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(54) Title: PROCESS FOR MANUFACTURING ALKYL 7-AMINO-5-METHYL-[1,2,5]OXADIAZOLO[3,4-B]PYRIDINE-CARBOXYLATE

(57) Abstract: This invention relates to a novel process for making alkyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridine-carboxylate.



WO 2021/233882 A1

**PROCESS FOR MANUFACTURING ALKYL 7-AMINO-5-METHYL-
[1,2,5]OXADIAZOLO[3,4-B]PYRIDINE-CARBOXYLATE**

FIELD OF THE INVENTION

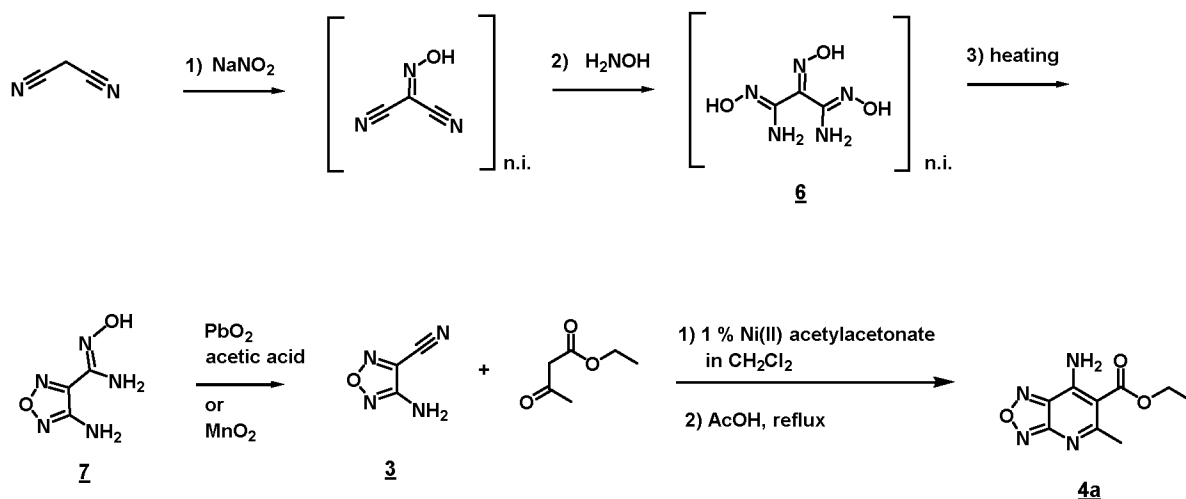
5 This invention relates to a novel technical scale process for making alkyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridine-carboxylate **4**. Alkyl 7-amino-5-methyl-[1,2,5]oxadiazolo[3,4-b]pyridine-carboxylate **4** is a key intermediate for preparing compounds described in WO 2018/024653, WO 2019/149657, WO 2019/149658 and WO 2019/149659.

10

BACKGROUND OF THE INVENTION

The synthesis of the 4-amino-1,2,5-oxadiazole-3-carbonitrile **3** via the intermediates **6** and **7** was described by T. Ichikawa et al. (J. Heterocycl. Chem. 1965, 253).

15 Scheme 1



n.i. = not isolated

In 2017, P.F. Pagoria et al. published a modification of Ichikawa's route with improved yield and purity (Chem. Heterocycl. Compounds 2017, 53, 760).

20

The main drawback of the literature synthesis of 4-amino-1,2,5-oxadiazole-3-carbonitrile **3** is that the intermediate compounds **6** and **7** (as well as compound **3**) are highly energetic substances. D.S. Bohle et al. describe that compound **6** „explodes at about 130 °C during DSC experiments, shattering the sample cup“ (J. Org. Chem 2000, 65,

1139). Moreover, to induce the cyclization of compound 6 to the oxadiazole 7, the aqueous reaction mixture has to be heated under reflux. This may cause safety issues, particularly in the upscale of this transformation.

5 Another important drawback of the literature synthesis is the use of lead compounds for the deoxygenation of oxadiazole 7 to the oxadiazole 3. The use of toxic lead during the preparation of pharmaceuticals is questionable, anyway. However, in the majority of the literature descriptions, the lead is even used in stoichiometric amounts or higher. Thus, the weight load of lead compound in relation to substrate is high. As a result, a lot of
10 toxic lead waste is generated.

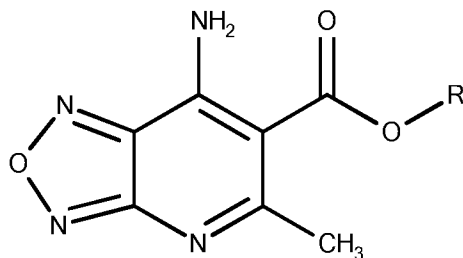
As an alternative to the lead containing reagents, WO 2018/44663 describes the use of manganese(IV) oxide as a mild oxidation agent. However, due to the formation of the amide as a side product in significant amounts, the crude product was purified by
15 column chromatography. This is a severe drawback for technical scale, as in large scale, column chromatography is very time-consuming and costly. Moreover, the risk of the highly energetic intermediates will not be overcome by this approach.

A.B. Sheremetev and V.A. Dorokhov et al. showed that ethyl acetoacetate adds to the
20 nitril group of 4-amino-1,2,5-oxadiazole-3-carbonitrile 3 in the presence of catalytic amounts of nickel(II) acetylacetonate in methylene chloride. By adding acetic acid and heating, ethyl 7-amino-5-methyl-[1,2,5]oxadiazolo[3,4-b]pyridine-carboxylate 4a is obtained via intramolecular cyclisation (Mendeleev Communication 1994, 4, 57; Russian Chemical Bulletin, Int. Ed., 2001, 50, 1280).

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for manufacturing alkyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridine-carboxylate 4

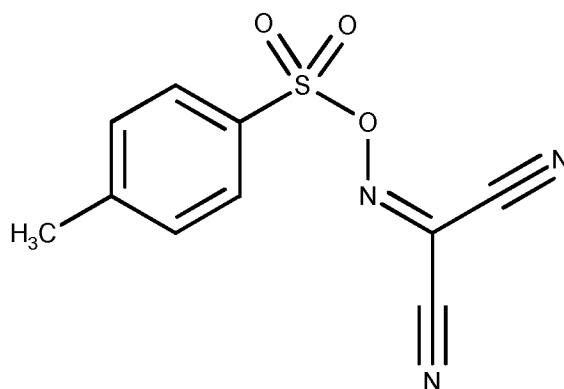
**4**,

wherein R is C₁₋₃-alkyl,

5 comprising

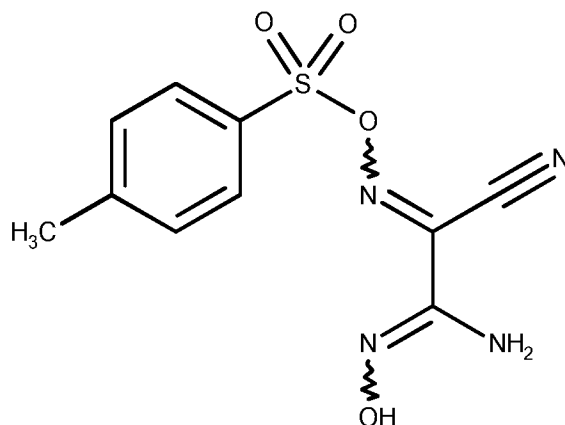
(a) reacting malononitrile with sodium nitrite in the presence of a suitable acid, preferably in the presence of hydrobromic acid, in a suitable solvent under slight overpressure;

10 (b) reacting the reaction mixture obtained by step (a) with a suitable toluenesulfonic acid derivative, preferably with p-toluenesulfonyl chloride, to obtain compound **1**;

**1**

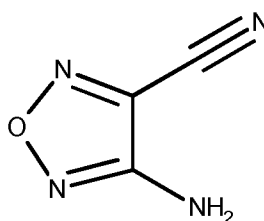
(c) optionally isolating compound **1**;

15 (d) reacting compound **1** in a suitable solvent with hydroxylamine to obtain compound **2**;

**2**

(e) optionally isolating compound **2**;

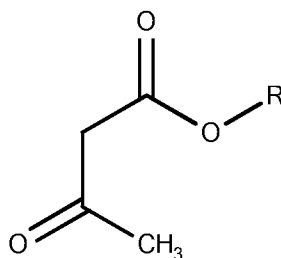
(f) cyclisation of compound **2** in the presence of a base under heating to about 70°C
 5 in a suitable solvent to obtain the oxadiazole **3**;

**3**

(g) removal of water from the reaction mixture by evaporation under reduced
 pressure;

10 (h) removal of p-toluenesulfonic acid salt(s) by filtration;

(i) *in situ*-condensation of compound **3** in the reaction mixture obtained after step (h)
 with the appropriate beta-keto ester of formula



wherein R is C₁₋₃-alkyl,

15 in the presence of a Lewis acid such as zinc dichloride in a suitable solvent; and

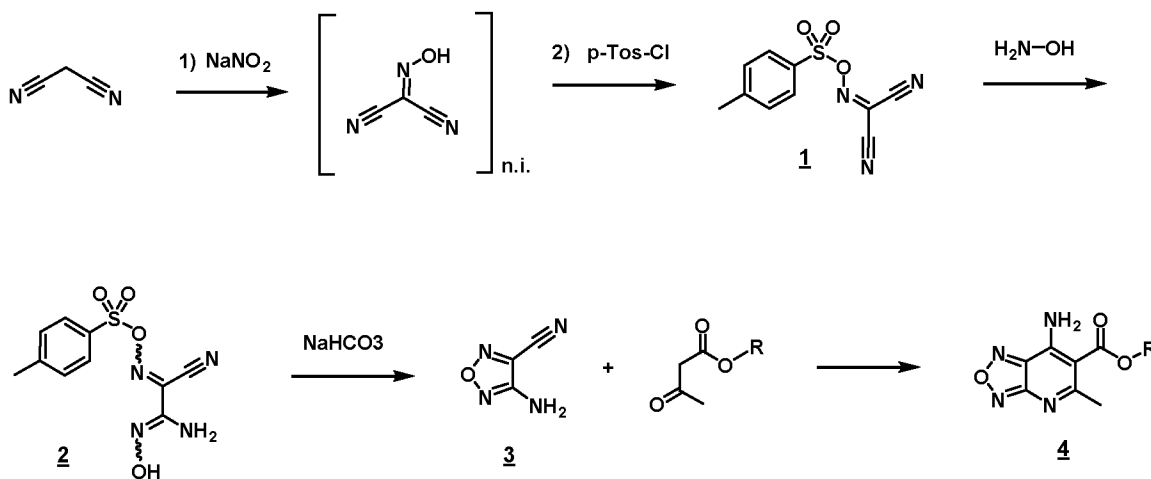
(j) isolating compound **4**.

In the above process, the beta-keto ester is a C₁₋₃-alkyl beta-keto ester. Preferably, the ethyl beta-keto ester is used. Correspondingly, in scheme 2 below, R is C₁₋₃-alkyl. Preferably, R is ethyl.

5

The process according to the invention can be used in technical scale.

Scheme 2 (n.i. = not isolated)



10

The process according to the present invention overcomes the disadvantages of processes of the prior art by having the distinction of

- 15
- 1) avoiding the highly energetic intermediates **6** and **7**,
 - 2) making use of inexpensive and readily accessible starting material and reagents,
 - 3) requiring the isolation of 2 intermediates and the final product, only, all of which can easily be carried out on/in technical scale,
 - 4) yielding alkyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridine-carboxylate **4** in
- 20 high purity with high overall yield.

Additional advantages of the process according to the invention are as follows:

- i) The cyclisation of the intermediate **2** to the oxadiazole **3** can be performed under mild reaction conditions (70 °C for several hours) without the need for

an oxidation reagent. This reduces the risks connected with the highly energetic compound **3**.

- 5 ii) The mild cyclisation conditions became possible due to the use of the tosylate group as a good leaving group that facilitates the intramolecular cyclisation of intermediate **2** to the oxadiazole **3**.
- iii) The intermediates **1** and **2** are highly crystalline compounds, which simplify isolation and purification.
- 10 iv) There is no need for isolation of the highly energetic oxadiazole compound **3** after *in situ* formation. After partial removal of water and removal of the p-toluenesulfonic acid salt(s), the reaction solution can be further processed in the cyclo-condensation with a suitable beta-keto ester to give the bicyclic oxadiazole compound **4** in good overall yield and purity.

15 Suitable acids for step (a) include hydrohalic acids like hydrochloric acid and hydrobromic acid, or organic acids like acetic acid. Preferably, hydrobromic acid is used.

A suitable solvent for step (a) is water.

20 Step (a) is preferably carried out under slight overpressure of up to 0.3 bar at a temperature of 0 to 25 °C, preferably at a temperature of 2 to 20 °C. The overpressure is caused by the reaction itself due to the formation of nitrogen oxides, and should be maintained up to a certain degree in order to obtain good yields.

25 Suitable toluenesulfonic acid derivatives useful as reagents for step (b) include p-toluenesulfonic acid anhydride and p-toluensulfonic acid chloride. Preferably, p-toluensulfonic acid chloride is used.

Suitable solvents for step (b) include lipophilic solvents like toluene as well as water, and the mixtures thereof.

30 Step (b) is preferably carried out at a temperature of 10 to 30 °C, more preferably at a temperature of about 20 °C.

In step (c), compound **1** is preferably precipitated via addition of an antisolvent like an alcohol such as 2-propanol, and isolated via filtration.

5 Suitable solvents for step (d) include ethers like tetrahydrofuran and alcohols like 2-propanol as well as water, and the mixtures thereof.

Step (d) is preferably carried out at a temperature of 10 to 30 °C, more preferably at a temperature of 20 to 25 °C.

10 In step (e), compound **2** is preferably precipitated via addition of an antisolvent like water and isolated via filtration.

Suitable bases for step (f) include organic bases like triethylamine or inorganic bases like alkali carbonates and alkali hydrogencarbonates. Examples for suitable carbonates
15 are lithium carbonate, sodium carbonate and potassium carbonate. Examples for suitable hydrogencarbonates are lithium hydrogencarbonate, sodium hydrogencarbonate and potassium hydrogencarbonate. Preferably, potassium hydrogencarbonate is used, as the resulting potassium p-toluenesulfonic acid salt has a low solubility in the solvent used and can thus be removed easily via filtration.

20 Suitable solvents for step (f) include ethers like 1,4-dioxane as well as water, and the mixtures thereof.

Step (f) is preferably carried out at a temperature of 20 to 100 °C, more preferably at a
25 temperature of 60 to 80 °C.

The appropriate beta-keto ester for step (i) is selected from the group consisting of a C₁₋₃-alkyl beta-keto ester. Preferably, the ethyl beta-keto ester is used.

30 Suitable Lewis acids for step (i) include zinc salts like zinc diacetate or zinc dichloride. Preferably, zinc dichloride is used as Lewis acid.

Suitable solvents for step (i) include an ether like 1,4-dioxane (preferred, if reaction step (i) is carried out *in situ*) or an alcohol like ethanol (preferred, if an addition isolation step of compound 3 is effected), or the mixtures thereof.

- 5 Step (i) is preferably carried out at a temperature of 20 to 100 °C, more preferably at a temperature of 60 to 80 °C.

In step (j), compound **4** is preferably precipitated via addition of an antisolvent like water and isolated via filtration.

10

General Definitions

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and context.

- 15 In case a compound of the present invention is depicted in form of a chemical name and as a formula, in case of any discrepancy, the formula shall prevail.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers, rotamers and all stereo,
20 optical and geometrical isomers (e.g. enantiomers, diastereomers, including E/Z isomers etc. ...) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well solvates thereof such as for instance hydrates.

25

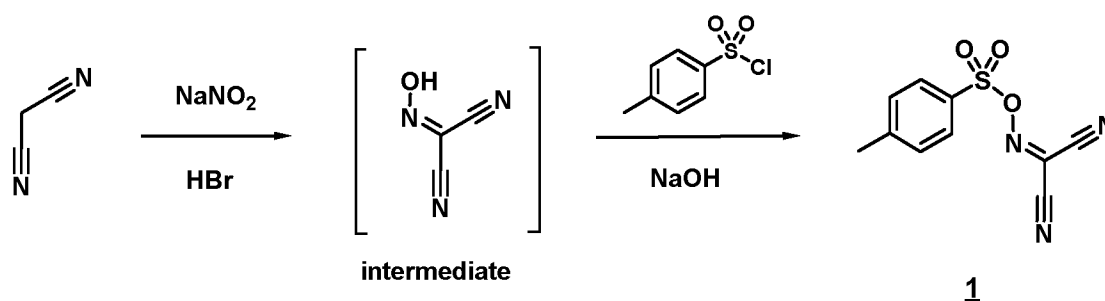
EXPERIMENTAL SECTION

Note: all intermediates are highly energetic compounds. Special care has to be taken on safety measures.

Example 1

Synthesis of (tosyloxy)carbonimidoyl dicyanide **1**

(Step 1 of the overall synthesis)



38.3 kg (227.1 mol) hydrobromic acid (48%) and subsequently 7.5 L of purified water (for rinsing) are added to a mixture of 7.5 kg (113.5 mol) malononitrile in 38 L of purified water. At a temperature of 7 °C, a solution of 15.7 kg (227.1 mol) sodium nitrite in 26.5 L of purified water are added during 2 hours. The feed tank is rinsed with 3.8 L of purified water and the reaction mixture is stirred for 30 minutes at 7 °C (formation of nitrous gases with a slight overpressure). During 1 hour the temperature is increased to 20 °C and the reaction mixture is stirred at 20 °C till the reaction to the intermediate is complete (control via TLC; reaction is complete in about 30 minutes to 1 hour. The reaction mixture is added to a mixture of 22.7 kg (119.2 mol) p-toluenesulfonyl chloride and 0.63 kg (2.25 mol) tetra-n-butyl-ammonium chloride in 30 L of toluene. The feed tank is rinsed with 7.5 L of purified water. At a temperature of 20 °C, a solution of 9.55 kg (119.2 mol) sodium hydroxide (50% in water) in 25 L of purified water is added during 45 minutes. The feed tank is rinsed with 3.5 L of purified water (the pH value should not exceed 4). The reaction mixture is stirred for 18 hours at 20 °C. After completion of the reaction (control via TLC), optionally 4 g of seed crystals of **1** (obtained from small scale experiments) and subsequently 30 L 2-propanol are added. The mixture is stirred for 1 hour. The suspension is centrifuged and the filter cake is

washed with 15 L of purified water and subsequently, it is washed two times with 15 L of 2-propanol. The product is dried in a vacuum drying cabinet under inertization at 30 °C.

Yield: 23.1 kg (82 % of theory) of **1** as a solid.

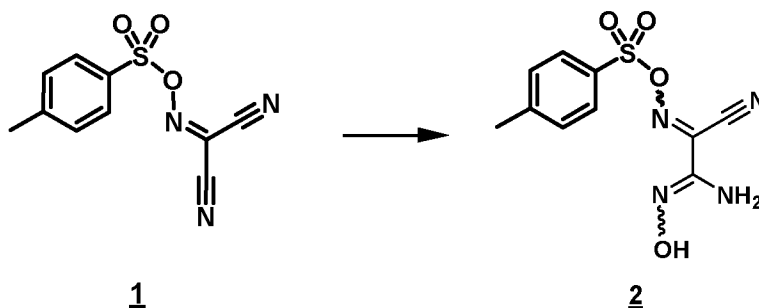
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.91 (d, 2H), 7.45 (d, 2H), 2.51 (s, 3H)

5

Example 2

Synthesis of 2-amino-2-(hydroxyimino)-N-(tosyloxy)acetimidoyl cyanide **2**

(Step 2 of the overall synthesis)



10

23.49 kg (94.24 mol) **1** are dissolved in 17 L tetrahydrofuran (stabilized) and 47 L 2-propanol. To this solution, a solution of 11.21 kg (127.28 mol) hydroxylamine (37.6 w % in water) in 24 L 2-propanol are added in a way, so that the temperature does not exceed 25 °C. The feed tank is rinsed with 17 L of 2-propanol. The suspension is stirred for 2 hours at 20 °C. After completion of the reaction (control via HPLC), 106 L of purified water are added at 20 °C during 30 minutes. The suspension is stirred for 1 hour at 20 °C. The suspension is centrifuged and the filter cake is washed two times with 35 L of 2-propanol. The product is dried in a vacuum drying cabinet at a temperature below 30 °C.

15

20

Yield: 20.36 kg (76.5 % of theory) of **2** as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 11.7 (s, 1H), 8.05 (d, 2H), 7.53 (d, 2H), 6.13 (bs, 2H), 2.45 (s, 3H)

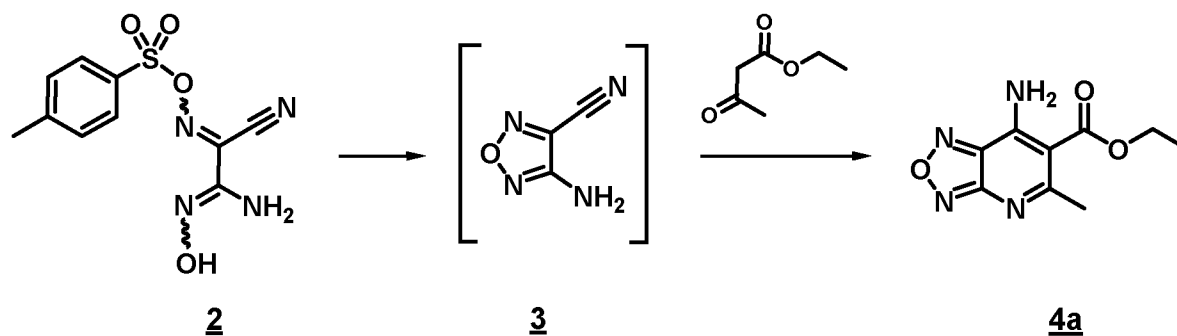
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Example 3

Synthesis of ethyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridine-carboxylate

4

(Steps 3 + 4 of the overall synthesis)



A mixture of 15.25 kg (54.02 mol) **2** and 8.11 kg (81.0 mol) potassium hydrogen carbonate in 152 L 1,4-dioxane and 4.6 L of purified water is stirred at 70 °C. After completion of the reaction (control via HPLC; ~8 hours), 45.8 L of solvent are evaporated under reduced pressure. 31 L of 1,4-dioxane are added and 61 L of solvent are evaporated under reduced pressure (removal of water). The suspension is cooled to 20 °C and filtered through a pressure filter into a second reaction vessel which contains a mixture of 7.37 kg (54.07 mol) of zinc dichloride in 15 L of 1,4-dioxane. The first reaction vessel is rinsed with 23 L of 1,4-dioxane and the solvent is filtered through the pressure filter into a second reaction vessel. 7.03 kg (54.02 mol) ethyl acetoacetate are added and the feed tank is rinsed with 8 L of 1,4-dioxane. The reaction mixture is stirred at 70 °C. After completion of the reaction (control via HPLC; reaction is complete in about 20 hours), the reaction mixture is cooled to 50 °C and 122 L of purified water are added. The mixture is stirred at 50 °C for 30 minutes. The suspension is cooled to 20 °C and stirred for 30 minutes. The suspension is centrifuged and the filter cake is washed two times with 15 L of purified water. The product is dried in a vacuum drying cabinet under inertization at 40 °C.

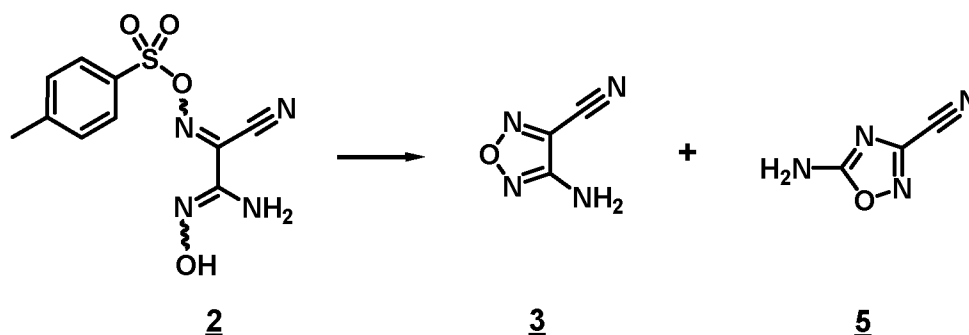
Yield: 7.71 kg (64.3 % of theory) of **4** as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 8.60 (bs, 2H), 4.35 (q, 2H), 2.60 (s, 3H), 1.32 (t, 3H)

Example 4

Synthesis of 4-amino-1,2,5-oxadiazole-3-carbonitrile **3 (and 5-amino-1,2,4-oxadiazole-3-carbonitrile **5** as unplanned side product)**

(Step 3 of the overall synthesis)



262 mg (3.54 mmol) lithium carbonate is added to a mixture of 1.0 g (3.54 mmol) **2** in 10 mL of 1,4-dioxane and 2 mL of purified water. The reaction mixture is stirred for 5 hours at 60 °C. After completion of the reaction (control via HPLC), the reaction mixture is cooled to 20 °C and 10 mL of purified water are added. The aqueous phase is extracted 3 times with toluene. The organic phase is dried over sodium sulfate. After filtration, the solvent is removed under reduced pressure. 260 mg of crude product are obtained as solid.

The crude product is purified via chromatography on silica gel using petrolether / ethylacetate (3:1) als eluent:

Yield: 200 mg (51 % of theory) of **3** as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 7.09 (bs, 2H)

¹³C NMR (100 MHz, DMSO-d₆) δ (ppm) = 156.9, 126.0, 108.2

¹⁵N NMR (40 MHz, DMSO-d₆) δ (ppm) = -11.9, -334.4

Yield: 22 mg (6 % of theory) of **5** as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 8.67 (bs, 2H)

¹³C NMR (100 MHz, DMSO-d₆) δ (ppm) = 172.9, 147.3, 109.9

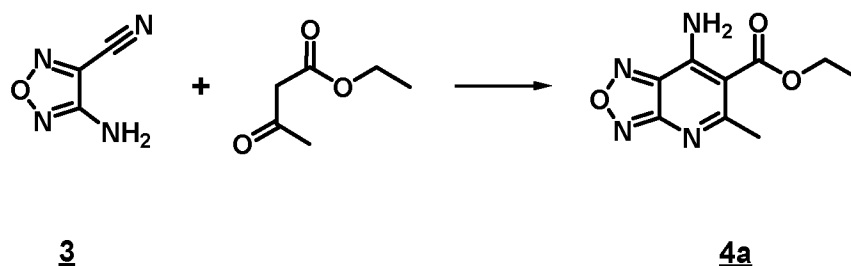
¹⁵N NMR (40 MHz, DMSO-d₆) δ (ppm) = -191.6, -311.6

Example 5

Synthesis of ethyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridine-carboxylate

4

(Step 4 of the overall synthesis)



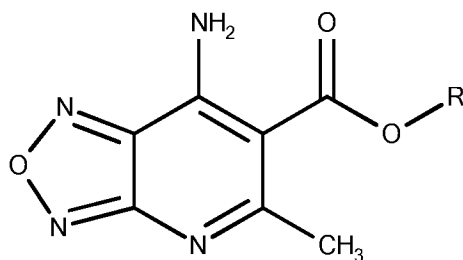
248 g (1.82 mol) zinc dichloride and subsequently 230 mL (1.82 mol) ethyl acetoacetate are added to a suspension of 200 g (1.82 mol) **3** in 1.6 L of ethanol. The reaction mixture is heated under reflux for 15 hours. After completion of the reaction (control via HPLC), the reaction mixture is cooled to 70 °C. 1.6 L of purified water are added. The suspension is cooled to 20 °C and stirred for 4 hours. The suspension is suction filtered and the filter cake is washed with 500 mL of ethanol/purified water (1:1). The product is dried in a vacuum drying cabinet at 40 °C.

Yield: 334 g (83 % of theory) of **4** as a solid.

¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 8.60 (bs, 2H), 4.35 (q, 2H), 2.60 (s, 3H), 1.32 (t, 3H)

Claims

1. Process for manufacturing alkyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridine-carboxylate 4



5

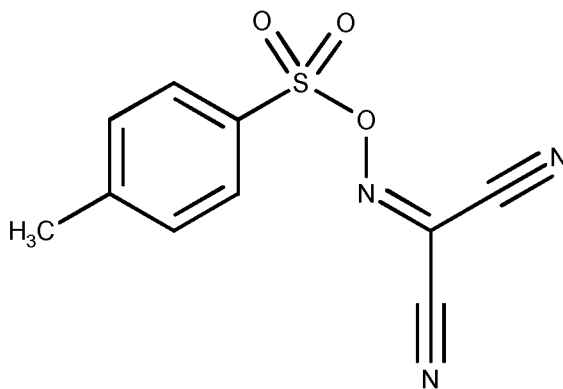
4,

wherein R is C₁₋₃-alkyl,

comprising

10

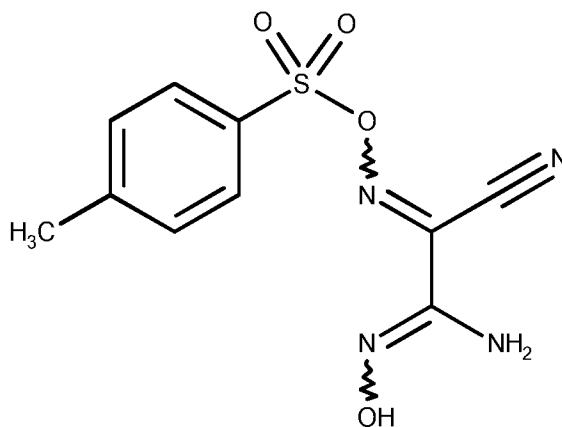
- (a) reacting malononitrile with sodium nitrite in the presence of a suitable acid in a suitable solvent under slight overpressure;
- (b) reacting the reaction mixture obtained by step (a) with a suitable toluenesulfonic acid derivative to obtain compound 1;



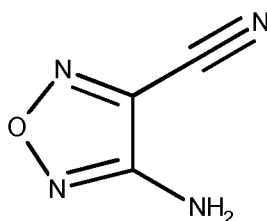
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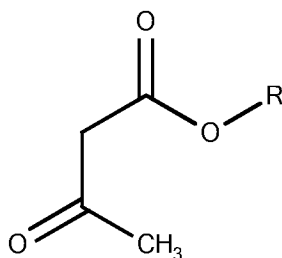
- (c) optionally isolating compound 1;
- (d) reacting compound 1 in a suitable solvent with hydroxylamine to obtain compound 2;

2

- (e) optionally isolating compound 2;
 (f) cyclisation of compound 2 in the presence of a base under heating to about
 5 70°C in a suitable solvent to obtain the oxadiazole 3;

3

- (g) removal of water from the reaction mixture by evaporation under reduced
 pressure;
 10 (h) removal of p-toluenesulfonic acid salt(s) by filtration;
 (i) *in situ*-condensation of compound 3 in the reaction mixture obtained after step
 (h) with the appropriate beta-keto ester of formula



, wherein R is C₁₋₃-alkyl, in the presence of a Lewis acid in a suitable solvent;

and

- (j) isolating compound 4.

2. The process according to claim 1 characterized in that isolation step (c) is carried out prior to reaction compound 1 is step (d).
5
3. The process according to claim 1 or 2 characterized in that step (e) is carried out prior to the cyclisation of compound 2 in step (f).
4. The process according to any one of the preceding claims characterized in that in
10 step (a), hydrochloric acid, hydrobromic acid or acetic acid are used as the suitable acid, and water is used as the solvent.
5. The process according to any one of the preceding claims characterized in that
15 step (a) is carried out under an overpressure of up to 0.3 bar at a temperature of 0-25°C.
6. The process according to any one of the preceding claims characterized in that in
20 step (a), hydrobromic acid is used as the suitable acid, and water is used as the solvent at a temperature of 0-20°C.
7. The process according to any one of the preceding claims characterized in that in
25 step (b) the toluenesulfonic acid derivative is toluenesulfonic acid anhydride or toluenesulfonic acid chloride, and the reaction is carried out at a temperature of 10 to 30 °C.
8. The process according to any one of the preceding claims characterized in that in
30 step (b) the toluenesulfonic acid derivative is toluenesulfonic acid chloride, and the reaction is carried out at a temperature of about 20 °C
9. The process according to any one of the preceding claims characterized in that in
step (c), compound 1 is precipitated via addition of an antisolvent and then isolated via filtration.

10. The process according to any one of the preceding claims characterized in that in step (c), compound 1 is precipitated via addition of an alcohol and then isolated via filtration.
- 5 11. The process according to any one of the preceding claims characterized in that in step (c), compound 1 is precipitated via addition of 2-propanol and then isolated via filtration.
- 10 12. The process according to any one of the preceding claims characterized in that in step (d), the reaction is carried out at a temperature of 10 to 30 °C, using ethers, alcohols, water, or mixtures thereof as solvent.
- 15 13. The process according to any one of the preceding claims characterized in that in step (d), the reaction is carried out at a temperature of 20 to 25 °C, using tetrahydrofuran, 2-propanol, water, or mixtures thereof as solvent.
- 20 14. The process according to any one of the preceding claims characterized in that in step (e), compound 2 is precipitated via addition of an antisolvent and then isolated via filtration.
- 25 15. The process according to any one of the preceding claims characterized in that in step (e), compound 2 is precipitated via addition of water and then isolated via filtration.
- 30 16. The process according to any one of the preceding claims characterized in that in step (f), the cyclisation is carried out in the presence of triethylamine, an alkali carbonate or an alkali hydrogencarbonate using ethers, water, or mixtures thereof as the solvent, at a temperature of 20 to 100 °C.
17. The process according to any one of the preceding claims characterized in that in step (f), the alkali carbonate is selected from the group consisting of lithium carbonate, sodium carbonate and potassium carbonate; and the alkali hydrogen-carbonate is selected from the group consisting of lithium hydrogencarbonate,

sodium hydrogencarbonate and potassium hydrogencarbonate; the ether is 1,4-dioxane; and the temperature is 60 to 80 °C.

5 18. The process according to any one of the preceding claims characterized in that in step (i), the *in situ*-condensation is carried out in the presence of a zinc salt as Lewis acid at a temperature of 20 to 100 °C, in a solvent selected from an ether, an alcohol, water, or mixtures thereof.

10 19. The process according to any one of the preceding claims characterized in that in step (i), the *in situ*-condensation is carried out in the presence of zinc dichloride as Lewis acid at a temperature of 60 to 80 °C in 1,4-dioxane as the solvent.

15 20. The process according to any one of the preceding claims characterized in that in step (j), compound **4** is precipitated via addition of an antisolvent and then isolated via filtration.

20 21. The process according to any one of the preceding claims characterized in that in step (j), compound **4** is precipitated via addition of water and then isolated via filtration.

22. The process according to any one of the preceding claims, wherein R is ethyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/063088

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/04
ADD.

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)
C07D

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 practicable, search terms used)

EPO-Internal, WPI 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.
A	<p>ICHIKAWA TAKEHIKO ET AL: "A new synthesis of adenine and 4-aminoimidazole-5-carboxamide", JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 2, no. 3, 1 September 1965 (1965-09-01), pages 253-255, XP055821014, US ISSN: 0022-152X, DOI: 10.1002/jhet.5570020307 cited in the application Reaction Scheme; page 254</p>	1-22
A	<p>----- WO 2005/019190 A2 (VERTEX PHARMA [US]; COME JON H [US] ET AL.) 3 March 2005 (2005-03-03) page 44 - page 45; examples 1-3 ----- -/--</p>	1-22

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 2021	15/07/2021

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Bissmire, Stewart
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/063088

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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