyl, thiazinyl, furyl, or quinolyl: a carboxylic acid group, a carboxylic ester group —CO_2R^3 as defined above, or a C_{1-6} alkanoyl group. When both groups R^1 and R^2 are ester radicals they may together form a cyclic ester group, for example isopropylidine of formula:



For the preparation of α-carboxy-3-thienylpenicillins and cephalosporins, R^1 and R^2 may conveniently both be carboxylic acid or ester radicals. It is convenient to prepare a diester compound of formula (I), i.e. where R^1 and R^2 both represent a group —CO_2R^3, and then half-saponify in order to produce the compound (I) wherein one of R^1 and R^2 is a carboxylic acid group, suitable for coupling the penicillin or cephalosporin nucleus.

Similarly for the preparation of an α-ester of an α-carboxy-3-thienyl penicillin or cephalosporin, the group R^3 may be chosen according to the eventual penicillin or cephalosporin required.

The compounds of formula (I) in which one of the groups R^1 and R^2 represents a carboxylic acid function may be converted to a penicillin or cephalosporin by an method known *per se,* for example as described in British Patent Specification Nos. 1,004,670, 1,125,557, 1,133,886, 1,193,302, W. German OLS No. 2,600,866.

The following Examples illustrate this invention.

Example 1

Preparation of diethyl thien-3-ylmalonate

Potassium hydroxide (0.14 g, 2.0 mmol) in ethanol (50 ml) was saturated with hydrogen sulphide at 0° for one hour. To this was added 4-*trans* ethyl 2-ethoxycarbonyl-5-chloro-3-chloromethylpenta-2,4-dienoate (0.62 g, 2.45 mmol), and addition of hydrogen sulphide was continued for one hour at room temperature. The reaction mixture was stirred for a further four hours. Potassium hydroxide (0.20 g, 2.8 mmol) was added and hydrogen sulphide passed for thirty minutes. The reaction mixture was stirred at room temperature for sixteen hours, diluted with water (50 ml) and extracted with ether (3 × 50 ml). The extracts were washed with saturated brine, *N* sodium bicarbonate solution, saturated brine, dried (Na_2SO_4) and evaporated to give the title compound (78% yield) purified by distillation, b.p. 119—127°/0.5 mm. δ ($CDCl_3$) 1.27 (6H, t, J 7Hz, CH_3), 4.20 (4H, q, J 7Hz, OCH_2), 4.75 (1H, s, CH),

7.20—7.43 (3H, m, thienyl protons), ν_{max}(film) 1730 cm^{-1}, λ_{max} (ethanol) 234 nm. $C_{11}H_{14}O_4S$ requires M, 242.0649. Found M^+, 242.0609.

Example 2

Preparation of diethyl thien-3-ylmalonate

4-*trans* Ethyl 2-ethoxycarbonyl-5-chloro-3-chloromethyl penta-2,4-dienoate (0.28 g, 1.0 mmol) in THF (5 ml) was treated with solid sodium sulphide nonahydrate (0.24 g, 1.0 mmol) and the mixture stirred at room temperature for sixteen hours. Ether (50 ml) was added; brine washing, drying (Na_2SO_4), charcoal and evaporation gave the title product (66% yield), spectral details as in Example 1.

Example 3

Preparation of diethyl thien-3-ylmalonate

Sodium sulphide ($Na_2S.9H_2O$) (12 g, 0.05 mol) was dissolved in water and the volume made up to 35 ml. Sodium bicarbonate (4.2 g, 0.05 mol) was added with stirring. After dissolution, methanol 30 ml) was added. After thirty minutes, sodium carbonate was filtered off, and the solids washed with methanol (15 ml). There is thus obtained a solution of sodium bisulphide (50 mmol) in aqueous methanol.

4-*trans* Ethyl 2-ethoxycarbonyl-5-chloro-3-chloromethylpenta-2,4-dienoate (1.4 g, 5 mmol) in methanol (50 ml) was treated at 10°C, dropwise with sodium bisulphide solution (8 ml, 5 mmol). After two hours at room temperature, a further aliquot of sodium bisulphide solution (8 ml, 5 mmol) was added and the mixture stirred overnight. The solution was concentrated (*ca* 5 ml) and water (50 ml) added. Ether extraction (3 x 50 ml), brine washing (50 ml) drying (Na_2SO_4), charcoal and evaporation gave the title product (68% yield), spectral details as in Example 1.

Example 4

Preparation of diethyl thien-3-ylmalonate

4-*trans* Ethyl 2-ethoxycarbonyl-5-chloro-3-chloromethylpenta-2,4-dienoate (0.28 g, 1.0 mmol) in methylene dichloride (10 ml) at 0—5°C was treated with hydrogen sulphide for ten minutes. A solution of triethylamine (0.28 ml, 2.0 mmol) in methylene dichloride (5 ml) was added over five minutes, and the solution stirred at room temperature for forty-five minutes, diluted with methylene dichloride (25 ml), washed with brine (25 ml) dried (Na_2SO_4) and evaporated to give the title product (62% yield), spectral details as in Example 1.

Example 5

Preparation of diethyl thien-3-ylmalonate

4-*cis* Ethyl 2-ethoxycarbonyl-5-chloro-3-chloromethyl penta-2,4-dienoate (0.84 g, 3.0 mmol) in tetrahydrofuran (15 ml) was stirred with sodium sulphide nonahydrate (0.72 g, 3.0 mmol) at room temperature for sixteen hours. The reaction mixture was diluted with ether, washed with brine, dried (Na_2SO_4), treated with charcoal, filtered and evaporated to give the title product (0.18 g, 28%), spectral details as in Example 1.

Example 6

Preparation of dimethyl thien-3-yl malonate.

4-*trans* Methyl -2- methoxycarbonyl -5-chloro-3-chloromethyl penta-2,4-dienoate (1.25 g., 5.0 mmol). in THF (15 ml) was stirred for 18 hours with sodium sulphide nonahydrate (1.68 g., 7.0mmol.). The solution was diluted with ether, washed with water, dried (Na_2SO_4) and evaporated to give the reaction product, which, on filtration through coarse Fluorosil (Registered Trade Mark) (3.5 g.), gave decolorized title compound (0.61 g., 57%), b.p. 96—98° (0.3 mm), ν_{max} (film) 1740 cm^{-1}, $\delta(CDCl_3)$ 3.77 (6H,s, 2 x CH_3), 4.82 (IH,s,—CH), 7.11—7.48 (3H, complex, thienyl protons). $C_9H_{10}O_4S$ requires M,214. Found: M^+, 214.

Example 7

Preparation of dibenzyl thien-3-ylmalonate.

4-*trans* Benzyl 2- benzyloxycarbonyl -5-chloro-3-chloromethylpenta - 2, 4-dienoate was treated with sodium sulphide as in Example 6 thus affording the title compound in 71% yield. Recrystallization from toluene petrol gave prisms, m.p. 49—50°, ν_{max} (CH_2Cl_2), 1740 cm^{-1}, $\delta(CDCl_3)$ 4.88 (IH,s, CH), 5.18 (4H,s, $2CH_2$), 7.33 (13H, complex, aryl and thienyl protons).

Example 8

Preparation of ethyl 2-thien-3'-yl-2-cyanoacetate.

4-*Trans* ethyl 2- cyano-5-chloro-3- chloromethylpenta -2, 4-dienoate was treated with sodium sulphide nonahydrate as in Example 6 thus affording the title compound in 30% yield, ν_{max} (CH_2Cl_2) 1720 cm^{-1}, $\delta(CDCl_3)$ 1.27 (3H,t,J 7 Hz, CH_2), 4.80 (IH,s, CH), 7.2—7.6 (3H, complex, thienyl protons).

Example 9

Preparation of methyl thien-3-ylacetate.

Potassium hydroxide (0.04 g., 0.6 mmol) in ethanol (10 ml) at 0° was saturated with H_2S for 15 minutes. 4-*Trans* methyl 5-chloro -3- chloromethylpenta-2, 4-dienoate (0.11 g., 0.56 mmol.) was added, and the solution stirred with continued H_2S addition for 1 hour. Further potassium hydroxide (0.04 g., 0.6 mmol.) in ethanol (2 ml.) was added. The solution was stirred at room temperature for 18 hours, diluted with water and extracted with ether, which was dried and evaporated to give the title compound (0.07 g.) ν_{max} ($CHCl_3$) 1730 cm^{-1}, δ($CDCl_3$) 3.71 (5H,s,—CH_2— and —CH_3), 7.0—7.6 (3H, complex, thienyl protons), λ_{max}(EtoH) 224 (ε 4,560), 265 nm (ε2,440). $C_7H_8O_2S$ requires M, 156 Found :M^+, 156.

(This compound may also be prepared using pre-formed sodium bisulphide in place of H_2S/KOH.)

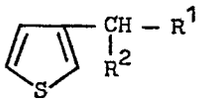
Example 10

Preparation of dimethyl thien-3-ylmalonate.

Potassium hydroxide (0.14 g., 2.0 mmol.) in ethanol (50 ml) was saturated with hydrogen sulphide at 0°C. To this was added methyl 2-methoxycarbonyl-5-chloro-3-chloromethylpenta-2, 4-dienoate (0.62 g., 2.45 mmol.) and addition of hydrogen sulphide was continued for 1 hour at room temperature. The reaction mixture was stirred for a further 4 hours. Potassium hydroxide (0.20 g., 2.8 mmol.) was added and hydrogen sulphide passed for 0.5 hours. The reaction mixture was stirred at room temperature for 16 hours, diluted with water and ether extracted. The extracts were washed with saturated brine, dried and evaporated to give the title compound (0.39 g., 74%), b.p. 96—98°C/0.3 mm. δ($CDCl_3$) 3.77 (6H, s, 2 x CH_3), 4.82 (1H, s, CH) 7.11—7.48 (3H, m, thienyl protons). ν_{max} (film) 1740 cm^{-1} $C_9H_{10}O_4S$ requires M.214. Found: M^+, 214.

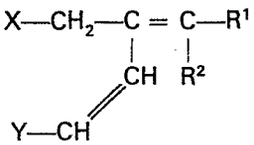
Claims

1. A process for the preparation of a thiophene of formula (I):



(I)

wherein R^1 represents a carboxylic acid group or an ester or amide derivative thereof or a nitrile group; and R^2 represents hydrogen, a hydrocarbon or heterocyclic group, a carboxylic acid group or an ester of amide derivative thereof, or an acyl, nitrile, isonitrile or optionally substituted imine group of formula —CH=NZ or —N=CHZ (where Z represents hydrogen, alkyl or aryl), or SO_2R^a —SR^a, —SO.R^a or —SO_2OR^a group wherein R^a represents C_{1-6} alkyl, or aryl, characterised in that a compound of formula (II):



(II)

wherein R^1 and R^2 are as defined with respect to formula (I) above; X represents a halogen atom, a hydroxyl group or a functionalised hydroxyl group; Y represents a halogen atom, a hydroxyl group, or an alkoxy group; is treated with a source of nucleophilic sulphur under basic conditions.

2. A process as claimed in claim 1 wherein the source of nucleophilic sulphur is the bisulphide ion.

3. A process as claimed in claim 1 wherein the compound of the formula (II) is treated with an alkali metal sulphide.

4. A process as claimed in claim 3 wherein the alkali metal sulphide is sodium sulphide.

5. A process as claimed in any one of claims 1 to 4 wherein X and Y are both halogen.

6. A process as claimed in claim 5 wherein the X and Y are both chlorine.

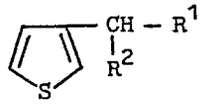
7. A process as claimed in any one of claims 1 to 6 wherein R^2 represents hydrogen, a carboxylic acid or ester group.

8. A process as claimed in claim 7 wherein R^2 is a carboxylic acid group or a carboxylic ester group of formula —CO_2R^3, wherein R^3 is C_{1-6} alkyl, benzyl, phthalidyl, indanyl, phenyl, mono-, di-, or tri-(C_{1-6})-alkyl substituted phenyl.

9. A process as claimed in any one of claims 1 to 6 wherein R^1 and R^2 both represent a carboxylic acid or ester group.

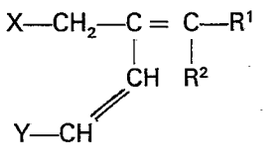
Revendications

1. Procédé pour la préparation d'un thiophène de formule (I):



(I)

dans laquelle R^1 représente un groupe acide carboxylique ou un dérivé ester ou amide de celui-ci ou un groupe nitrile; et R_2 représente de l'hydrogène, un groupe hydrocarboné ou hétérocyclique, un groupe acide carboxylique ou un dérivé ester ou amide de celui-ci; ou un groupe acyle, nitrile, isonitrile ou imine éventuellement substitué de formule —CH=NZ ou —N=CHZ, où Z représente de l'hydrogène, un alkyle ou un aryle, ou SO_2R^a, —SR^a, —SO.R^a ou —SO_2R^a, où R^a représente un alkyle en C_{1-6} ou un aryle, caractérisé en ce qu'on traite un composé de formule (II):



(II)

dans laquelle R^1 et R^2 ont la même signification que dans le cas de la formule (I) ci-dessus; X représente un atome d'halogène, un groupe hydroxy ou un groupe hydroxy fonctionnalisé; Y représente un atome d'halogène, un groupe hydroxy ou un groupe alcoxy avec une source de soufre nucléophile dans ces conditions basiques.

2. Procédé suivant la revendication 1, caractérisé en ce que la source de soufre nucléophile est l'ion bisulfure.

3. Procédé suivant la revendication 1, caractérisé en ce que le composé de formule (II) est traité avec un sulfure de métal alcalin.

4. Procédé suivant la revendication 3, caractérisé en ce que le sulfure de métal alcalin est le sulfure de sodium.

5. Procédé suivant l'une quelconque des revendications 1 à 4, caractérisé en ce que X et Y sont tous deux un halogène.

6. Procédé suivant la revendication 5, caractérisé en ce que X et Y sont tous deux du chlore.

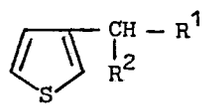
7. Procédé suivant l'une quelconque des revendications 1 à 6, caractérisé en ce que R^2 représente de l'hydrogène un groupe acide ou ester carboxylique.

8. Procédé suivant la revendication 7, caractérisé en ce que R^2 est un groupe acide carboxylique ou un groupe ester carboxylique de formule —CO_2R^3, où R^3 est un groupe alkyle en C_{1-6}, benzyle, phtalidyle, indanyle, phènyle, mono- di- ou tri- alkyl (C_{1-6}) phènyle.

9. Procédé suivant l'une quelconque des revendications 1 à 6, caractérisé en ce que R^1 et R^2 représentent tous deux un groupe acide ou ester carboxylique.

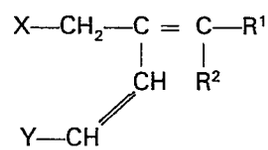
Patentansprüche

1. Verfahren zur Herstellung eines Thiophens der allgemeinen Formel (I)



(I)

in der R^1 eine Carboxylgruppe oder deren Ester- oder Amid-Derivat oder eine Nitrilgruppe darstellt und R^2 ein Wasserstoffatom, ein Kohlenwasserstoffrest oder ein heterocyclischer Rest, eine Carboxylgruppe oder deren Ester- oder Amid-Derivat, ein Acylrest, eine Nitril- oder Isonitrilgruppe oder eine gegebenenfalls substituierte Iminogruppe der Formel —CH=NZ oder —N=CHZ ist, wobei Z ein Wasserstoffatom, einen Alkyl- oder Arylrest oder eine der Gruppen —SO_2R^a, —SR^a, —SO.R^a oder —SO_2OR^a bedeutet, in denen R^a einen Alkylrest mit 1 bis 6 Kohlenstoffatomen oder einen Arylrest darstellt, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel (II)



(II)

in der R^1 und R^2 im Hinblick auf die vorstehende allgemeine Formel (I) definiert sind, X ein Halogenatom, eine Hydroxylgruppe oder eine in eine Hydroxylgruppe überführbare Gruppe ist und Y ein Halogenatom, eine Hydroxylgruppe oder eine Alkoxygruppe bedeutet, unter basischen Bedingungen mit einer Quelle von nucleophilem Schwefel behandelt wird.

2. Verfahren nach Anspruch 1, wobei die Quelle von nucleophilem Schwefel ein Bisulfid-Ion ist.

3. Verfahren nach Anspruch 1, wobei eine Verbindung der allgemeinen Formel (II) mit einem Alkalimetallsulfid behandelt wird.

4. Verfahren nach Anspruch 3, wobei das Alkalimetallsulfid Natriumsulfid ist.

5. Verfahren nach einem der Ansprüche 1 bis 4, wobei X und Y Halogenatome sind.

6. Verfahren nach Anspruch 5, wobei X und Y Chloroatome sind.

7. Verfahren nach einem der Ansprüche 1 bis 6, wobei R^2 ein Wasserstoffatom, eine Carboxylgruppe oder Estergruppe darstellen.

8. Verfahren nach Anspruch 7, wobei R^2 eine Carboxylgruppe oder eine Estergruppe der allgemeinen Formel $—CO_2R^3$ ist, in der R^3 C_{1-6}-Alkyl, Benzyl, Phthalidyl, Indanyl, Phenyl, mono-, di- oder tri-(C_{1-6}-Alkyl)-substituiertes Phenyl ist.

9. Verfahren nach einem der Ansprüche 1 bis 6, wobei beide Reste R^1 und R^2 eine Carboxylgruppe oder Estergruppe darstellen.