



(86) Date de dépôt PCT/PCT Filing Date: 2004/12/22
(87) Date publication PCT/PCT Publication Date: 2005/07/14
(45) Date de délivrance/Issue Date: 2012/04/10
(85) Entrée phase nationale/National Entry: 2006/06/20
(86) N° demande PCT/PCT Application No.: EP 2004/014596
(87) N° publication PCT/PCT Publication No.: 2005/063753
(30) Priorités/Priorities: 2003/12/23 (US60/531,613);
2003/12/23 (EP03029728.7)

(51) Cl.Int./Int.Cl. *C07D 487/04* (2006.01),
A01N 43/90 (2006.01)
(72) Inventeur/Inventor:
GEBHARDT, JOACHIM, DE
(73) Propriétaire/Owner:
DOW AGROSCIENCES LLC, US
(74) Agent: SMART & BIGGAR

(54) Titre : PROCEDE DE PREPARATION DE TRIAZOLOPYRIMIDINES
(54) Title: PROCESS FOR THE PREPARATION OF TRIAZOLOPYRIMIDINES

(57) **Abrégé/Abstract:**

Process for the preparation of unsubstituted or substituted 2-amino-[1,2,4]triazolopyrimidines which comprises combining A) 2-amino-pyrimidine or its derivatives with alkyloxycarbonyl isothiocyanate or aryloxycarbonyl isothiocyanate with B) hydroxyl ammonium salt and a base wherein the reaction is carried out in a polar aprotic organic solvent in the temperature range of from 40 to 150 °C.



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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
14 July 2005 (14.07.2005)

PCT

(10) International Publication Number
WO 2005/063753 A1

(51) International Patent Classification⁷: **C07D 487/04**,
A01N 43/90

(21) International Application Number:
PCT/EP2004/014596

(22) International Filing Date:
22 December 2004 (22.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03029728.7 23 December 2003 (23.12.2003) EP
60/531,613 23 December 2003 (23.12.2003) US

(71) Applicant (for all designated States except US): **BASF AKTIENGESELLSCHAFT** [DE/DE]; 67056 Ludwigshafen (DE).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **GEBHARDT, Joachim** [DE/DE]; Pegauer Str. 51, 67157 Wachenheim (DE).

(74) Common Representative: **BASF AKTIENGESELLSCHAFT**; 67056 Ludwigshafen (DE).

(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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, 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, 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

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: PROCESS FOR THE PREPARATION OF TRIAZOLOPYRIMIDINES

(57) Abstract: Process for the preparation of unsubstituted or substituted 2-amino-[1,2,4]triazolopyrimidines which comprises combining A) 2-amino-pyrimidine or its derivatives with alkylloxycarbonyl isothiocyanate or aryloxycarbonyl isothiocyanate with B) hydroxyl ammonium salt and a base wherein the reaction is carried out in a polar aprotic organic solvent in the temperature range of from 40 to 150 °C.



73776-229

Process for the preparation of triazolopyrimidines

Description

Triazolopyrimidine derivatives are valuable building blocks in pharmaceutical or agrochemical synthesis, e.g. fungicide, insecticide, or herbicide synthesis.

- 5 WO 02/36595 A2 (Dow Agrosiences LLC) describes a synthesis route to 2-amino-5,7-dimethoxy[1,2,4]-triazolo[1,5-a]pyrimidine via reaction of 2-amino-4,6-dimethoxy pyrimidine plus ethoxycarbonyl isothiocyanate.

- The latter reaction is carried out at room temperature in tetrahydrofuran (THF) and the intermediate was isolated. This intermediate was then reacted with
10 hydroxylamine hydrochloride and diisopropylamine in ethanol at room temperature yielding the 2-amino-5,7-dimethoxy[1,2,4]-triazolo[1,5-a]pyrimidine.

Yields of this two step process are not satisfying and the synthesis is not simple enough e.g. to be scaled up for commercial purposes.

- The object of the present invention is to provide a simple process which leads to
15 2-amino-triazolopyrimidines in high yields, which in turn can be used as building blocks e.g. in agrochemical synthesis, such as fungicide, insecticide or herbicide synthesis.

- Therefore the process as described herein as well as the use of such process in the preparation of 2-amino[1,2,4]-triazolo[1,5-a]pyrimidine structure containing
20 agrochemicals or pharmaceuticals has been found.

- In one aspect of the present invention, there is provided process for the preparation of unsubstituted or substituted 2-amino-[1,2,4]triazolopyrimidines which comprises combining A) 2-Amino-pyrimidine or its derivatives with alkyloxycarbonyl isothiocyanate or aryloxycarbonyl isothiocyanate with B) hydroxyl ammonium salt and
25 a base wherein the reaction is carried out in a polar aprotic organic solvent in the temperature range of from 40 to 150°C.

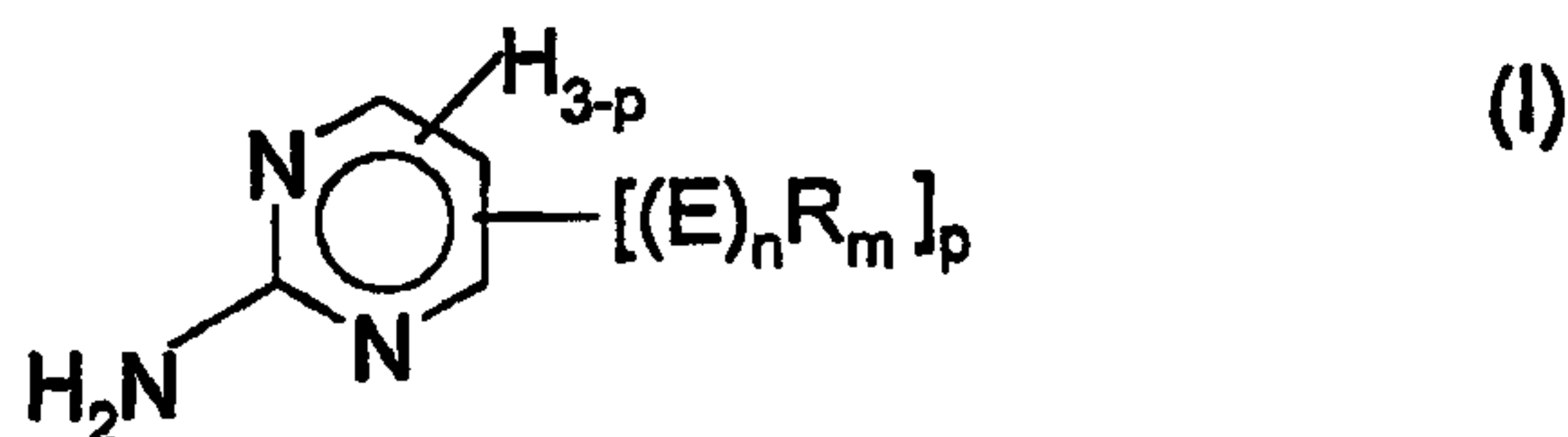
73776-229

In an embodiment of the present invention, there is provided the process as described herein wherein the pH value in step B) is increased over time and finally maintained in the range of from 5.5 to 7.5.

In another aspect of the present invention, there is provided process for the
 5 preparation of N-([1,2,4]triazolo[1,5-a]pyrimidin-yl)aryl sulfonamides or
 N-([1,2,4]triazolo[1,5-a]pyrimidin-yl)heteroaryl sulfonamides which comprises
 preparing unsubstituted or substituted 2-amino-[1,2,4]triazolopyrimidines according to
 claim 1 to 6 and subsequently reacting the yielded unsubstituted or substituted
 2-amino-[1,2,4]triazolopyrimidines with an arylsulfonylhalogenide Ar-SO₂-Hal or an
 10 heteroarylsulfonylhalogenide Hetar-SO₂-Hal.

Stage A of the process of the instant invention is the combination of a substituted or
 unsubstituted 2-amino-pyrimidin and alkoxycarbonyl isothiocyanate or
 aryloxycarbonyl-isothiocyanate.

Preferred unsubstituted or substituted 2-amino-pyrimidines are such of formula I



15

In which the variables have the following meaning.

E = independently the same or different are O, S, N, P;

R = independently the same or different are C₁₋₁₀-alkyl, C₆₋₂₀-aryl, C₇₋₂₀-arylalkyl, C₇₋₂₀-

alkylaryl which each of those may be substituted with one or more of the following groups: F, Cl, Br, I, C₁₋₂₀-alkoxy, C₆₋₂₀-aryloxy, non substituted or preferably substituted amino; F, Cl, Br, I;

n = 0 or 1

5 m = 1 for E = O, S

m = 2 for E = N, P

p = 0, 1, 2 or 3

10 Preferred groups R are linear or branched C₁₋₆-alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, t-butyl, neo-pentyl, n-pentyl, n-hexyl or C₇₋₂₀-arylalkyl such as benzyl or diphenylmethyl.

Preferred groups E are oxygen (O) or nitrogen (N).

15 Preferably E is O, p is 1 or 2 and the ER-groups are positioned meta to each other.

Most preferably R is C₁₋₆-alkyl, E is O, p is 2 and the ER-groups are positioned meta to each other.

20 Suitable compounds of formula I are 2-amino-pyrimidine; 2-amino-4,6-dimethoxy-pyrimidine; 2-amino-4,6-diethoxy-pyrimidine; 2-amino-4,6-di-n-propoxy pyrimidine; 2-amino-4,6-di-n-butoxy pyrimidine.

25 The alkoxycarbonyl or aryloxycarbonyl isothiocyanate of the present invention have preferably the following formula II:



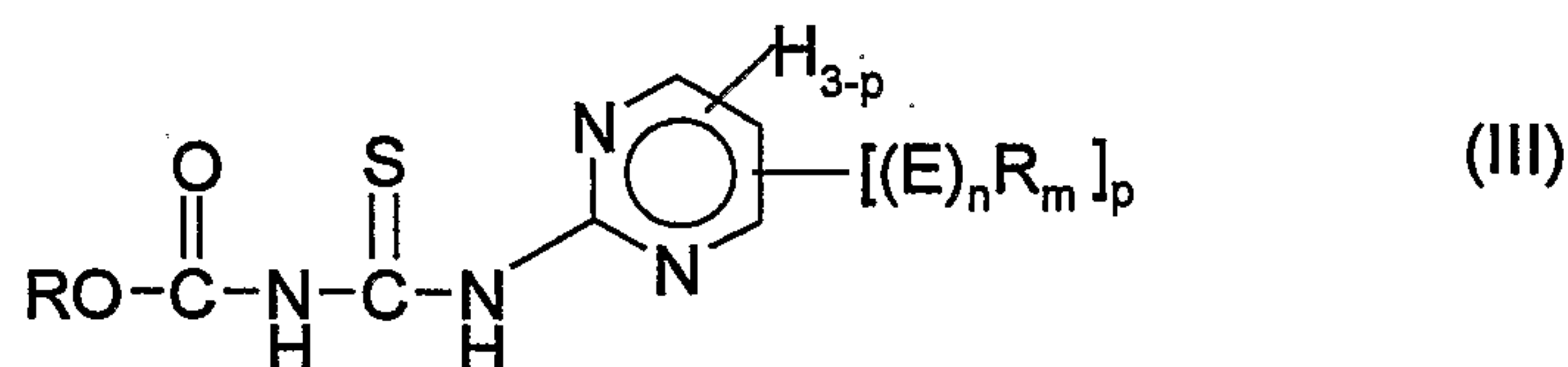
In which R has the same meaning - including the preferable meanings - as for compounds of formula I.

30 Suitable compounds of formula II are methoxycarbonylisothiocyanate, ethoxycarbonylisothiocyanate.

35 Compounds of formula II are known in the literature and can be prepared by known methods e.g. by reaction of the respective organochloroformates with alkalimetal (K, Na, Rb, Cs) or alkaline earth metal (e.g. Ca, Ba, Sr) thiocyanates in an organic solvent (see for example J. Heterocycl. Chem. 5, 837 (1968); J. Org. Chem. 55 (18), 5230-5231 (1990); US 4160037; US 4778921; US 5194673). The organic solvent is preferably the one in which the reactions of the instant invention are conducted.

40

The foregoing combination yields a N-pyrimidin-2-yl-N'-carboalkoxy (or aryloxy)thiourea of the formula III



In which the variables have the same meaning - including the preferable meaning - as in formula I above.

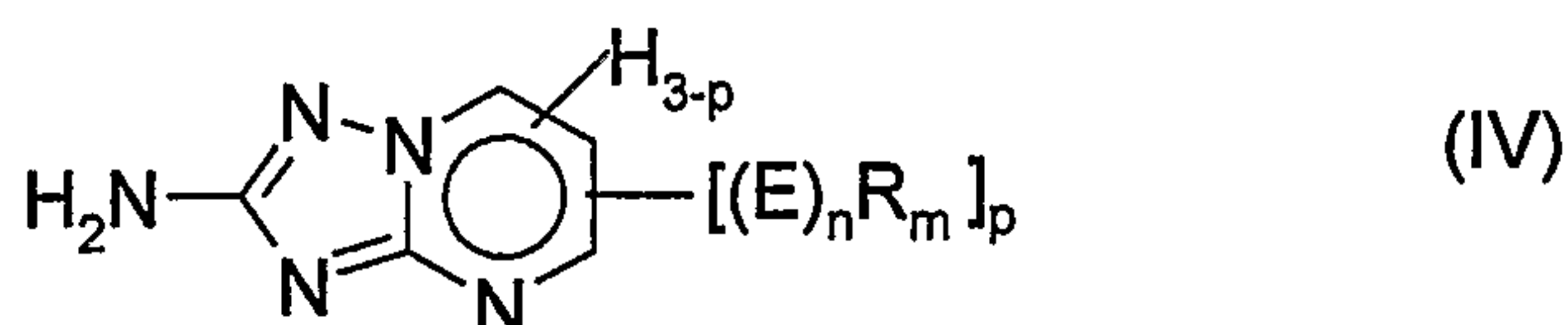
- 10 Suitable compounds III are the ones with $\text{E} = \text{O}$, $\text{R} = \text{C}_{1-6}\text{-alkyl}$, $m = 1$, $p = 1, 2$ or 3 , preferably are compounds III in which $\text{E} = \text{O}$, $\text{R} = \text{C}_{1-6}\text{-alkyl}$, $m = 1$, $p = 2$ in which the ER groups are positioned meta to each other. Very suitable compounds III are the following: N-(4,6-dimethoxypyrimidin-2-yl)-N'-carboethoxythiourea, N-(4,6-

15 Stage B of the instant invention is the combination of the compound III with a hydroxylammonium salt such as hydroxyl ammonium sulfate, hydroxyl ammonium chloride, hydroxyl ammonium nitrate, hydroxyl ammonium phosphate, preferably hydroxyl ammonium sulfate, in the presence of a base.

20 Preferable bases are alkali metal hydroxides (e.g. KOH, NaOH, RbOH, CsOH), earth alkali metal hydroxides (e.g. $\text{Mg}(\text{OH})_2$, $\text{Ca}(\text{OH})_2$, $\text{Ba}(\text{OH})_2$, $\text{Sr}(\text{OH})_2$) and organic bases like amines -preferably tertiary amines - pyridines and other herterocyclic organic bases, preferably cyclic amine bases. Most preferable bases are alkali hydroxides, in particular caustic soda (NaOH).

25 Preferably the base, e.g. caustic soda, is initially slowly added to establish a pH value of the reaction mixture of from 1 to 7,5 which is then maintained at pH 5 to 7,5, in particular pH 6,5 to 7,0 until the reaction is completed.

30 The above reaction sequence yields finally the respective 2-amino-[1,2,4]triazolopyrimidine IV



35 In which the variables, including their preferable meaning, have the same meaning as under formula I.

Suitable compounds IV are the ones in which E = O, R = C₁₋₆-alkyl, m = 1, p = 1, 2 or 3
 Preferable are compounds IV in which E = O, R = C₁₋₆-alkyl, m = 1, p = 2 in which the
 ER-groups are positioned meta to each other or in other words which occupy the 5-
 5 and 7-position (according to Chemical Abstract Nomenclature) of the triazolo
 pyrimidine ring system in formula (IV).

Very suitable compounds IV are: 2-amino-5,7-dimethoxy[1,2,4]triazolopyrimidine,
 2-amino-5,7-diethoxy[1,2,4]triazolopyrimidine, 2-amino-5,7-di n or di iso
 10 propoxy[1,2,4]triazolopyrimidine, 2-amino-5,7-di n- or di tert. or di iso
 butoxy[1,2,4]triazolopyrimidine, in particular 2-amino-5,7-
 dimethoxy[1,2,4]triazolopyrimidine.

Usually stages A and B are conducted in polar aprotic solvents such as nitriles
 15 (e.g. aceto nitrile), ethers (e.g. thf, dimethoxyethane, dimethoxymethane,
 diethoxymethane, diisopropylether, 1,4-dioxan, methyltertbutylether (MTBE)), ketons
 (e.g. acetone, diethylketone, methylisobutylketone) or preferably in carboxylic acid
 esters, such as C₁₋₂₀-carboxylic-acid – C₁₋₁₀-alkylesters or the respective C₇₋₂₀-
 alkylarylesters or C₇₋₂₀-arylalkylesters.

20 Preferably C₁₋₂₀ carboxylic acid C₁₋₁₀-alkylesters are used as solvents.

Mixtures of the above-mentioned solvents are also suitable.

25 Most preferably the solvent in stage A is the same as the solvent in stage B.

Very most preferably the solvent in stage A and/or in stage B is a carboxylic acid ester,
 such as C₁₋₂₀-carboxylic-acid C₁₋₁₀-alkylester, preferably C₁₋₆-carboxylic-acid C₁₋₆-
 alkylester in which the carboxylic acid is a straight chain aliphatic carboxylic acid or a
 30 benzoic acid and the alcohol alkyl moiety is a straight chain alkyl; suitable examples for
 the carboxylic acid esters are methylacetate, ethylacetate, n-propylacetate,
 i-propylacetate, n-butylacetate, in particular ethylacetate.

Preferably reactions in stage A and/or stage B are conducted at temperatures of from
 35 40 to 150 °C, preferably 60 to 100 °C, most preferably 70 to 90 °C.

Very most preferably reactions of stage A as well as stage B are conducted under
 reflux of the respective solvent e.g. from 60 to 100°C, preferably 70 to 90°C.

40 Sometimes it might be necessary to conduct the reaction under pressure in order to
 achieve the abovementioned reaction temperatures.

73776-229

Preferably no intermediates are isolated in the process of the instant invention ("one pot procedure"), although this isolation is easily possible by generally known methods.

- 5 The overall reaction time of stages A and B is usually of from 2 to 14 hours, preferably 5 to 6 hours.

The reaction products IV are in general worked up and isolated with the usual organic techniques.

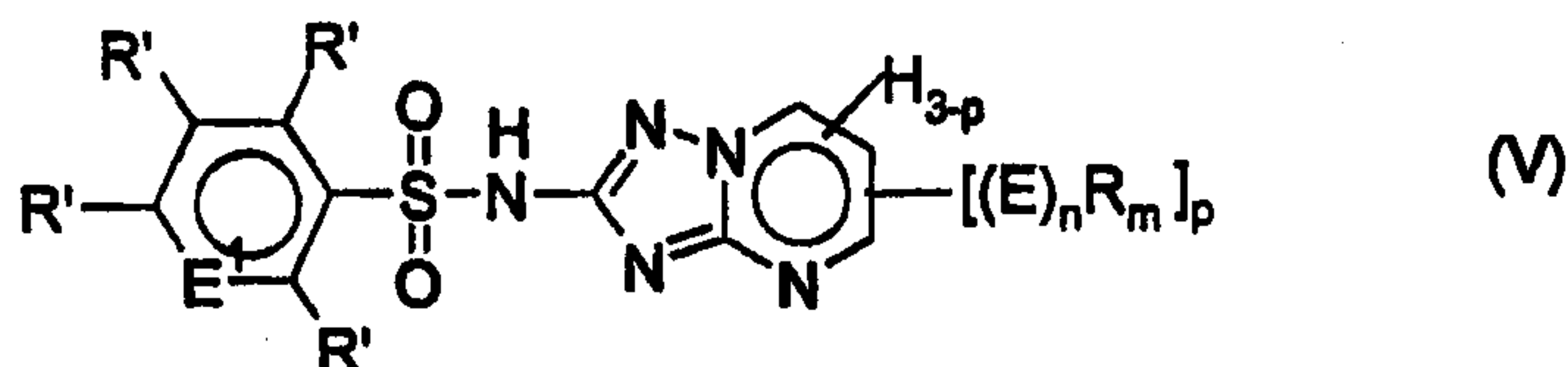
10

The process of the instant invention can be used in the synthesis of agrochemicals or pharmaceuticals e.g. agrochemicals as described in WO 02/36595 A2 (DOW Agrosiences LLC) or US 5,571,775 (DOW Elanco).

15

For example compounds IV, obtained by the process of the instant invention can be reacted with aryl – or heteroarylsulfonyl halogenides Ar-SO₂-Hal or (Hetaryl)-SO₂-Hal yielding respective N-([1,2,4]triazolo[1,5-a]pyrimidin-2-yl) aryl or heteroaryl sulfonamide compounds V, as described in WO 02/36595 A2 (DOW Agrosiences LLC)

20



in which the variables have the same meaning as in formula I and R' independently the same or different is H or R and E¹ is CR' or N, preferably N.

25

Suitable compounds V are for example:

3-Pyridinesulfonamide, N-(5,7-dimethoxy[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl), as disclosed in Research Disclosure July 2002, 1230-1231;

30

3-Pyridinesulfonamide, N-(5,7-diethoxy[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy (trifluoromethyl).

35 The process of the instant invention leads in a simple, usually one pot procedure, to the valuable compounds IV in high yield, usually overall yield above 85 %, in particular over 90%.

Examples

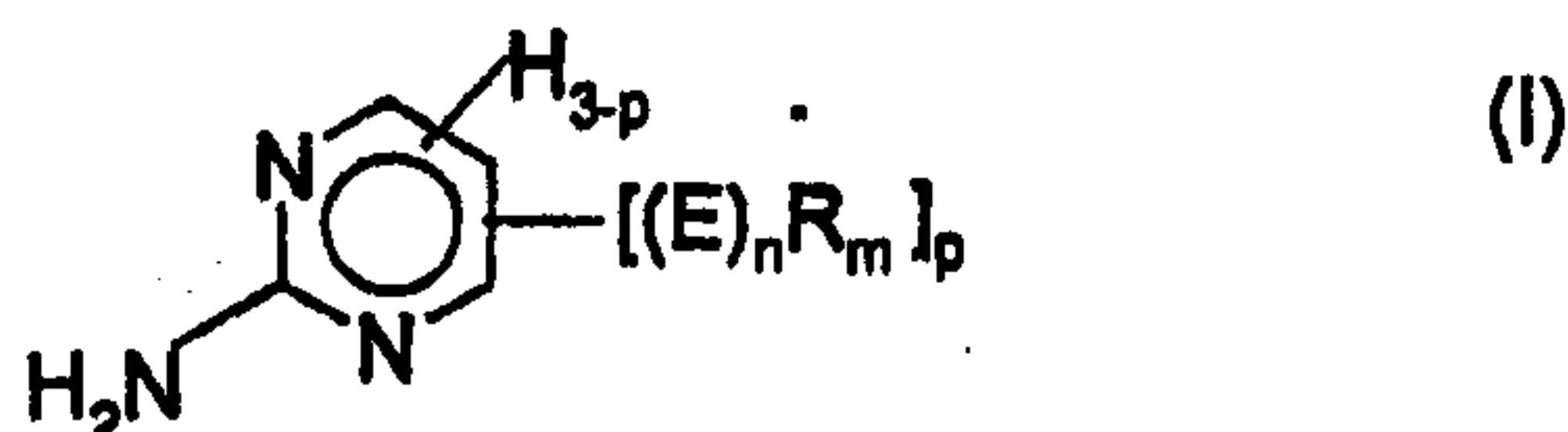
One pot procedure for the synthesis of 2-amino-5,7-dimethoxy [1,2,4]triazolopyrimidine (ADTP) from 2-amino-4,6-dimethoxypyrimidine (ADP)

- 5 11.9 g (0.075 mol) ADP was dissolved in 68 g ethyl acetate. 11 g (0.0825 mol) ethoxycarbonyl isothiocyanate was added within 20 min. at 78°C (no exotherm). The mixture was stirred over 5 h at reflux (78-79°C). 49.2 g (0.075 mol) hydroxylammonium sulfate (25 % solution in water) were added and the mixture heated to 71°C (reflux
- 10 acetropene). 50 g (0.1 mol) diluted caustic soda (2 mol/l) was added within 1 h to establish the pH from 1.3 to 6.5 and hold at 6.5-7.0 (offgas CO₂ and H₂S, slightly exotherm). The mixture was stirred over 6 h under reflux (71°C) for reaction completion. The mixture was cooled down over night to 20°C. The product (ADTP) was filtrated and washed 3 times with each 25 g water to remove the salt (Na content after
- 15 first wash 0.42 %, after second 0.20 %, after third 0.025 %). Finally the solid ADTP was dried. Yield: 91.1 % in respect to ADP, purity 95.3 % (quantitative HPLC assay).

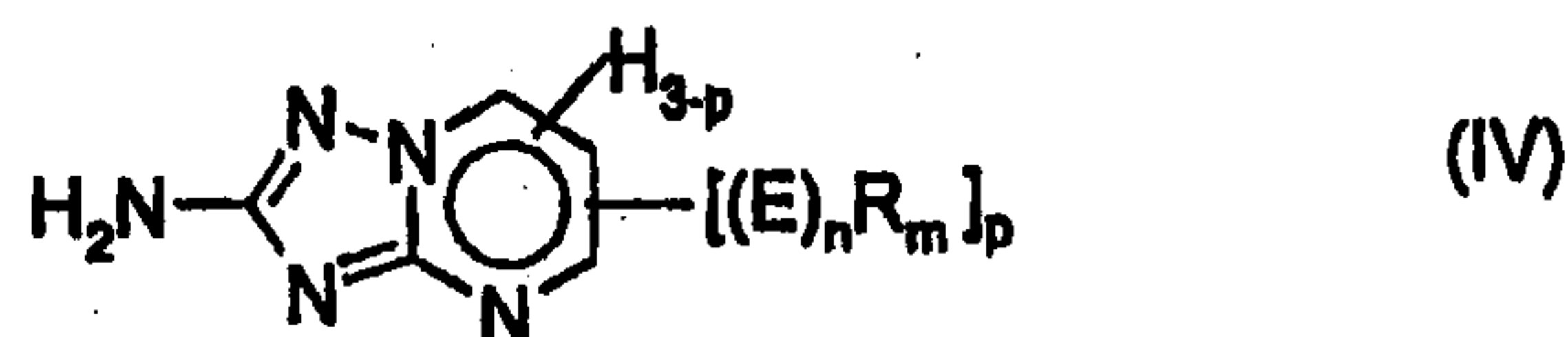
73776-229

CLAIMS:

1. Process for the preparation of unsubstituted or substituted 2-amino-
[1,2,4]triazolopyrimidines which comprises combining A) 2-Amino-pyrimidine or
its derivatives with alkylloxycarbonyl isothiocyanate or aryloxycarbonyl
isothiocyanate with B) hydroxyl ammonium salt and a base wherein the reaction
is carried out in a polar aprotic organic solvent in the temperature range of from
40 to 150 °C.
2. The process according to claim 1 wherein the pH value in step B) is increased
over time and finally maintained in the range of from 5.5 to 7.5.
3. The process as in claim 1 or 2, wherein the hydroxylammonium salt is
hydroxylammonium sulfate.
4. The process as claimed in any one of claims 1 to 3, wherein the polar aprotic
solvent is selected from the group consisting of carboxylic acid esters.
5. The process as claimed in any one of claims 1 to 4 wherein the 2-amino-
pyrimidine or its derivatives is described by formula I



and the 2-amino-[1,2,4]triazolopyrimidine is described by formula IV



wherein the variables have the following meaning:

E = independently the same or different are O, S, N, P;

R = independently the same or different are C₁₋₁₀-alkyl; C₆₋₂₀-aryl; C₇₋₂₀-arylalkyl;

C₇₋₂₀-alkylaryl which each of those may be substituted with one or more of the

following groups: F, Cl, Br, I, C₁₋₂₀-alkoxy, C₆₋₂₀-aryloxy, non substituted or
substituted amino; F, Cl, Br, I;

73776-229

- n = 0 or 1
m = 1 for E = O, S
m = 2 for E = N, P
5 p = 0, 1, 2 or 3.
6. Process as claimed in any one of claims 1 to 5, wherein the process is conducted without isolation of intermediates.
- 10 7. **Process for the preparation of N-([1,2,4]triazolo[1,5-a]pyrimidin-yl)aryl sulfonamides or N-([1,2,4]triazolo[1,5-a]pyrimidin-yl)heteroaryl sulfonamides which comprises preparing unsubstituted or substituted 2-amino-[1,2,4]triazolopyrimidines according to claim 1 to 6 and subsequently reacting the yielded unsubstituted or substituted 2-amino-[1,2,4]triazolopyrimidines with an arylsulfonylhalogenide Ar-**
15 **SO₂-Hal or an heteroarylsulfonylhalogenide Hetar-SO₂-Hal.**
8. Use of a process as claimed in any one of claims 1 to 6 in the synthesis of N-([1,2,4]triazolo[1,5-a]pyrimidin-yl) structure containing agrochemicals or pharmaceuticals.