(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 March 2022 (17.03.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/053317 A1

(51) International Patent Classification:
C07D 263/34 (2006.01)

(21) International Application Number:
PCT/EP2021/073489

(22) International Filing Date:
25 August 2021 (25.08.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CN2020/114732
11 September 2020 (11.09.2020) CN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

WO 2022/053317 A1

(54) Title: A PROCESS FOR PRODUCING OXAZOLE COMPOUNDS

(57) Abstract: The present invention provides a process for producing oxazole compounds by direct cyclodehydration of acyloxy enamines in the presence of anhydride. According to the present invention, the oxazole compounds can be produced in a higher yield compared to prior arts.

A process for producing oxazole compounds

Technical Field

The present invention is related to a new process for producing oxazole compounds.

Background of the Invention

Oxazole compounds represent a vast class of heterocyclic aromatic organic compounds. Oxazole compounds have become increasingly important because of biological activities and their use as intermediates for the preparation of new biological materials. The wide range of biological activities of oxazole compounds includes anti-inflammatory, analgesic, antibacterial, antifungal, hypoglycemic, antiproliferative, anti-tuberculosis, muscle relaxant and HIV inhibitor activity. In addition, oxazole derivatives are important intermediates for preparation of biological compounds such as vitamin B6.

Various processes for preparation of oxazole compounds have been developed. One attractive process is direct cyclodehydration of acyloxy enamines because acyloxy enamines have been introduced early N-atom and installed the carboxylic acids. (see Xin Liu et al., Org. Lett., Vol. 14, No. 21, 2012)

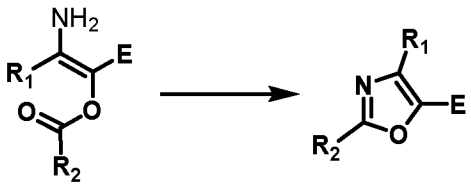
The inventor surprisingly discovered that oxazole compounds can be produced in a significantly improved yield when the direct cyclodehydration of acyloxy enamines is carried out in the presence of an anhydride.

Summary of the Invention

Therefore, the present invention provides a process for producing oxazole compounds by direct cyclodehydration of acyloxy enamines in the presence of an anhydride. According to the present invention, the oxazole compounds can be produced in a higher yield compared to prior arts.

Detailed Description of the Invention

Particularly, the present invention provides a process for producing a compound of formula (I), comprising treating a compound of formula (II) with an acid in the presence of an anhydride to obtain the compound of formula (I),



(II) (I)

wherein:

R_1 is H, or lower alkyl or aryl optionally substituted by one or more substituents;

R_2 is H, or lower alkyl or aryl optionally substituted by one or more substituents, or C(=O)R'; and

E is C≡N or C(=O)R', and

R' is H, lower alkyl, aryl or lower alkoxyl.

In the present invention, the term "lower alkyl" as used refers to C_1-C_{10} alkyl, i.e., branched or unbranched, cyclic or non-cyclic, saturated hydrocarbon comprising 1-10 carbon atoms. Preferably, the "lower alkyl" is C_1-C_6 alkyl, including but not limited to methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, cyclobutyl, pentyl, iso-pentyl, tert-pentyl, cyclopentyl, hexyl, isohexyl, tert-hexyl, cyclohexyl, octyl, isooctyl, tert-octyl, cyclooctyl, nonyl, isononyl, tert-nonyl, cyclononyl, decyl, isodecyl, tert-decyl, cyclodecyl. More preferably, the "lower alkyl" is methyl or ethyl.

In the present invention, the term "aryl" as used refers to aromatic hydrocarbon such as phenyl, benzyl, xylyl and naphthalenyl.

In the present invention, the term "lower alkoxyl" as used refers to the structure represented by (lower alkyl)-O-, wherein the lower alkyl is as defined above.

In the present invention, the term "substituent" or "substituents" as used refers to lower alkyl, lower alkoxyl, hydroxyl, halo, $-NH_2$, $-NO_2$, cyano and/or isocyano.

In the present invention, the term “halo” or “halogen” as used refers to a group of elements including fluorine (F), chlorine (Cl), bromine (Br) and iodine (I), preferably refers to Cl or Br.

In the present invention, R_1 is preferably H, or lower alkyl or phenyl optionally substituted by one or more substituents. More preferably, R_1 is H or C_1-C_6 alkyl or phenyl optionally substituted by one or more substituents. Further preferably, R_1 is H or methyl or ethyl or phenyl optionally substituted by one or more substituents. The most preferably, R_1 is H or CH_3.

In the present invention, R_2 is preferably H, or lower alkyl or phenyl optionally substituted by one or more substituents, or C(=O)R’ wherein R’ is H or lower alkoxyl. More preferably, R_2 is H or C_1-C_6 alkyl or phenyl optionally substituted by one or more substituents, or C(=O)R’ wherein R’ is H or lower alkoxyl. Further preferably, R_2 is H or methyl or ethyl or phenyl optionally substituted by one or more substituents, or C(=O)R’ wherein R’ is H or methoxy or ethoxy. The most preferably, R_2 is H, methyl, ethyl, phenyl, -C(O)OH, -C(O)OCH_3 or C(O)OCH_2CH_3.

In the present invention, E is preferably C≡N or C(=O)R’ wherein R’ is lower alkoxyl such as methoxy and ethoxy.

In one embodiment of the present invention, R_1 is methyl and R_2 is H or methyl or phenyl or COOH.

In one embodiment of the present invention, R_1 is methyl; R_2 is H or methyl or phenyl or COOH; and E is C≡N. In another embodiment, R_1 is methyl; R_2 is H or methyl or phenyl or COOH; and E is C(=O)R’ wherein R’ is lower alkoxyl such as methoxy and ethoxy.

In the present invention, the acid may be any protic acid including organic acids and inorganic acids capable of donating a proton (hydrogen ion H^+), or any Lewis acid, or mixture thereof. Example of the organic acids includes but is not limited to formic acid, acetic acid, glycolic acid,

propanoic acid, 3-hydroxypropanic acid, butanoic acid, succinic acid, pentatonic acid, trimethylacetic acid, methanesulfonic acid (MSA), trifloroacetic acid (TFA), p-toluenesulfonic acid (*p*-TSA), ascorbic acid and citric acid. Example of the inorganic acids includes but is not limited to hydrochloric acid, sulfuric acid and nitric acid. Example of the Lewis acid includes but is not limited to $Cu(OTf)_2$, $In(OTf)_3$, $Bi(OTf)_3$, AgOTf, $Zn(OTf)_2$, $BF_3{\cdot}Et_2O$, $InCl_3$ and mixture thereof. Preferably, the acid is formic acid.

In the present invention, the acid may be added into the reaction in a catalytic amount. Preferably, the acid is added in an amount of from 0.01 moles to 30 moles, more preferably from 0.05 moles to 25 moles, further preferably from 0.08 mole to 20 moles, the most preferably from 0.1 moles to 18 moles such as 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0 and 18.0 moles, per 1 mole of the compound of formula (II).

In the present invention, the anhydride may be acetic anhydride, propionic anhydride or *o*-phthalic anhydride. It may be added into the reaction in an amount of from 0.01 moles to 10 moles, preferably from 0.05 moles to 5 moles, more preferably from 0.1 mole to 1 moles such as 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1 mole, per 1 mole of the compound of formula (II).

Preferably, the reaction of the present invention is carried out in a solvent. The suitable solvent may be any aprotic solvent suitable for the reaction. Example of the aprotic solvent includes but is not limited to tetrahydrofuran (THF), ethyl acetate, acetone, dimethylformamide (DMF), acetonitrile, dimethyl sulfoxide (DMSO), dichloromethane (DCM), dimethyl carbonate, butyl acetate, methyl tert-butyl ether (MTBE), nitromethane, and nitroethane; and cyclic carbonates such as ethylene carbonate (EC), propylene carbonate (PC), and butylene carbonate (BC), and mixture thereof. Preferably, the solvent is DCM or PC. The solvent may be added in an amount of from 0.1 L to 20 L, preferably from 0.5 L to 15 L, more preferably from 1.0 L to 10 L such as 1.0, 1,5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9, 9.0, 9.5 and 10 L, per 1 mole of the compound of formula (II).

The compound of the formula (II) may be synthesized by known process in the art, e.g., as disclosed *Org. Lett.* **2018**, *20*, 1256−1260; *Org. Lett.* **2012**, *14*, 5480-5483.

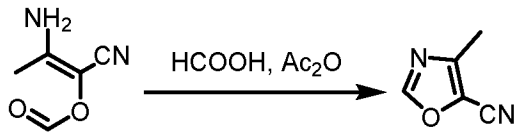
The reaction of the present invention may be carried out at the temperature from 20°C to 120°C, preferably from 50°C to 100°C, more preferably from 80°C to 90°C. The obtained compound of formula (I) may be easily isolated and purified by any known process, such as distillation, rectification and column chromatography.

According to the present invention, the oxazole compounds of formula (I) can be produced in an efficient way with high yield. In addition, the present invention can significantly reduce the used amount of acids in the reaction and thus reduce salt by-products which is difficult to isolate and impact quality of the final product.

The present invention and the advantage will be further illustrated by the following examples.

Examples

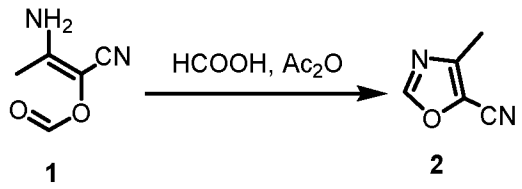
Example 1



1 **2**

Into a 20 mL round-bottomed flask, 2-amino-1-cyanopropenyl formate **1** (416 mg, purity 90%) was added in one portion to the solution of formic acid (2 mL) and acetic anhydride (1 mL) in propylene carbonate (5 ml) at 90°C. The reaction mixture was stirred at the same temperature for 30 mins and then cooled down to room temperature. The compound **2** was obtained and quantitative NMR indicated the yield was 91%.

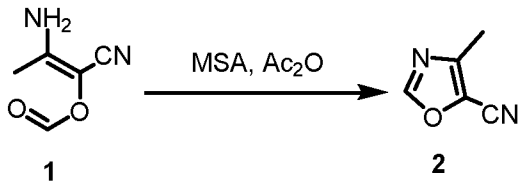
Example 2



1 2

Into a 20 mL round-bottomed flask, the solution of 2-amino-1-cyanopropenyl formate **1** (416 mg, purity 90%) in dichloromethane (5 ml) was added to the mixture of formic acid (2 mL) and acetic anhydride (1 mL) at room temperature. The reaction mixture was stirred overnight at the same temperature. The compound **2** was obtained and quantitative NMR indicated the yield was 57%.

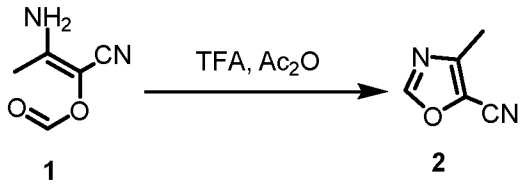
Example 3



1 2

Into a 20 mL round-bottomed flask, 2-amino-1-cyanopropenyl formate **1** (416 mg, purity 90%) was added in one portion to the solution of methanesulfonic acid (MSA) (100 ul) and acetic anhydride (200 ul) in propylene carbonate (5 ml) at 90°C. The reaction mixture was stirred at the same temperature for 30 mins and then cooled down to room temperature. The compound **2** was obtained and quantitative NMR indicated the yield was 69%.

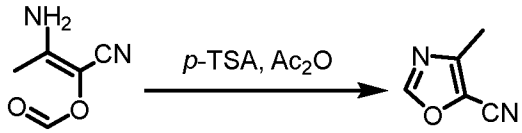
Example 4



1 2

Into a 20 mL round-bottomed flask, 2-amino-1-cyanopropenyl formate **1** (416 mg, purity 90%) was added in one portion to the solution of trifloroacetic acid (TFA) (2 ml) and acetic anhydride (200 ul) in propylene carbonate (5 ml) at 90°C. The reaction mixture was stirred at the same temperature for 30 mins and then cooled down to room temperature. The compound **2** was obtained and quantitative NMR indicated the yield was 35%.

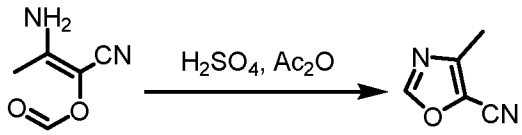
Example 5



1 2

Into a 20 mL round-bottomed flask, 2-amino-1-cyanopropenyl formate **1** (416 mg, purity 90%) was added in one portion to the solution of *p*-toluenesulfonic acid monohydrate (*p*-TSA) (50 mg) and acetic anhydride (400 ul) in propylene carbonate (5 ml) at 90°C. The reaction mixture was stirred at the same temperature for 30 mins and then cooled down to room temperature. The compound **2** was obtained and quantitative NMR indicated the yield was 56%.

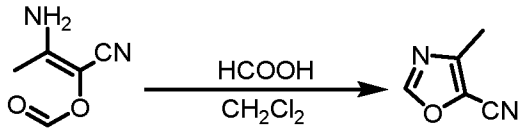
Example 6



1 2

Into a 20 mL round-bottomed flask, 2-amino-1-cyanopropenyl formate **1** (416 mg, purity 90%) was added in one portion to the solution of sulfuric acid (50 ul) and acetic anhydride (100 ul) in propylene carbonate (5 ml) at 90°C. The reaction mixture was stirred at the same temperature for 30 mins and then cooled down to room temperature. The compound **2** was obtained and quantitative NMR indicated the yield was 46%.

Comparative Example 1

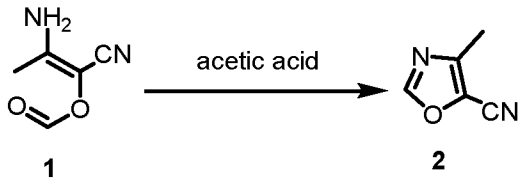


1 2

Into a 20 mL round-bottomed flask, 2-amino-1-cyanopropenyl formate **1** (138mg, purity 90%) and formic acid (2 ml) were dissolved in dichloromethane (5 ml) at room temperature. The

reaction mixture was stirred at the same temperature for 3 hours to obtain the compound **2**. Quantitative NMR indicated the yield is 15%.

Comparative Example 2

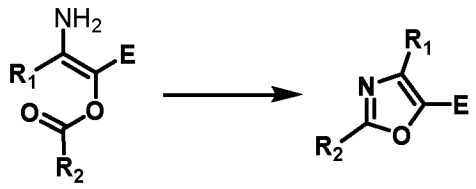


1 **2**

Into a 20 mL round-bottomed flask, the solution of 2-amino-1-cyanopropenyl formate **1** (138 mg, purity 90%) in propylene carbonate (5 ml) was added dropwise to the mixture of acetic acid (2 ml) at 110°C. The reaction mixture was stirred at the same temperature for 2 hours and then cooled down to room temperature. The compound **2** was obtained and quantitative NMR indicated the yield was 39%.

Claims

1. A process for producing a compound of formula (I), comprising treating a compound of formula (II) with an acid in the presence of an anhydride to obtain the compound of formula (I),



(II) (I)

wherein:

R_1 is H, or lower alkyl or aryl optionally substituted by one or more substituents;

R_2 is H, or lower alkyl or aryl optionally substituted by one or more substituents, or C(=O)R'; and

E is C≡N or C(=O)R', and

R' is H, lower alkyl, aryl or lower alkoxyl.

2. The process of Claim 1, wherein R_1 is H, or lower alkyl or phenyl optionally substituted by one or more substituents; preferably, R_1 is H or C_1-C_6 alkyl or phenyl optionally substituted by one or more substituents; more preferably, R_1 is H or methyl or ethyl or phenyl optionally substituted by one or more substituents; and the most preferably, R_1 is H or CH_3.

3. The process of Claim 1, wherein R_2 is H, or lower alkyl or phenyl optionally substituted by one or more substituents, or C(=O)R' wherein R' is H or lower alkoxyl; preferably, R_2 is H or C_1-C_6 alkyl or phenyl optionally substituted by one or more substituents, or C(=O)R' wherein R' is H or lower alkoxyl; more preferably, R_2 is H or methyl or ethyl or phenyl optionally substituted by one or more substituents, or C(=O)R' wherein R' is H or methoxy or ethoxy; and the most preferably, R_2 is H, methyl, ethyl, phenyl, -C(O)OH, -C(O)OCH_3 or C(O)OCH_2CH_3.

4. The process of Claim 1, wherein E is C≡N or C(=O)R' wherein R' is lower alkoxyl such as methoxy and ethoxy.

5. The process of Claim 1, wherein R_1 is methyl and R_2 is H or methyl or phenyl or COOH.

6. The process of Claim 1, wherein R_1 is methyl, R_2 is H or methyl or phenyl or COOH, and E is C≡N; or R_1 is methyl, R_2 is H or methyl or phenyl or COOH, and E is C(=O)R' wherein R' is lower alkoxyl such as methoxy and ethoxy.

7. The process of any one of Claims 1-6, wherein the acid is a protic acid including organic acid and inorganic acid, or any Lewis acid, or mixture thereof.

8. The process of Claim 7, wherein the organic acid is selected from the group consisting of formic acid, acetic acid, glycolic acid, propanoic acid, 3-hydroxypropanic acid, butanoic acid, succinic acid, pentatonic acid, trimethylacetic acid, methanesulfonic acid (MSA), trifloroacetic acid (TFA), p-toluenesulfonic acid (*p*-TSA), ascorbic acid, citric acid and mixture thereof.

9. The process of Claim 7, wherein the inorganic acids is selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid and mixture thereof.

10. The process of Claim 7, wherein the Lewis acid is selected from the group consisting of $Cu(OTf)_2$, $In(OTf)_3$, $Bi(OTf)_3$, AgOTf, $Zn(OTf)_2$, $BF_3{\cdot}Et_2O$, $InCl_3$ and mixture thereof.

11. The process of any one of Claims 1-7, wherein the acid is added in an amount of from 0.01 moles to 30 moles, more preferably from 0.05 moles to 25 moles, further preferably from 0.08 mole to 20 moles, the most preferably from 0.1 moles to 18 moles such as 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0 and 18.0 moles, per 1 mole of the compound of formula (II).

12. The process of any one of Claims 1-11, wherein the anhydride is acetic anhydride, propionic anhydride or *o*-phthalic anhydride.

13. The process of any one of Claims 1-12, wherein the reaction of the present invention is carried out in a solvent.

14. The process of Claim 13, wherein the solvent is an aprotic solvent。

15. The process of Claim 13, wherein the solvent is selected from a group consisting of tetrahydrofuran (THF), ethyl acetate, acetone, dimethylformamide (DMF), acetonitrile, dimethyl sulfoxide (DMSO), dichloromethane (DCM), dimethyl carbonate, butyl acetate, methyl tert-butyl ether (MTBE), nitromethane, and nitroethane; and cyclic carbonates such as ethylene carbonate (EC), propylene carbonate (PC), and butylene carbonate (BC), and mixture thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/073489

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D263/34
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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LIU XIN ET AL: "Direct ?-Acyloxylation of Enamines via PhIO-Mediated Intermolecular Oxidative C?O Bond Formation and Its Application to the Synthesis of Oxazoles", ORGANIC LETTERS, vol. 14, no. 21, 2 November 2012 (2012-11-02), pages 5480-5483, XP055837609, US ISSN: 1523-7060, DOI: 10.1021/ol3025583 Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/ol3025583> table 3-page 5483	1-15

Y	CN 103 880 766 B (XINFA PHARMACEUTICAL CO LTD) 13 January 2016 (2016-01-13) paragraph [0029] - paragraph [0031]	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2021	18/11/2021

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, Fax: (+31-70) 340-3016	Gavriliu, Daniela

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ARNOLD R MARTIN ET AL: "Heterocyclic Ring-Closure Reactions. I. A Novel Oxazole Synthesis from S.S'-Dialkyl or -Diaryl Dithiooxaldiimidates and Aromatic Aldehydes", THE JOURNAL OF ORGANIC CHEMISTRY,, vol. 31, no. 11, 1 November 1966 (1966-11-01), pages 3612-3615, XP055511549, the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/073489

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 103880766 B	13-01-2016	NONE	