

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 October 2006 (19.10.2006)

PCT

(10) International Publication Number
WO 2006/108491 A1

(51) International Patent Classification:
C07D 263/32 (2006.01)

(21) International Application Number:
PCT/EP2006/002509

(22) International Filing Date: 18 March 2006 (18.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
A 598/2005 11 April 2005 (11.04.2005) AT

(71) Applicant (for all designated States except US): **DSM FINE CHEMICALS AUSTRIA NFG GMBH & CO KG** [AT/AT]; St.Peter-Strasse 25, A-4021 Linz (AT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HIEBL, Johann** [AT/AT]; Libellenweg 20, A-4030 Linz (AT). **STANEK, Michael** [AT/AT]; Pillweinstrasse 43/3/18, A-4020 Linz (AT). **SCHULTE, Jan, Hilko** [DE/AT]; Franckstr. 26, A-4020 Linz (AT).

(74) Agent: **LINDINGER, Ingrid**; DSM Fine Chemicals Austria Nfg GmbH & Co KG, St-Peter-Strasse 25, A-4021 Linz (AT).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

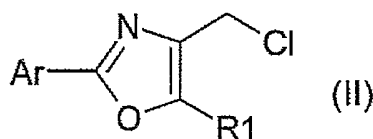
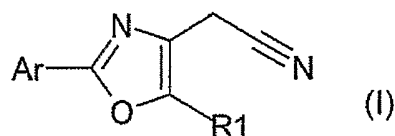
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMPROVED PROCESS FOR PREPARING OXAZOLE NITRILES



(57) Abstract: An improved process for preparing oxazole nitriles of formula (I) in which Ar is aryl or heteroaryl and R1 is H or alkyl, which comprises reacting a corresponding oxazole chloride of formula (II) in which Ar and R1 are as defined above, in a solvent with an alkali metal cyanide in the presence of a phase-transfer catalyst to give the desired oxazole nitrile of formula (I).

Improved process for preparing oxazole nitriles

Oxazole nitriles such as, for instance, 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetonitrile, are valuable intermediates in the synthesis of pharmaceuticals which are employed for example for the prophylaxis and/or treatment of diabetes II.

The use of such oxazole nitriles for preparing active pharmaceutical ingredients is disclosed for example in US 6,673,815. In Example 4 of the US patent, 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetonitrile is obtained in a yield of 37% from the corresponding chloride by reaction with NaCN in DMSO. The chloride is in this case obtained according to Malamas et al., J. Med. Chem. 39 (1), 1996; 237-245, by reacting the corresponding benzaldehyde with 2,3-butanedione monoxime and subsequent deoxygenation with phosphorus oxychloride.

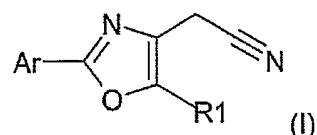
In WO 02/092084 too, the corresponding chloride is reacted with NaCN in DMSO to give the nitrile. Once again, the yield is very low, not exceeding 50%. According to J. Med. Chem. 2001, 44, pp. 2061-2064, the chloride is reacted with KCN in the presence of KI in DMF to give the desired nitrile. The disadvantage in this case is the use of the costly auxiliary reagent KI.

A further possibility for preparing the nitriles is, according to US 6,673,815, reaction of the corresponding alcohol in accordance with the reference Aesa et al., Synth. Commun. 1996, 26(5), 909-914 with acetone cyanohydrin in the presence of triphenylphosphine-diethyl azodicarboxylate.

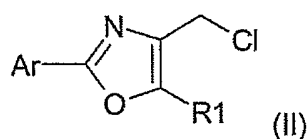
It was an object of the present invention to find an improved process for preparing oxazole nitriles which starts from easily and inexpensively obtainable starting materials, which enables reaction in an efficient and industrially achievable manner and easy

purification of the reaction mixture, which affords the desired oxazole nitrile in higher yields.

The present invention accordingly relates to an improved process for preparing oxazole nitriles of the formula



in which Ar is aryl or heteroaryl and R1 is H or alkyl, which comprises reacting a corresponding oxazole chloride of the formula



in which Ar and R1 are as defined above, in a solvent with an alkali metal cyanide in the presence of a phase-transfer catalyst to give the desired oxazole nitrile of the formula (I).

Oxazole nitriles of the formula (I) are prepared by the process of the invention.

In the formula (I) Ar is aryl or heteroaryl and R1 is H or alkyl.

Aryl and heteroaryl mean in this connection aromatic compounds which preferably have 4 to 20 C atoms. The heteroaryl compounds additionally have 1 to 3 heteroatoms from the group of O, N or S. Possibilities in this connection are monocyclic or polycyclic aromatic groups to which further rings (cycloalkyl, cycloheteroalkyl or heteroaryl) may be fused where appropriate.

Examples of such aromatic compounds are phenyl, naphthyl, cyclopentadienyl, indenyl, fluorenyl, indanyl, tetralinyl, pyrrolyl, furyl, thienyl, pyridyl, pyrimidinyl, indolyl, cumaronyl, quinolinyl, chromenyl, chromanyl, etc.

Preferably aryl means phenyl or naphthyl and heteroaryl pyridyl.

The aryl and heteroaryl radicals may moreover be optionally substituted one or more times. Examples of suitable substituents are alkyl, preferably C₁-C₆-alkyl, alkoxy, preferably C₁-C₆-alkoxy, halogen such as, for instance, chlorine, bromine or fluorine, mono- or polyhaloalkyl, mono- or polyhaloalkoxy, alkenyl, preferably C₂-C₈-alkenyl, optionally substituted phenyl, optionally substituted amine, hydroxy, nitro, carboxyl, carboxylic ester, etc.

The aryl or heteroaryl radical is preferably unsubstituted or substituted once or twice by hydroxy, C₁-C₄-alkyl, C₁-C₄-alkoxy, chlorine, trifluoromethyl or phenyl.

R₁ is H or alkyl, where alkyl means saturated or mono- or polyunsaturated, linear, branched or cyclic hydrocarbon chains having 1 to 20 C atoms, preferably having 1 to 8 C atoms. Examples thereof are methyl, ethyl, i-propyl, tert-butyl, cyclohexyl, propenyl, etc.

The inventive preparation of the oxazole nitriles of the formula (I) starts from the corresponding oxazole chloride of the formula (II).

Ar and R₁ in formula (II) are as defined above.

Suitable oxazole chlorides can be prepared as in the prior art as described, for instance, in Chem. Pharm. Bull., 1971, 19, pp. 2050; J. Med. Chem., 1996, 39, pp. 237-245; J. Med. Chem., 2000, 43, p. 995-1010, US 5468760, US 5480896, WO 03/043985, etc.

It is particularly advantageous to purify the oxazole chloride, after the reaction of the corresponding

oxazole N-oxide with POCl_3 as in the prior art, by extraction with water and, where appropriate, recrystallization in methanol or a methanol/water mixture, because the purity of the product can be
5 increased considerably thereby in an efficient and industrially achievable manner.

The inventive reaction of the oxazole chlorides of the formula (II) to give the desired oxazole nitriles of
10 the formula (I) takes place in a suitable solvent with an alkali metal cyanide in the presence of a phase-transfer catalyst.

Suitable solvents for the inventive process are
15 aromatic hydrocarbons, which may be optionally halogenated, such as, for instance, toluene, xylenes, chlorobenzenes, etc., or mixtures thereof with water. A mixture of toluene and water is preferably employed as solvent.

20 Suitable examples of alkali metal cyanide are NaCN , LiCN , KCN , etc.

The cyanide is in this case employed in at least the equivalent amount or in an excess relative to the
25 oxazole chloride.

The cyanide is preferably used in an amount of from 1.0 to 2.5 mol per mol of oxazole chloride and particularly preferably from 1.1 to 1.5 mol per mol of oxazole
chloride.

30 Suitable phase-transfer catalysts are quaternary phosphonium salts such as, for instance, $(\text{alkyl})_4\text{P}^+\text{Hal}^-$, $(\text{aryl})_4\text{P}^+\text{Hal}^-$, $\text{alkylaryl-P}^+\text{Hal}^-$, etc. or quaternary ammonium salts such as, for instance,
35 tetraalkylammonium halides, tetraarylammonium halides, alkylarylammonium halides or cyanides, etc., which are described for example in C.M. Starks, C.L. Liotta, M.C. Halpern, Phase Transfer Catalysis; Chapman & Hall; New York, 1994.

Halide means in this case preferably bromide or chloride. The tetraalkyl moiety consists of four alkyl groups, which may be identical or different, and comprise 1 to 16 C atoms. The aryl moiety may be for example phenyl or benzyl.

Quaternary ammonium salts are preferably employed.

Examples of suitable phase-transfer catalysts are tetrabutylammonium bromide (TBAB), tributylmethylammonium chloride (TBMAC), trimethylbenzylammonium chloride, etc.

The phase-transfer catalyst is employed in the inventive reaction in an amount of from 0.001 to 0.1 mol per mol of oxazole chloride. An amount of from 0.01 to 0.05 mol per mol of oxazole chloride is preferred.

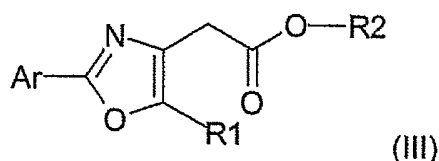
The reaction temperature is 50 to 120°C, preferably 75 to 90°C.

To carry out the process, preferably all the reagents (oxazole chloride, solvent, cyanide, phase-transfer catalyst) are introduced simultaneously and then heated to the desired temperature, preferably while stirring. Alternatively, the cyanide can also be added last, at the desired reaction temperature. After the reaction is complete, the reaction mixture is cooled to a temperature of from 5 to 30°C, preferably to 15 to 25°C, and an aqueous base such as, for instance, a dilute Na₂CO₃ or NaHCO₃ solution is added and, after phase separation, the organic phase is, where appropriate after extraction one or more times with the aqueous base, concentrated. The remaining residue is recrystallized where appropriate in a suitable solvent. Examples of suitable solvents for this are diisopropyl ether, tert-butyl methyl ether, methanol, etc.

Oxazole nitriles of the formula (I) are prepared in higher yields compared with the prior art, and in high

purity, from easily obtainable precursors in a simple manner which is easy to achieve industrially.

The oxazole nitriles of the formula (I) which are prepared according to the invention are moreover outstandingly suitable for further reaction to give the corresponding oxazole carboxylic esters of the formula



10

in which Ar is aryl or heteroaryl, R1 is H or alkyl and R2 is alkyl or aryl, for example by converting the appropriate oxazole nitrile into the desired oxazole carboxylic esters in the presence of a mineral acid and of an alcohol of the formula R2OH and subsequent hydrolysis with water.

15

Example 1: Preparation of 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetonitrile

20

a) Preparation of the oxazole chloride

1465 g (13.8 mol) of benzaldehyde, 1244 g (12.3 mol) of 2,3-butanedione monoxime and 4.8 l of conc. acetic acid were mixed and this mixture was cooled to 4°C while stirring. Then, over the course of 100 min, 1500 g (41.1 mol) of HCl gas were passed in at an internal temperature of 4-12°C. The reaction mixture was stirred at the same temperature for 1 h and then, at 10-20°C, 21 l of t-butyl methyl ether (MTBE) were added over the course of 45 min. The MTBE addition was initially exothermic. The mixture was then stirred at 5°C for a further 30 min and subsequently the resulting solid was filtered off. The solid was washed with MTBE and dried in vacuo at 50°C.

35

Yield: 2498 g of oxazole N-oxide (11.07 mol, 90%).

2220 g of oxazole N-oxide were suspended in 19.9 l of methylene chloride, and this mixture was cooled to 5°C. Then, over the course of 15 min, 2837 g (18.5 mol) of POCl₃ were added at an internal temperature of 5-7°C. Stirring at 5-7°C for 30 min was followed by slow warming to 40°C and stirring at this temperature for 3 h. After cooling to 5°C, 34.7 l of water were added over the course of 2 h. The phases were separated and the organic phase was extracted with 17.3 l of water. The organic phase was concentrated in vacuo, and the residue was recrystallized from methanol/water (14.4 l/14.4 l) and washed with 10 l of water. Filtration and drying resulted in 1940 g (9.35 mol, 95%) of the oxazole chloride.

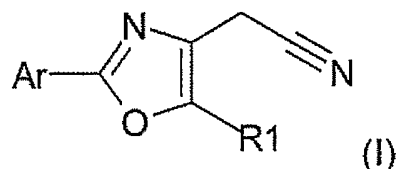
b) Reaction of the oxazole chloride

1634 g (7.87 mol) of oxazole chloride, 463 g (9.44 mol) of NaCN, 28 g (0.119 mol) of tributylmethyammonium chloride, 4.9 l of toluene and 0.24 l of H₂O were introduced into the reactor, and this mixture was heated at 80-85°C while stirring vigorously for 6 h. After the reaction mixture had cooled to 20°C, dilute aqueous Na₂CO₃ solution was added and, after phase separation, the organic phase was extracted twice with dilute aqueous Na₂CO₃ solution. The residue after concentration of the organic phase in vacuo was dissolved in diisopropyl ether, filtered through activated carbon and crystallized. 1435 g (7.24 mol, 92%) of the oxazole nitrile were obtained.

Claims:

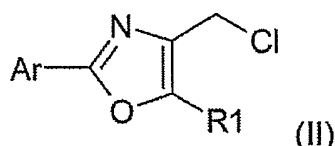
1. An improved process for preparing oxazole nitriles of the formula

5



in which Ar is aryl or heteroaryl and R1 is H or alkyl, which comprises reacting a corresponding oxazole chloride of the formula

10



in which Ar and R1 are as defined above, in a solvent with an alkali metal cyanide in the presence of a phase-transfer catalyst to give the desired oxazole nitrile of the formula (I).

15

2. The process as claimed in claim 1, wherein the reaction takes place in a solvent from the group of optionally halogenated aromatic hydrocarbons or in a mixture thereof with water.

20

3. The process as claimed in either of claims 1 or 2, wherein the cyanide is employed in an amount of from 1.0 to 2.5 mol per mol of oxazole chloride.

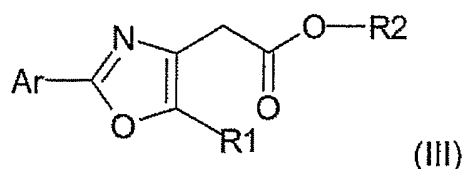
25

4. The process as claimed in any of claims 1 to 3, wherein a quaternary phosphonium salt or a quaternary ammonium salt is employed as phase-transfer catalyst.

30

5. The process as claimed in any of claims 1 to 4, wherein the phase-transfer catalyst is employed in an amount of from 0.001 to 0.1 mol per mol of oxazole chloride.
- 5 6. The process as claimed in any of claims 1 to 5, wherein the reaction is carried out at from 50 to 120°C.
- 10 7. The process as claimed in any of claims 1 to 6, wherein the oxazole nitrile of the formula (I) is isolated by adding, after the reaction has taken place, an aqueous base to the reaction mixture, after which a phase separation takes place, the
15 organic phase is, where appropriate after extraction with the aqueous base, concentrated, and the remaining residue is recrystallized where appropriate.
- 20 8. The process as claimed in any of claims 1 to 7, wherein the chloride of the formula (II) employed is prepared by reacting the corresponding oxazole N-oxide with POCl₃, extracting with water and, where appropriate, subsequently recrystallizing in
25 methanol or a methanol/water mixture.
9. The use of oxazole nitriles of the formula (I) prepared as claimed in any of claims 1 to 8 for preparing oxazole carboxylic esters of the formula

30



in which Ar is aryl or heteroaryl, R1 is H or alkyl and R2 is alkyl or aryl.

35

10. The use as claimed in claim 9, wherein an appropriate oxazole nitrile of the formula (I) is converted into the desired oxazole carboxylic ester of the formula (II) in the presence of a mineral acid and of an alcohol of the formula R₂OH and subsequent hydrolysis with water.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/002509

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D263/32

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

B. FIELDS SEARCHEDMinimum 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 practical, search terms used)

EPO-Internal, 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	BROOKS D A ET AL: "Design and synthesis of 2-methyl-2-{4-[2-(5-methyl-2-aryloxazol-4-yl)ethoxy]phenoxy}propionic acids: a new class of dual PPARalpha/gamma agonists" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 13, 21 June 2001 (2001-06-21), pages 2061-2064, XP002184099 ISSN: 0022-2623 cited in the application Scheme 1 ----- -/-	1-8

☒ 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 document 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

14 June 2006

Date of mailing of the international search report

21.08.06

Name and mailing address of the ISA/

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

Authorized officer

Gavrilu, D

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/002509

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/18355 A (ELI LILLY AND COMPANY; BROOKS, DAWN, ALISA; CONNOR, SCOTT, EUGENE; DOM) 7 March 2002 (2002-03-07) page 80 - page 81 page 42, line 3 - page 43, line 10 -----	1-8
A	US 2003/055265 A1 (BINGGELI ALFRED ET AL) 20 March 2003 (2003-03-20) cited in the application example 21 -----	1-8
A	US 4 661 610 A (MUELLER ET AL) 28 April 1987 (1987-04-28) the whole document -----	1-8
A	GB 1 139 940 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 15 January 1969 (1969-01-15) the whole document -----	1-8 9,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/002509

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8

Processes for preparation of compounds of formula (I) from compounds of formula (II) in the presence of a phase-transfer catalyst.

2. claims: 9-10

Process for preparing a compound of formula (III), using as starting material a compound of formula (I)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/002509

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0218355	A	07-03-2002	AU 8465801 A	13-03-2002
			CA 2420178 A1	07-03-2002
			EP 1313715 A1	28-05-2003
			JP 2004509084 T	25-03-2004

US 2003055265	A1	20-03-2003	AT 327753 T	15-06-2006
			BG 108362 A	31-03-2005
			BR 0209821 A	01-06-2004
			CA 2445145 A1	21-11-2002
			CN 1509173 A	30-06-2004
			CZ 20033037 A3	16-06-2004
			WO 02092084 A1	21-11-2002
			HR 20030889 A2	31-08-2005
			HU 0400992 A2	30-08-2004
			JP 2004529174 T	24-09-2004
			MA 27025 A1	20-12-2004
			MX PA03010435 A	09-03-2004
			NO 20035086 A	14-11-2003
			NZ 529033 A	24-06-2005
			PL 367087 A1	21-02-2005
			RU 2278859 C2	27-06-2006
			SK 13852003 A3	05-10-2004
			ZA 200308538 A	31-01-2005

US 4661610	A	28-04-1987	DE 3527338 A1	05-02-1987
			EP 0211271 A1	25-02-1987

GB 1139940	A	15-01-1969	NONE	
