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- (54) Benævnelse: **FREMGANGSMÅDE TIL AT FREMSTILLE ALKYL 7-AMINO-5-METHYL-[1,2,5]OXADIAZOLO[3,4-B]PYRIDIN-CARBOXYLAT**
- (56) Fremdragne publikationer:  
**WO-A1-2019/149657**  
**WO-A1-2019/149658**  
**WO-A1-2019/149659**  
**WO-A2-2005/019190**  
**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**



## Description

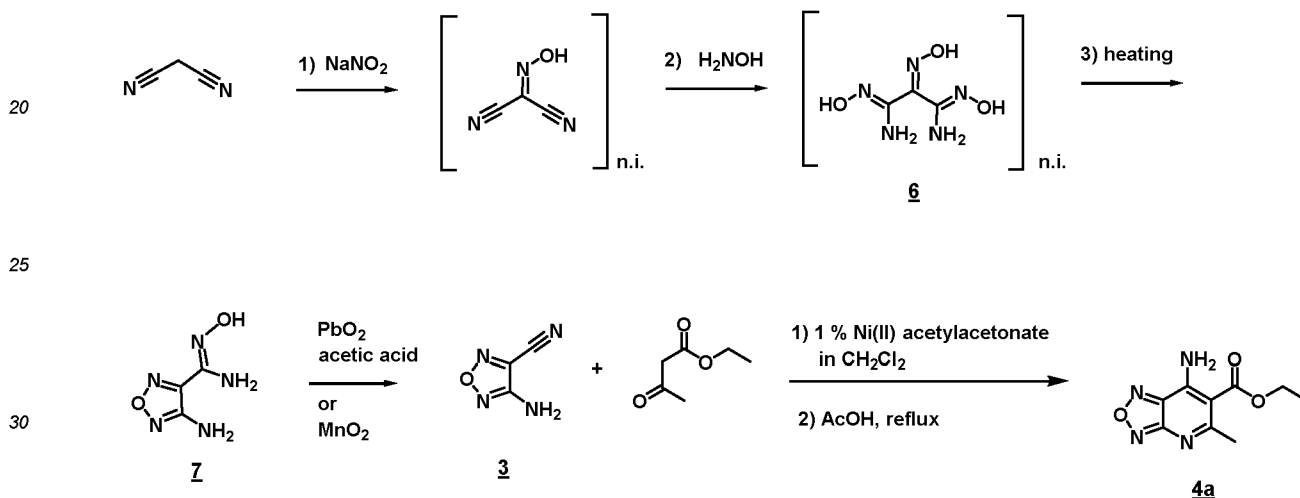
## FIELD OF THE INVENTION

5 [0001] 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

[0002] 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).

Scheme 1



n.i. = not isolated

[0003] 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).

[0004] 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.

[0005] Another important drawback of the literature synthesis is the use of lead compounds for the deoximation 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 toxic lead waste is generated.

[0006] 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 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.

[0007] A.B. Sheremetev and V.A. Dorokhov et al. showed that ethyl acetoacetate adds to the 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).

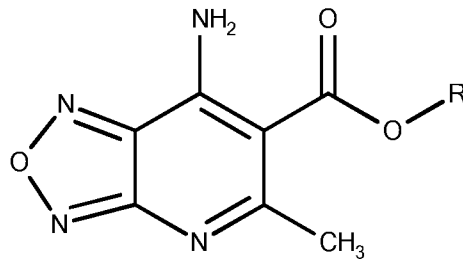
## DETAILED DESCRIPTION OF THE INVENTION

[0008] The present invention provides a process for manufacturing alkyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridine-carboxylate 4

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4,

wherein R is C<sub>1-3</sub>-alkyl, comprising

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(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;

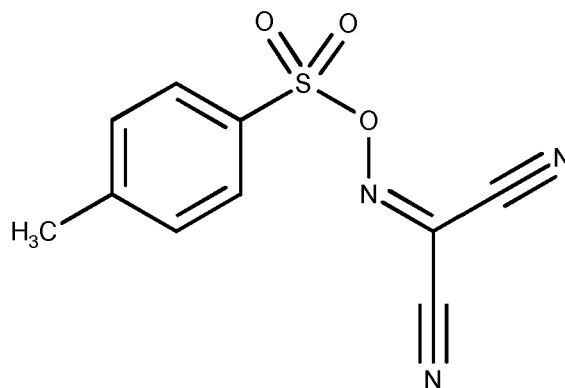
(b) reacting the reaction mixture obtained by step (a) with a suitable toluenesulfonic acid derivative, preferably with p-toluenesulfonyl chloride, to obtain compound 1;

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(c) optionally isolating compound 1;

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

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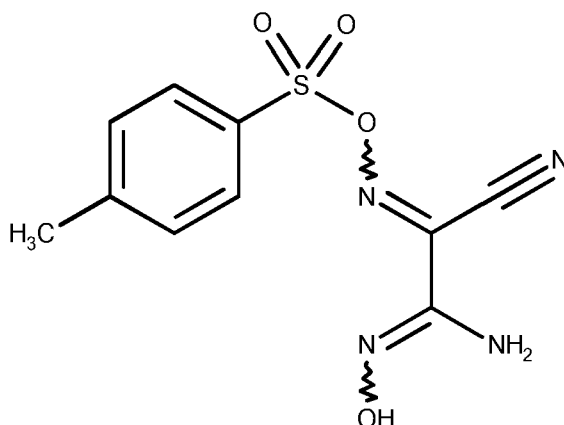
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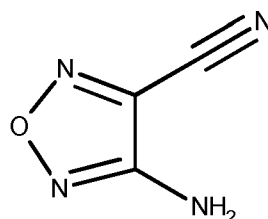
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(e) optionally isolating compound 2;(f) cyclisation of compound 2 in the presence of a base under heating to about 70°C in a suitable solvent to obtain the oxadiazole 3;

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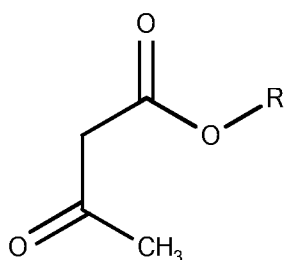
(g) removal of water from the reaction mixture by evaporation under reduced pressure;

(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

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wherein R is C<sub>1-3</sub>-alkyl,

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

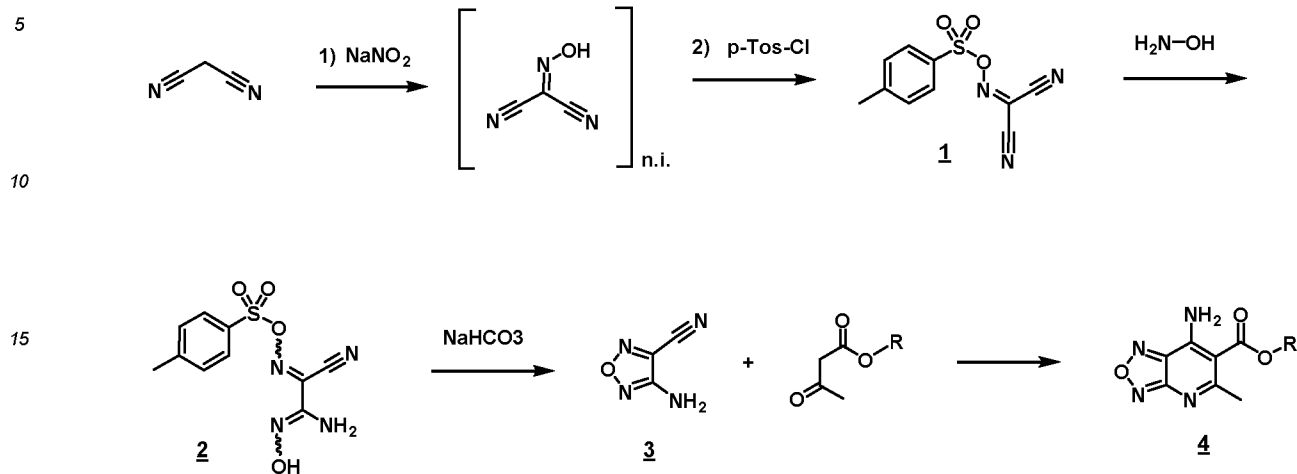
(j) isolating compound 4.

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**[0009]** In the above process, the beta-keto ester is a C<sub>1-3</sub>-alkyl beta-keto ester. Preferably, the ethyl beta-keto ester is used. Correspondingly, in scheme 2 below, R is C<sub>1-3</sub>-alkyl. Preferably, R is ethyl.

**[0010]** The process according to the invention can be used in technical scale.

Scheme 2 (n.i. = not isolated)



[0011] The process according to the present invention overcomes the disadvantages of processes of the prior art by having the distinction of

- 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 high purity with high overall yield.

[0012] 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.
- 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.
- 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.

[0013] 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.

[0014] A suitable solvent for step (a) is water.

[0015] 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.

[0016] Suitable toluenesulfonic acid derivatives useful as reagents for step (b) include p-toluenesulfonic acid anhydride and p-toluenesulfonic acid chloride. Preferably, p-toluenesulfonic acid chloride is used.

[0017] Suitable solvents for step (b) include lipophilic solvents like toluene as well as water, and the mixtures thereof.

[0018] Step (b) is preferably carried out at a temperature of 10 to 30 °C, more preferably at a temperature of about 20 °C.

[0019] In step (c), compound 1 is preferably precipitated via addition of an antisolvent like an alcohol such as 2-propanol, and isolated via filtration.

[0020] Suitable solvents for step (d) include ethers like tetrahydrofuran and alcohols like 2-propanol as well as water, and the mixtures thereof.

[0021] Step (d) is preferably carried out at a temperature of 10 to 30 °C, more preferably at a temperature of 20 to 25 °C.

[0022] In step (e), compound 2 is preferably precipitated via addition of an antisolvent like water and isolated via filtration.

[0023] Suitable bases for step (f) include organic bases like triethylamine or inorganic bases like alkali carbonates and alkali hydrogencarbonates. Examples for suitable carbonates 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.

[0024] Suitable solvents for step (f) include ethers like 1,4-dioxane as well as water, and the mixtures thereof.

[0025] Step (f) is preferably carried out at a temperature of 20 to 100 °C, more preferably at a temperature of 60 to 80 °C.

[0026] The appropriate beta-keto ester for step (i) is selected from the group consisting of a C<sub>1-3</sub>-alkyl beta-keto ester. Preferably, the ethyl beta-keto ester is used.

[0027] Suitable Lewis acids for step (i) include zinc salts like zinc diacetate or zinc dichloride. Preferably, zinc dichloride is used as Lewis acid.

[0028] 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.

[0029] Step (i) is preferably carried out at a temperature of 20 to 100 °C, more preferably at a temperature of 60 to 80 °C.

[0030] In step (j), compound 4 is preferably precipitated via addition of an antisolvent like water and isolated via filtration.

### General Definitions

[0031] 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.

[0032] 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.

[0033] Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers, rotamers and all stereo, 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.

### EXPERIMENTAL SECTION

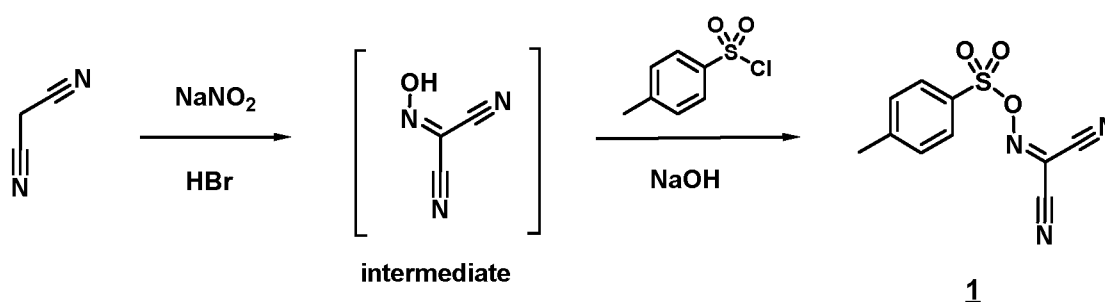
[0034] Note: all intermediates are highly energetic compounds. Special care has to be taken on safety measures.

#### Example 1

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

(Step 1 of the overall synthesis)

[0035]



[0036] 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.

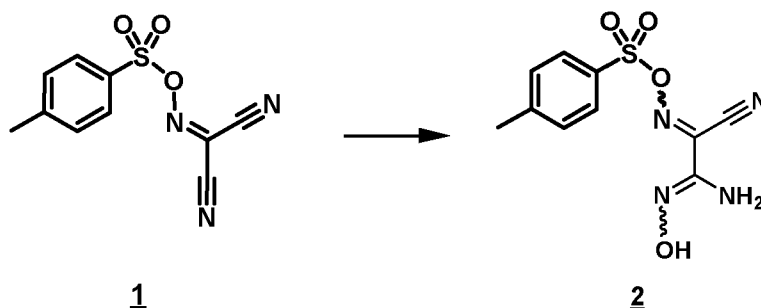
Yield: 23.1 kg (82 % of theory) of **1** as a solid.  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) = 7.91 (d, 2H), 7.45 (d, 2H), 2.51 (s, 3H)

### Example 2

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

(Step 2 of the overall synthesis)

[0037]



[0038] 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.

Yield: 20.36 kg (76.5 % of theory) of **2** as a solid.  
<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ (ppm) = 11.7 (s, 1H), 8.05 (d, 2H), 7.53 (d, 2H), 6.13 (bs, 2H), 2.45 (s, 3H)

### 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)

[0039]



$^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 156.9, 126.0, 108.2

$^{15}\text{N}$  NMR (40 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = -11.9, -334.4

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

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 8.67 (bs, 2H)

$^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 172.9, 147.3, 109.9

$^{15}\text{N}$  NMR (40 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = -191.6, -311.6

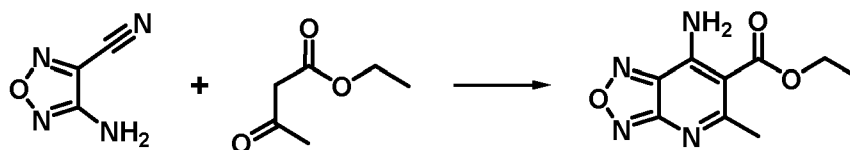
### Example 5

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

(Step 4 of the overall synthesis)

[0044]

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**3**

**4a**

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[0045] 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.

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

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 8.60 (bs, 2H), 4.35 (q, 2H), 2.60 (s, 3H), 1.32 (t, 3H)

## REFERENCES CITED IN THE DESCRIPTION

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

## Patent documents cited in the description

- WO 2018024653 A [0001]
- WO 2019149657 A [0001]
- WO 2019149658 A [0001]
- WO 2019149659 A [0001]
- WO 201844663 A [0006]

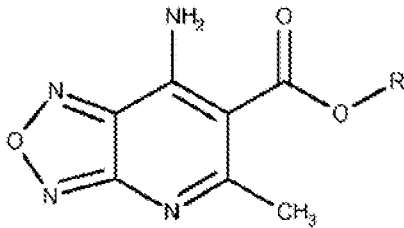
## Non-patent literature cited in the description

- T. ICHIKAWA et al. *J. Heterocycl. Chem*, 1965, vol. 253 [0002]
- *Chem. Heterocycl. Compounds*, 2017, vol. 53, 760 [0003]
- D.S. BOHLE. *J. Org. Chem*, 2000, vol. 65, 1139 [0004]
- A.B. SHEREMETEV, V.A. DOROKHOV. *Mendeleev Communication*, 1994, vol. 4, 57 [0007]
- *Russian Chemical Bulletin, Int. Ed*, 2001, vol. 50, 1280 [0007]

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## P A T E N T K R A V

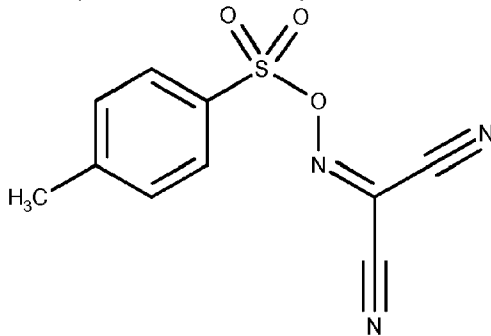
1. Fremgangsmåde til at fremstille alkyl 7-amino-5-methyl-[1,2,5]-oxadiazolo[3,4-b]pyridin-carboxylat **4**

**4**,

5 hvor R er C<sub>1-3</sub>-alkyl,  
omfattende

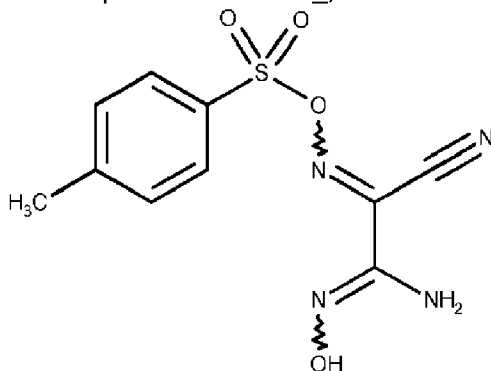
(a) at reagere malononitril med natriumnitrit i tilstedeværelsen af en passende syre i et passende opløsningsmiddel under let overtryk;

10 (b) at reagere reaktionsblandingen opnået i trin (a) med et passende toluensulfonisk syrederivat til at opnå forbindelse **1**;

**1**

(c) eventuel isolere forbindelse **1**;

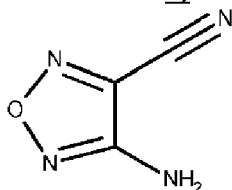
(d) at reagere forbindelse **1** i et passende opløsningsmiddel med hydroxylamin til at opnå forbindelse **2**;

**2**

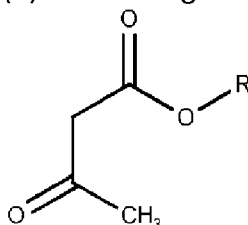
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(e) eventuel isolere forbindelse **2**;

- (f) krystalisering af forbindelse 2 ved tilstedeværelsen af en base under opvarmning til omkring 70° i et passende opløsningsmiddel til at opnå oxadiazolen 3;

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- 5 (g) at fjerne vand fra reaktionsblandingen ved fordampning under reduceret tryk;  
 (h) at fjerne p-toluensulfonisk(e) syresalt(e) ved filtrering;  
 (i) *in situ*-kondensation af forbindelse 3 i reaktionsblandingen opnået efter trin (h) med hensigtsmæssig beta-ketoester ifølge formel



- 10 hvor R er C<sub>1-3</sub>-alkyl, i tilstedeværelsen af en Lewissyre i et passende opløsningsmiddel;  
 og  
 (j) at isolere forbindelsen 4.

- 15 2. Fremgangsmåde ifølge krav 1 kendetegnet ved at isolationstrinnet (c) udført før reaktionsforbindelse 1 i trin (d).

3. Fremgangsmåde ifølge krav 1 eller 2 kendetegnet ved at trin (e) er udført før krystallisationen af forbindelse 2 i trin (f).

- 20 4. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (a), hydroklorisk syre, hydrobromisk syre eller eddikesyre er anvendt som passende syre, og vand er anvendt som opløsningsmiddel.

5. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at trin (a) er udført under et overtryk af op til 0,3 bar ved en temperatur på 0-25°C.

- 25 6. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (a), hydrobromisk syre er anvendt som en passende syre, og vand er anvendt som opløsningsmiddel ved en temperatur på 0-20°C.

7. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (b) det toluensulfoniske syrederivat er toluensulfonisk syreanhydrid eller toluensulfonisk syreklorid og reaktionen er udført ved en temperatur på 10 til 30°C.
8. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (b) toluensulfonisk syrederivat er toluensulfonisk syreklorid, og reaktionen er udført ved en temperatur på omkring 20°C.
9. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (c), forbindelse 1 er udfældet via tilføjelse af et antiopløsningsmiddel og dernæst isoleret via filtration.
10. 10. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (c), forbindelse 1 er udfældet via tilføjelse af en alkohol og dernæst isoleret via filtration.
11. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (c), forbindelse 1 er udfældet via tilføjelse af 2-propanol og dernæst isoleret via filtration.
12. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (d), reaktionen er udført ved en temperatur på 10 til 30°C, ved at bruge ætere, alkoholer, vand og blandinger deraf som opløsningsmiddel.
13. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (d), reaktionen er udført ved en temperatur på 20 til 25°C, ved at bruge tetrahydrofuran, 2-propanol, vand, eller blandinger deraf som opløsningsmiddel.
14. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet i at i trin (e), forbindelse 2 er udfældet via tilføjelse af et antiopløsningsmiddel og derefter isoleret via filtrering.
15. 15. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (e), forbindelse 2 er udfældet via tilføjelse af vand og derefter isoleret via filtrering.
16. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (f), krystallisation er udført i tilstedeværelsen af triethylamin, en alkalikarbonat eller en alkalihydrogenkarbonat ved at anvende ætere, vand, eller en blanding deraf som opløsningsmiddel ved en temperatur på 20 til 100°C.

17. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (f), alkalikarbonaten er valgt fra gruppen bestående af litiumkarbonat, natriumkarbonat og kaliumkarbonat; og alkalihydrogenkarbonaten er valgt fra gruppen bestående af litiumhydrogenkarbonat, natriumhydrogenkarbonat og kaliumhydrogenkarbonat, 5 æteren er 1,4-dioxan; og temperaturen er 60 til 80°C.

18. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (i), *in-situ*-kondensationen er udført i tilstedeværelsen af zinksalt som Lewisyre ved en temperatur på 20 til 100°C, i et opløsningsmiddel valgt fra en æter, en alkohol, vand eller blandinger deraf.

10 19. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (i), *in-situ*-kondensation er udført i tilstedeværelsen af zinkdichlorid som Lewisyre ved en temperatur på 60 til 80°C i 1,4-dioxan som opløsningsmiddel.

15 20. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (j), forbindelse **4** er udfældet via tilføjelse af et antiopløsningsmiddel og derefter isoleret via filtrering.

21. Fremgangsmåde ifølge et hvilket som helst af foregående krav kendetegnet ved at i trin (j), forbindelse **4** er udfældet via tilføjelse af vand og derefter isoleret via filtrering.

22. Fremgangsmåde ifølge et hvilket som helst af foregående krav, hvor R er ethyl.