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Declarations under Rule 4.17:

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— *of inventorship (Rule 4.17(iv)) for US only*

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(54) Title: MODIFIED HECK REACTION

(57) Abstract: The present invention includes a method for the preparation of a cinnamonitrile by addition of an aryl to acrylonitrile in the presence of a heterogeneous palladium catalyst, a phosphine, a base and a salt. The reaction can be conducted not only on aryl compounds activated with electron withdrawing groups, but also on neutral and even on deactivated aryl compounds.

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MODIFIED HECK REACTION

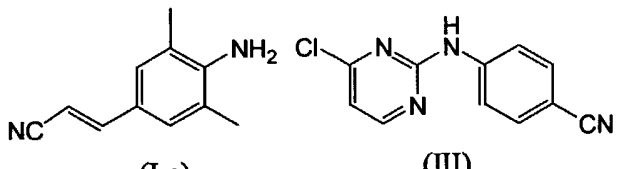
Field of the invention

The present invention provides a method for the preparation of a cinnamonitrile by addition of an aryl compound to acrylonitrile in the presence of a heterogeneous palladium catalyst, a phosphine, a base and a salt. The reaction can be conducted not only on aryl compounds activated with electron withdrawing groups, but also on neutral and even on deactivated aryl compounds.

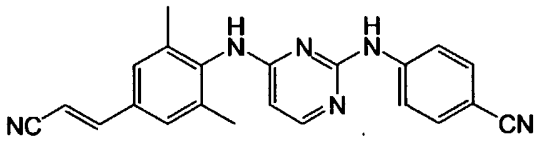
Background of the invention

The palladium-catalyzed coupling between organohalides or triflates and alkenes is named the Heck reaction. The reaction uses a catalytic amount of a palladium (0) complex and an equivalent of base. Typically the palladium (0) complex used is homogeneous and has the disadvantage of being difficult to remove from the reaction product to a level below what is allowed for medicinal products. One solution to this problem is to use heterogeneous palladium, for example palladium on charcoal (Pd/C). The latter usually does not have the reactivity of homogeneous palladium catalysts. In addition, heterogeneous palladium sometimes catalyzes the undesired dehalogenation of the organohalide. Finally, the palladium may also leach from the charcoal and be difficult to remove from the reaction product.

In the preparation of the non-nucleoside reverse transcriptase inhibitor (II), (E)-4-amino-3,5-dimethylcinnamonitrile (I-a) is coupled to the pyrimidine (III).

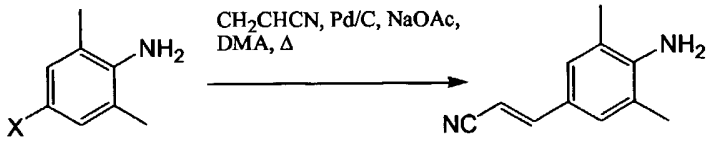


(I-a) (III)



(II)

As described in WO-2004/016581, we prepared (I-a) by coupling 4-iodo-2,6-dimethylaniline (IV) (X = I) to acrylonitrile in the presence of palladium on charcoal, sodium acetate as a base and dimethylacetamide as a solvent.



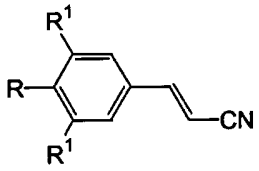
(IV) X = I or Br (I-a)

Unexpectedly, 4-iodo-2,6-dimethylaniline (IV) (X = I) proved not to be stable on storage and we were obliged to switch to 4-bromo-2,6-dimethylaniline (IV) (X = Br). This intermediate, however, failed to react under the reaction conditions described in WO-2004/016581.

When 4-bromo-2,6-dimethylaniline (IV) (X = Br) was coupled to acrylonitrile using a homogeneous palladium catalyst, various undesired side products were formed alongside the desired compound (I-a). Consequently, we recognized that there is a need for a method of preparing a cinnamonitrile by addition of an aryl compound to acrylonitrile in the presence of a heterogenous palladium catalyst and a base.

Description of the invention

The present invention provides a method for the preparation of a compound of formula (I)

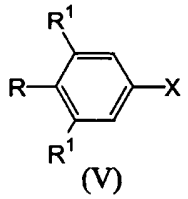


(I)

a salt or a stereoisomer thereof, wherein

R represents amino, methoxy, nitro, hydrogen, cyano, $-C(=O)R^2$, $-C(=O)OR^2$, or $-C(=O)NR^2R^2$; wherein each R^2 independently represents hydrogen or C_{1-6}alkyl; and each R^1 independently represents hydrogen or methyl; comprising:

heating an intermediate of formula (V)



(V)

wherein X represents chloro, bromo, iodo, triflate, hexaflate, nonaflate, tosylate, nosylate, or a diazonium group; and R and R^1 are as defined hereinbefore;
to reflux temperature in a dipolar aprotic solvent in the presence of
acrylonitrile;
palladium on charcoal;
a phosphine;
a base; and
a salt.

The reaction can be conducted not only on aryl compounds activated with electron withdrawing groups (R = nitro), but also on neutral (R = H) and even on deactivated aryl compounds (R = amino or methoxy).

Preferably, the dipolar aprotic solvent base is selected from the group comprising dimethylformamide, dimethylacetamide, N-methylpyrrolidone and hexamethylphosphotriamide.

Preferably, the phosphine is selected from the group comprising tri-o-tolylphosphine, triphenylphosphine, tris(2,4-dimethoxyphenyl) phosphine, tris(2,4,6-trimethoxyphenyl)phosphine, 2-(dicyclohexylphosphino) biphenyl, 2-(di-t-butylphosphino)-biphenyl, 1,1'-bis(diphenylphosphino)ferrocene (dppf), (oxy-2,1-phenylene)bis-(diphenylphosphine) (DPEPHOS), tricyclohexyl-phosphine, tri-t-butylphosphonium tetrafluoroborate, 1,3-bis(diphenylphosphino) propane (dppp), and 1,4-bis(diphenylphosphino)butane (dppb).

Preferably, the base is an alkali metal carboxylate or carbonate such as, for example, sodium acetate, potassium acetate, cesium carbonate, or an amine such as, for example, tributylamine; and the salt is a quaternary ammonium salt or an alkali metal halide salt such as, for example, tetrabutyl ammonium chloride or lithium chloride.

The reaction is conveniently conducted so that for each mole of the intermediate of formula (V),
the amount of dipolar aprotic solvent ranges from 0.5 to 2 L;
the amount of acrylonitrile ranges from 1.05 to 2.5 equivalents;
the amount of palladium on charcoal ranges from 0.01 to 0.1 equivalents;
the amount of phosphine ranges from 0.01 to 0.1 equivalents;
the amount of base ranges from 1 to 1.5 equivalents; and
the amount of salt ranges from 0.5 to 1.5 equivalents.

Preferably, for each mole of the intermediate of formula (V),
the amount of solvent is about 1L;
the amount of acrylonitrile is about 1.5 equivalents;
the amount of palladium on charcoal is about 0.05 equivalents;
the amount of phosphine is about 0.05 equivalents;
the amount of base is about 1.2 equivalents; and
the amount of salt is about 1 equivalent.

In order to facilitate the purification of the compound of formula (I), the reaction mixture is heated while stirring under an inert atmosphere until less than 2% of the intermediate of formula (V) remains.

Various iodoaryl compounds were reacted with acrylonitrile in the presence of palladium on charcoal, tri-o-tolylphosphine, tetrabutylammonium chloride in dimethylacetamide. Table 1 summarizes the results of these experiments.

Table 1 (X=I)

R	R^1	reaction time (h)	E (%)	Z (%)
H	H	0.5	75.8	24.2
NO_2	H	0.5	75.9	24.1
OCH_3	H	1	75.5	24.5
NH_2	H	1	77.9	22.1
NH_2	CH_3	2	79.5	20.5

All starting materials are completely converted within 2 hours and there does not appear to be any difference between activated and deactivated aryl compounds; the ratio of E/Z isomers ranges from about 75/25 to about 80/20.

Various bromoaryl compounds were reacted with acrylonitrile in the presence of palladium on charcoal, tri-o-tolylphosphine, tetrabutylammonium chloride in dimethylacetamide. Table 2 summarizes the results of these experiments.

Table 2 (X=Br)

R	R^1	reaction time (h)	E (%)	Z (%)
H	H	24	70.3	29.7
NO_2	H	0.5	74.8	25.2
OCH_3	H	24	73.8	26.2
NH_2	H	4	77.0	23.0
NH_2	CH_3	24	80.4	19.6

All starting materials are completely converted within 24 hours. Here, there clearly is a difference between activated and deactivated aryl compounds. Lower yields can be explained by the formation of undesired side products. The ratio of E/Z isomers ranges from about 70/30 to about 80/20.

Following art known separation and purification steps, the compound of formula (I) is isolated from the reaction mixture. The ratio of E/Z isomers of the compound of formula (I) may be increased to more than 95/5 by dissolving said isolated compound in an alcohol such as, for example, ethanol or propylene glycol monomethylether in the presence of an acid such as, for example, hydrochloric acid, and isolating the compound of formula (I). The latter alcohol is preferred as it gives a higher yield. The compound of formula (I) wherein R represents amino may be isolated as a salt form by adding one or more equivalents of an acid to said alcohol solution; allowing the salt to precipitate upon cooling; and isolating the salt of the compound of formula (I) wherein R represents amino.

Experimental part

A 3 L reaction vessel was charged under nitrogen gas with 34.6 g palladium on charcoal (Pd/C 10%), 64 g sodium acetate, 180.6 g tetrabutylammonium chloride, 650 ml of dimethylacetamide, 130 g 4-bromo-2,6-dimethylaniline, 9.9 g tris (o-tolyl)-phosphine and 64,7 ml acrylonitrile. The heterogeneous reaction mixture was stirred and heated to reflux temperature. Reflux started between 120°C and 130°C and the

temperature was kept at 140°C during 26 hours (or longer until less than 2% of the original amount of 4-bromo-2,6-dimethylaniline remained). The reaction mixture was allowed to cool to room temperature and filtered. The filter was washed twice with 75 ml toluene and the residue was discarded. The filtrates were combined and evaporated under reduced pressure. The thus obtained oily residue was dissolved in 650 ml toluene and 650 ml water, and stirred for 30 minutes. The toluene layer was separated and the water later and intermediate layer were extracted once with 650 ml toluene and once again with 325 ml toluene. The combined organic layers were washed with 650 ml water and evaporated under reduced pressure. The ratio of E/Z isomers was 80/20.

The thus obtained oily residue was redissolved in propylene glycol monomethyl ether and heated at about 60 °C during 30 minutes. A solution of 119 ml HCl (6 N) in 2-propanol was added dropwise at 60°C and the reaction mixture was stirred for another 30 minutes at 60°C. The reaction mixture was allowed to cool to room temperature and stirred overnight. The precipitate was filtered of, washed twice with 100 ml 2-propanol and dried under reduced pressure at 50°C. The ratio of E/Z isomers was > 95/5.

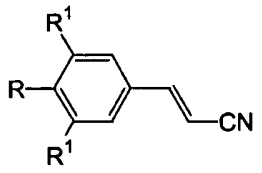
^{1}H-NMR data (400 MHz in DMSO-d6, shift in ppm relative to TMS; coupling constant in Hz; s = singlet, d = doublet)

(E) isomer: 7,13 (d, J = 16,4 Hz, 1H) ; 6,9 (s, 2H) ; 5,5 (d, J = 16,8 Hz , 1H) ; 3,9 (broad s, 2H) ; 2,09 (s, 6H)

(Z) isomer: 6,9 (s, 2H) ; 6,81 (d, J = 12,4 Hz, 1H) ; 5,15 (d, J = 11,9 Hz , 1H) ; 3,9 (broad s, 2H) ; 2,11 (s, 6H)

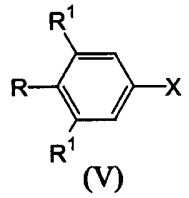
Claims

1. A method for the preparation of a compound of formula (I)



(I)

a salt or a stereoisomer thereof, wherein
R represents amino, methoxy, nitro, hydrogen, cyano, $-C(=O)R^2$, $-C(=O)OR^2$, or $-C(=O)NR^2R^2$; wherein each R^2 independently represents hydrogen or C_{1-6}alkyl; and each R^1 independently represents hydrogen or methyl; comprising:
heating an intermediate of formula (V)



(V)

wherein X represents chloro, bromo, iodo, triflate, hexaflate, nonaflate, tosylate, nosylate, or a diazonium group; and R and R^1 are as defined hereinbefore;
to reflux temperature in a dipolar aprotic solvent in the presence of
acrylonitrile;
palladium on charcoal;
a phosphine;
a base; and
a salt.

2. The method according to claim 1 wherein the dipolar aprotic solvent base is selected from the group comprising dimethylformamide, dimethylacetamide, N-methylpyrrolidone and hexamethylphosphotriamide.

3. The method according to claim 1 wherein the phosphine is selected from the group comprising tri-o-tolylphosphine, triphenylphosphine, tris(2,4-dimethoxyphenyl) phosphine, tris(2,4,6-trimethoxyphenyl)phosphine, 2-(dicyclohexylphosphino) biphenyl, 2-(di-t-butylphosphino)biphenyl, 1,1'-bis(diphenylphosphino)ferrocene

(dppf), (oxy-2,1-phenylene)bis-(diphenylphosphine) (DPEPHOS), tricyclohexyl-phosphine, tri-t-butylphosphonium tetrafluoroborate, 1,3-bis(diphenylphosphino) propane (dppp), and 1,4-bis(diphenylphosphino)butane (dppb).

4. The method according to claim 1 wherein the base is an alkali metal carboxylate or carbonate, or an amine; and the salt is a quaternary ammonium salt or an alkali metal halide salt.

5. The method according to claim 1 wherein for each mole of the intermediate of formula (V),
the amount of dipolar aprotic solvent ranges from 0.5 to 2 L;
the amount of acrylonitrile ranges from 1.05 to 2.5 equivalents;
the amount of palladium on charcoal ranges from 0.01 to 0.1 equivalents;
the amount of phosphine ranges from 0.01 to 0.1 equivalents;
the amount of base ranges from 1 to 1.5 equivalents; and
the amount of salt ranges from 0.5 to 1.5 equivalents.

6. The method of claim 5 wherein for each mole of the intermediate of formula (V),
the amount of solvent is about 1L;
the amount of acrylonitrile is about 1.5 equivalents;
the amount of palladium on charcoal is about 0.05 equivalents;
the amount of phosphine is about 0.05 equivalents;
the amount of base is about 1.2 equivalents; and
the amount of salt is about 1 equivalent.

7. The method of claim 1 wherein the reaction mixture is heated while stirring under an inert atmosphere until less than 2% of the intermediate of formula (V) remains.

8. The method of claim 1 wherein the compound of formula (I) is isolated from the reaction mixture following art known separation and purification steps.

9. The method of claim 8 for the preparation of a compound of formula (I) wherein the E/Z ratio is more than 95/5, further comprising the steps of
- dissolving the compound of formula (I) isolated from the reaction mixture in an alcohol in the presence of an acid; and
- isolating the compound of formula (I).

10. The method of claim 9 for the preparation of a salt form of the compound of formula (I) wherein R represents amino, comprising the step of adding one or more equivalents of an acid to said alcohol solution; allowing the salt to precipitate upon cooling; and isolating the salt of the compound of formula (I) wherein R represents amino.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/052759

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C253/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/016581 A (JANSSEN PHARMACEUTICA N.V; SCHILS, DIDIER, PHILIPPE, ROBERT; WILLEMS,) 26 February 2004 (2004-02-26) cited in the application example A1	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2005	10/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Slootweg, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/052759

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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