

(CONVENTION. By one or more persons and/or a company.) Form 4

606744

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

(1) Here
insert (in
full) Name
or Names of
Applicant or
Applicants,
followed by
Address (es).

XX (1) HOECHST AKTIENGESELLSCHAFT,
We

of 45 Bruningstrasse,

D-6230 Frankfurt/Main 80,

Federal Republic of Germany.

(2) Here
insert Title
of invention.

hereby apply for the grant of a Patent for an invention entitled: (2)

PROCESS FOR THE PREPARATION OF

1-ARYLPYRAZOLE-3-CARBOXYLIC ACID ESTERS

(3) Here insert
number(s)
of basic
application(s)

which is described in the accompanying complete specification. This application is a
Convention application and is based on the application numbered (3)

P 37 29 598.5

(4) Here insert
Name of basic
Country or
Countries, and
basic date or
dates

for a patent or similar protection made in (4) Federal Republic
of Germany on 4th September, 1987.

APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED 20.11.90

My
Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys,
50 Queen Street, Melbourne, Victoria, Australia.

DATED this 1st day of September, 1988.

(5) Signa-
ture (s) of
Applicant (s)
or
Seal of
Company and
Signatures of
its Officers as
prescribed by
its Articles of
Association.

(5)

HOECHST AKTIENGESELLSCHAFT

By:

D.B. MISCHLEWSKI

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER PART XVI.
FOR A PATENT.

In support of the Convention application made under Part XVI. of the Patents Act 1952 by HOECHST AKTIENGESELLSCHAFT of 45, Brüningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany for a patent for an invention entitled:

Process for the preparation of 1-arylpyrazole-3-carboxylic acid esters

We, Günter Isenbruck, 173 Biebricher Allee, D-6200 Wiesbaden,
Franz Lapice, 2 Sandweg, D-6233 Kelkheim (Taunus),
Federal Republic of Germany

do solemnly and sincerely declare as follows:

1. We are authorized by HOECHST AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.
2. The basic application as defined by Section 141 of the Act was made in the Federal Republic of Germany under No. P 37 29 598.5 on September 4, 1987 by HOECHST AKTIENGESELLSCHAFT
3. a) Erich Sohn, 14 Troppauer Straße, D-8906 Gersthofen
b) Rudolf Kunstmann, 9 Schlesierstraße, D-8901 Aystetten
a) and b) Federal Republic of Germany

we/are the actual inventor(s) of the invention and the facts upon which HOECHST AKTIENGESELLSCHAFT

is entitled to make the application are as follows:

The said HOECHST AKTIENGESELLSCHAFT

is the assignee of the said
Erich Sohn and Rudolf Kunstmann

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Frankfurt/Main, Federal Republic of Germany
this 10th day of August, 1988

To the Commissioner of Patents

HOECHST AKTIENGESELLSCHAFT

ppa Isenbruck

i.V. Lapice

PAT 510

Prokurist Authorized Signatory

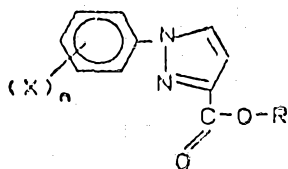
ppa. Isenbruck

i.V. Lapice

(12) PATENT ABRIDGMENT (11) Document No. AU-B-21818/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 606744

- (54) Title
PROCESS FOR THE PREPARATION OF 1-ARYLPYRAZOLE-3-CARBOXYLIC ACID
ESTERS
- International Patent Classification(s)
(51)⁵ C07D 231/14
- (21) Application No. : 21818/88 (22) Application Date : 02.09.88
- (30) Priority Data
- (31) Number (32) Date (33) Country
3729598 04.09.87 DE FEDERAL REPUBLIC OF GERMANY
- (43) Publication Date : 09.03.89
- (44) Publication Date of Accepted Application : 14.02.91
- (71) Applicant(s)
HOECHST AKTIENGESELLSCHAFT
- (72) Inventor(s)
ERICH SOHN; RUDOLF KUNSTMANN
- (74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS, Locked Bag 5, HAWTHORN VIC
3122
- (56) Prior Art Documents
AU 31373/89 C07D 231/14, A01N 43/40, 43/48
AU 79308/87 C07D 231/14, 403/10, 231/16
- (57) Claim

1. A process for the preparation of compounds of the
formula I



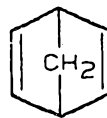
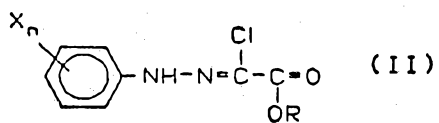
(I),

in which the

Xs independently of one another denote halogen, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halogeno- (C_1-C_6) -alkyl or halogeno- (C_1-C_6) -alkoxy,
R denotes H or (C_1-C_6) -alkyl and
n denotes an integer from 1 to 5,
which comprises reacting a chlorohydrazone of the
formula II

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(III)

with norbornadiene of the formula III.

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Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class

Int. Class

Application Number:

Lodged:

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:

Name of Applicant: HOECHST AKTIENGESELLSCHAFT

Address of Applicant: 45 Bruningstrasse, D-6230 Frankfurt/Main 80,
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Actual Inventor: ERICH SOHN and RUDOLF KUNSTMANN.

Address for Service: EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

PROCESS FOR THE PREPARATION OF 1-ARYLPYRAZOLE-3-CARBOXYLIC
ACID ESTERSThe following statement is a full description of this invention, including the best method of performing it known to ^{us}

Description

Process for the preparation of 1-arylpyrazole-3-carboxylic acid esters

5

1-Arylpyrazole-3-carboxylic acid esters of the formula I indicated below are highly effective safeners for herbicides (DE-A 3,633,840). The synthesis of these pyrazoles described therein is effected by a cyclization reaction of phenylhydrazines with 4-ethoxy-2-oxobut-3-enoic acid esters. The desired 3-pyrazolecarboxylic acid ester is produced in this reaction in the form of a mixture with the corresponding 5-pyrazolecarboxylic acid ester. An involved separation of isomers is necessary as a result; the undesired by-product must then be disposed of. The process also exhibits considerable technical disadvantages.

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It is also known that pyrazoles are accessible by 1,3-dipolar cycloaddition reactions. Thus phenylsydnones can be reacted with acetylenes to give pyrazoles (DE-A 1,261,125). Mixtures of isomers (of 3-pyrazolecarboxylic and 4-pyrazolecarboxylic acid esters) are, however, also formed in this reaction.

The selective synthesis of 3-pyrazolecarboxylic acid esters has only been described by the following complicated, multi-stage route of synthesis: N-phenyl-C-acetylnitrilimine is cyclo-condensed with norbornadiene to give pyrazolinonorborene and the product is then aromatized to give 3-acetylpyrazole and the latter is degraded to the acid by means of $I_2/NaOH$ [R. Huisgen et al., Chem. Ber. 101, 536 to 551, (1968)]. Esterification finally affords the desired product.

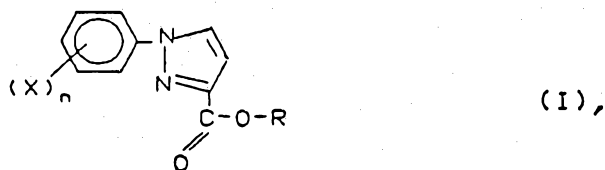
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The disadvantages associated with carrying out the known processes are overcome by means of the process according to the invention for the preparation of

3-pyrazolecarboxylic acid esters.

It has been found, surprisingly, that in the reaction of N-phenyl-C-alkoxycarbonylnitrilimines with norbornadiene the compounds of the formula I are obtained selectively and in high yields.

The present application therefore relates to a process for the preparation of 1-arylpyrazole-3-carboxylic acid esters of the formula I



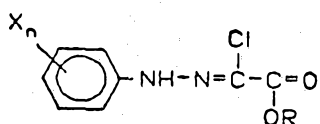
in which the

Xs independently of one another denote halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, halogeno-(C₁-C₆)-alkyl or halogeno-(C₁-C₆)-alkoxy,

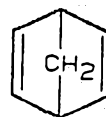
R denotes H or (C₁-C₆)-alkyl and

n an integer from 1 to 5,

which comprises reacting a chlorohydrazone of the formula II



(II)



(III)

with norbornadiene of the formula III.

The reaction of phenylalkoxycarbonylnitrilimines with compounds containing electron-rich double bonds was already known: reaction with cyclic enamines (Fusco et al. Gazz. Chim. Ital. 91 (1961) 1233 et seq.) or with bismorpholinoethane compounds (Synthesis 1976 684/685). Symmetrical ethene compounds only afforded small yields of the desired product in this reaction.

It could, therefore, also not have been expected that N-phenyl-C-alkoxycarbonylnitrilimines would react in excellent yields with compounds which, like norbornadiene, possess non-polarized, electron-deficient double bonds.

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The process according to the invention is preferably used for the preparation of compounds of the formula I in which R denotes (C₁-C₄)-alkyl, X denotes halogen, C₁-halogenoalkyl or C₁-halogenoalkoxy and n denotes 1 to 3.

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Halogenoalkyl or halogenoalkoxy radicals are to be understood as meaning especially the radicals -CF₃ and -OCF₃.

15

The components of the formulae II and III can be reacted without a solvent, but can preferably be reacted in an inert organic solvent such as, for example, benzene, toluene, xylene, chlorobenzene, monoethylene, diethylene or triethylene glycol ether, dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone or pyridine.

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The process is advantageously carried out in the presence of an organic or inorganic auxiliary base, such as, for example, a trialkylamine, pyridine, an alkali metal carbonate or dicarbonate, alkaline earth metal carbonate or dicarbonate, alkali metal hydroxide or alkali metal alcoholate.

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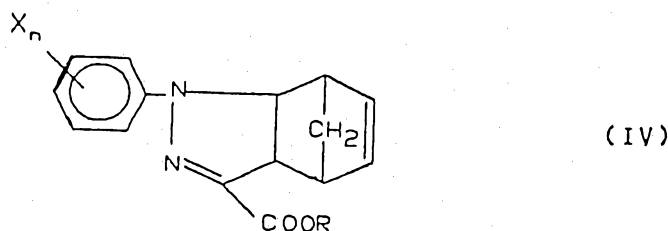
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It is advantageous to employ the base in excess, advantageously in up to 10 times the molar amount, relative to the compound II.

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It is advantageous to employ norbornadiene in an excess of up to 20-fold, usually a 5-molar to 15-molar excess, relative to (II). The process is carried out between 0° and 200°C. The intermediate product of the formula IV is formed initially in the reaction and this reacts further to give the end product on being heated further. If the reaction is carried out initially at relatively low

temperatures (0° to 80°C), the intermediate product of the formula IV can be isolated by adding a soluble auxiliary base.



10 Reaction temperatures from 60° to 200°C , preferably 70° to 160°C , are required for the subsequent cleavage of the intermediate product IV.

15 The chlorohydrazones of the formula II are accessible by customary processes. They can, for example, be obtained from the corresponding anilines by diazotization and coupling with 2-chloroacetoacetic acid esters.

20 The chlorohydrazones obtained in this synthesis can be used without prior purification, immediately after the addition of the solvent, for cyclocondensation with norbornadiene.

The following examples serve to illustrate the invention further.

25 1. Preparation examples

Example 1:

Ethyl 1-(2,4-dichlorophenyl)-pyrazole-3-carboxylate.

30 14.8 g (0.05 mol) of ethyl 2-chloroglyoxylate-2',4'-dichlorophenylhydrazone (IIa) in 50 ml of toluene are stirred with 50 ml of norbornadiene and 20 ml of triethylamine for 1 hour at 70°C . After cooling, the precipitate is filtered off with suction and rinsed with 20 ml of
35 toluene, and the toluene phases are concentrated to dryness in a WV^{*}). The residue is subjected to gradient

*⁾ WV = water pump vacuum

chromatography on silica gel (mobile phase: petroleum ether (40 to 70°) changing to pure ethyl acetate). 14.5 g (82% of theory) of a colorless oil are obtained. This is identified by means of NMR spectroscopy. 3.5 g (0.01 mol) of the 1-(2,4-dichlorophenyl)-3-ethoxycarbonylpyrazolo-[2,2,1]-bicyclo-heptene thus prepared are heated at 150°C in WV for 3 hours, and, after cooling, the product is recrystallized from petroleum ether; this gives 2.6 g (88% of theory) of product, needles of melting point 88 to 90°C.

Example 2:

Ethyl 1-(2,4-dichlorophenyl)-pyrazole 3-carboxylate
29.6 g (0.1 mol) of ethyl 2-chloroglyoxylate-2',4'-dichlorophenylhydrazone (IIa) in 100 ml of toluene are stirred with 50 ml of norbornadiene and 40 ml of triethylamine for 1 hour at 70°C; after cooling, the precipitate is filtered off with suction and washed with 30 ml of toluene, and the combined toluene phases are evaporated in WV. The residue is heated at 160°C in WV for 3 hours and, after cooling, is taken up in 150 ml of ethyl acetate/100 ml of water, and the solution is washed with 100 ml of dilute hydrochloric acid, 100 ml of NaHCO₃ solution and 100 ml of water, dried over MgSO₄ and concentrated to dryness in WV. Column chromatography gives 25.6 g (90% of theory) of the desired product: crystals of melting point 88 to 90°C.

Example 3:

Ethyl 1-(2,4-dichlorophenyl)-pyrazole-3-carboxylate
14.8 g of (IIa) in 100 ml of toluene are stirred with 50 ml of norbornadiene and 30 ml of pyridine at 100°C for 40 hours. After cooling, the mixture is concentrated to dryness in WV and the residue is worked up as described under Example 2. This gives 4.3 g (30% of theory) of crystals of melting point 88 to 89°C.

Example 4:

Methyl 1-(2,4-dichlorophenyl)-pyrazole-4-carboxylate
14.6 g (0.05 mol) of methyl 2-chloroglyoxylate-2',

4'-dichlorophenylhydrazine in 100 ml of toluene are stirred with 50 ml of norbornadiene and 10 g of NaHCO_3 for 24 hours at 70°C . After cooling, the mixture is worked up as described under Example 2: this gives 6.2 g (46% of theory) of crystals of melting point 105 to 107°C .

Example 5:

Ethyl 1-(2,4-dichlorophenyl)-pyrazole-3-carboxylate

5.9 g (0.020 mol) of IIa in 50 ml of DMF are stirred with 20 ml of norbornadiene and 5 g of NaHCO_3 for 2 hours at room temperature; the resulting precipitate is filtered off with suction and rinsed with 20 ml of DMF. The filtrate is concentrated to dryness in WV and the resulting residue is heated at 160°C for 3 hours. Column chromatography (petroleum ether (30 to 70°) changing to ethyl acetate on silica gel) gives 4.6 g (81% of theory) of crystals of melting point 88 to 90°C .

DMF = dimethylformamide.

Example 6:

Ethyl 1-(2,4-dichlorophenyl)-pyrazole-3-carboxylate

5.9 g (0.02 mol) of IIa in 50 ml of DMF are stirred at 100°C for 8 hours with 20 ml of norbornadiene and 6 g of K_2CO_3 . After cooling, the precipitate is filtered off with suction and is rinsed with 20 ml of DMF. The filtrate is concentrated to dryness in WV and the residue is chromatographed as described in Example 5. This gives 2.1 g (37% of theory) of crystals of melting point 88 to 90°C .

Example 7:

Ethyl 1-(2,4-dichlorophenyl)-pyrazole-3-carboxylate

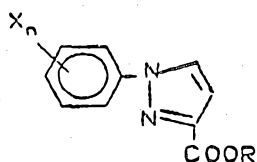
5.9 g (0.02 mol) of IIa are stirred in 50 ml of DMF with 20 ml of norbornadiene for 40 hours at 140°C . The mixture is concentrated to dryness in WV and the residue is chromatographed over silica gel. This gives 1.9 g (33% of theory) of crystals of melting point 88 to 90°C .

Example 8:

Ethyl 1-(2,4-dichlorophenyl)-pyrazole-3-carboxylate

5.9 g (0.02 mol) of IIa in 40 ml of DMSO are stirred with 20 ml of norbornadiene and 6 g of KHCO_3 for 3 hours at room temperature and then for 3 hours at 150°C . The mixture is poured into 100 ml of water, and the precipitate is filtered off with suction. Column chromatography of the filtrate gives 4.7 g (82% of theory) of crystals of melting point 88 to 90°C .

The following esters of the formula I can be synthesized analogously.



Compound Example No.	X_n	R	m.p. $^\circ\text{C}$	yield %	Analogously to Example No.
9	2,4- Br_2	C_2H_5	103-5	68	1
10	4-O-n- C_4H_9 -2- CF_3	C_2H_5	oil	78	2
11	4- CH_3O	C_2H_5	oil	71	1
12	3-Cl-2,6-(C_2H_5) $_2$	C_2H_5	oil	64	1
13	4-F-3- CF_3	C_2H_5	24-29	73	5
14	2-Cl-4- CF_3	C_2H_5	38-41	78	8
15	2,4- F_2 -3,5- Cl_2	C_2H_5	oil	61	1
16	4-Cl-2-F-5- OCH_3	C_2H_5	90-92	79	2
17	2,6-(C_2H_5) $_2$	C_2H_5	oil	72	2

Example 18:

1-(2,4-Dichlorophenyl)-pyrazole-3-carboxylic acid

20 ml of norbornadiene and 10 g of KOH powder are added with cooling to 5.9 g (0.02 mol) of IIa in 100 ml of toluene, and the mixture is stirred for 24 hours at room temperature. The organic phase is washed with 50 ml of dilute hydrochloric acid and is dried and concentrated to

- 8 -

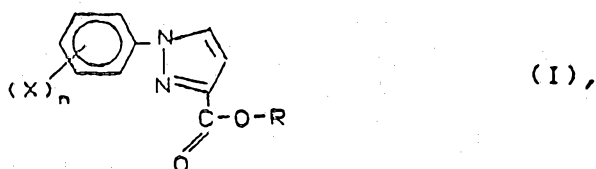
dryness in WV. The resulting viscous oil is heated at 160°C in WV for 3 hours and, after cooling, the product is recrystallized from ethanol. This gives 3.2 g (62% of theory) of crystals of melting point 177 to 180°C.

Patent claims

HOE 87/F 261

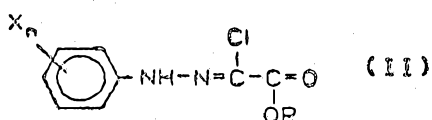
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for the preparation of compounds of the formula I



in which the

- Xs independently of one another denote halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, halogeno-(C₁-C₆)-alkyl or halogeno-(C₁-C₆)-alkoxy,
 R denotes H or (C₁-C₆)-alkyl and
 n denotes an integer from 1 to 5,
 which comprises reacting a chlorohydrazone of the formula II



with norbornadiene of the formula III.

2. The process as claimed in claim 1, wherein, in formula II, R denotes (C₁-C₄)-alkyl, X denotes halogen, C₁-halogenoalkyl or C₁-halogenoalkoxy and n denotes 1, 2 or 3.
3. The process as claimed in claim 1 or 2, wherein the reaction is carried out in an inert organic solvent.
4. The process as claimed in one of claims 1 to 3, wherein the reaction is carried out in the presence of an organic or inorganic auxiliary base.
5. The process as claimed in one or more of claims 1 to 4,

wherein the reaction is carried out at temperatures between 0° and 200°C.

6. The process as claimed in one or more of claims 1 to 4, wherein the process is carried out first between 0° and 80°C and subsequently between 80°C and 160°C.
7. The process as claimed in claim 4, 5 or 6, wherein the auxiliary base is employed in a molar to 10 times molar amount, relative to the component II.
8. The process as claimed in one or more of claims 1 to 7, wherein norbornadiene is employed in a molar to 20 times molar amount, relative to the component II.

DATED THIS 1st day of September, 1988

HOECHST AKTIENGSELLSCHAFT

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