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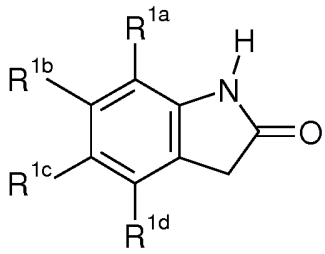
(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF SUBSTITUEREDE 1,3-DIHYDRO-2H-INDOL-2-ONER**

(56) Fremdragne publikationer:
CONNOLLY T J ET AL: "Non-reductive desulfenylation of 3-thioalkyl-2-oxindoles", SYNLETT, GEORG THIEME VERLAG, DE, 1. Juli 1996 (1996-07-01), Seiten 663-664, XP002545539, ISSN: 0936-5214

Description

1,3-Dihydro-2*H*-indol-2-ones of the formula (I)



(I)

are intermediates for active ingredients used in the provision of pharmaceutical or crop-protection compositions.

Compounds of the formula (I) can be prepared, for example, by reduction from 3-(alkylsulfanyl)-1,3-dihydro-2*H*-indol-2-ones. The latter compounds are readily preparable on a laboratory scale. For their reduction, however, the only processes described to date are processes which are difficult to operate on an industrial scale. They are expensive and, furthermore, may also present safety challenges.

The prior art has already disclosed metal-catalyzed or metal salt-catalyzed processes for the conversion of thioalkyl-substituted indol-2-one compounds of the formula (II) into the 3-unsubstituted indole compounds of the formula (I). The compilation below of these known reduction methods, which, however, are suitable only for the laboratory scale, is a record of the fact that the development of suitable methods in this area is based on efforts which have already expended over a long period of time.

The reagents used in the prior-art processes listed below are indicated in parentheses in each case:

- P.G. Grassmann, T.J van Bergen, Journal of the American Chemical Society 1973, pp. 2718-2719 (Raney nickel),
- US Patent Specification 4,160,032, based on an application filed in 1974 (palladium and Raney nickel),
- D. A. Walsh, D. A. Shamblee, W. J. Welstead, L. F.

Sancilio, J. Med. Chem 1982, 25, 446 - 451 (Raney nickel),

- Y. Tamura, J. Uenishi, H. D. Choi, J. Haruta, H. Ishibashi, Chem. Pharm. Bull. 1984, 32, 1995 - 1997 (zinc powder in acetic acid),
- D. A. Walsh, D. A. Shamblee, US Patent Specification 4,503,073 (tin in hydrochloric acid instead of Raney nickel),
- Y. Horiguchi, A. Sonobe, T. Saitoh, J. Toda, T. Sano, Chem. Pharm. Bull. 2001, 49, 1132 - 1137 ($NiCl_2$ and $NaBH_4$), and
- M. Miller, W. Tsang, A. Merritt, D. J. Procter, Chem. Commun. 2007, 498 - 500 (SmI_2).

For the same conversion, i.e., the conversion of thioalkyl-substituted indol-2-one compounds of the formula (II) into the 3-unsubstituted indole compounds of the formula (I), T. J. Connolly and T. Durst, Synlett 1996, 663- 664 disclose the further possibility of using PPh_3 in combination with *p*-TsOH as a reagent.

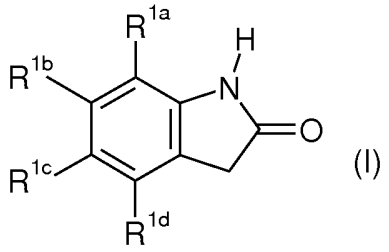
So the known processes utilize either a heavy metal reagent or triphenylphosphine. In the former case, wastes containing heavy metal are produced. For both environmental and economic reasons, this is not desirable. In the second case, the reaction product formed from the triphenylphosphine must be separated from the reaction mixture. This separation can be accomplished usually only by chromatography, with additional effort and expense.

Moreover, the respective reagent has a high molar mass and nevertheless must be used stoichiometrically. This is a disadvantage on economic grounds.

The processes known from the prior art, however, are useful only on the laboratory scale, and, on account of the chemical properties of the metal compounds used as reagents, also have disadvantages, the disadvantages having even greater consequences when the processes are employed on an operational scale.

Against this background, the object of the invention lies in the development of a process that allows the compound of the formula (I) to be prepared on an operational scale and that does not exhibit the disadvantages of the processes known from the prior art.

The object is achieved by means of a single-stage process for preparing a compound of the formula (I)



(I)

, in which

R^{1a} to R^{1d} independently of one another are selected from the group consisting of

hydrogen, fluorine, chlorine, bromine, and trifluoromethyl,

(C_1-C_6)-alkyl, the alkyl radical being unsubstituted or being substituted by one or more substituents selected from the group consisting of (C_1-C_4)-alkoxy or (C_3-C_7)-cycloalkyl,

(C_3-C_7)-cycloalkyl, the cycloalkyl radical being unsubstituted or being substituted by one or more substituents selected from the group consisting of (C_1-C_4)-alkyl or (C_3-C_7)-cycloalkyl or (C_1-C_4)-alkoxy,

(C_1-C_6)-alkoxy, the alkoxy radical being branched or unbranched and being unsubstituted or substituted by one or more substituents selected from the group consisting of (C_1-C_4)-alkoxy or (C_3-C_7)-cycloalkyl,

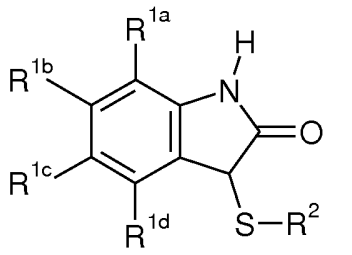
(C_3-C_7)-cycloalkoxy, the cycloalkoxy radical being unsubstituted or being substituted by one or more substituents selected from the group consisting of (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy,

(C_1-C_6)-alkylthio, the alkylthio radical being branched or unbranched and being unsubstituted or substituted by one or more substituents selected from the group consisting of (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy,

(C_3-C_7)-cycloalkylthio, the cycloalkylthio radical being unsubstituted or being substituted by one or more substituents

selected from the group consisting of (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, and
phenyl or 1-naphthyl or 2-naphthyl or a five- or six-membered heteroaromatic ring having 1 to 2 heteroatoms, the heteroatoms being selected independently of one another from the group consisting of O or N, and the aryl or heteroaryl radical being unsubstituted or being substituted by one or more substituents selected from the group consisting of (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy or (C_3-C_7)-cycloalkyl or (C_1-C_4)-alkylthio,

starting from a compound of the formula (II)



(II)

, in which

R^{1a} to R^{1d} are defined as in formula (I), and
R^2 is an unsubstituted or substituted (C_1-C_{14})-alkyl, (C_3-C_7)-cycloalkyl, benzyl or a $CH_2-C(O)O-(C_1-C_6)$-alkyl,
characterized in that
a) a compound of the formula (II) is dissolved or suspended in a polar solvent,
b) a sulfur-containing salt is added to the solution or suspension,
and
c) the reaction mixture is heated under reflux at a temperature which corresponds at most to the boiling temperature of the polar solvent.

The process of the invention allows simple, safe, and cost-effective preparation of compounds of the formula (I) from compounds of the formula (II).

The process can be carried out safely even on the operational scale. Advantageously, moreover, the process can be flexibly tailored to the existing apparatus.

A particularly surprising and very advantageous feature is that the process of the invention does not produce intensely odored waste gases of the kind which really are to be expected from such a reaction. A presumed basis for this advantage is that the sulfur-containing leaving group is bound in a nonvolatile form.

Preferred phenyl substituents R^{1a}, R^{1b}, R^{1c}, and R^{1d} are radicals selected independently of one another from the group consisting of hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, fluorine, chlorine, bromine, and trifluoromethyl.

Particularly preferred phenyl substituents R^{1a}, R^{1b}, R^{1c}, and R^{1d} are radicals selected independently of one another from the group consisting of hydrogen, methoxy, fluorine, and chlorine.

Preferred for the radical R^2 is unsubstituted or substituted (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, benzyl or $CH_2-C(O)O-(C_1-C_6)$-alkyl, the substituents being selected independently of one another from the group consisting of hydrogen, (C_1-C_6)-alkyl or (C_3-C_7)-cycloalkyl.

A preferred polar solvent is water, a (C_1-C_4) alcohol or a mixture of water and a (C_1-C_4) alcohol. In this context, it is possible to employ, inter alia, a mixture of water and a polar solvent which is stable under the reaction conditions but is other than a (C_1-C_4) alcohol. The polar solvent wholly or at least partly dissolves the sulfur-containing salt that acts as a reducing agent.

In a further preferred embodiment, the sulfur-containing salt is selected from the group consisting of alkali metal or alkaline earth metal sulfite, alkali metal or alkaline earth metal bisulfite, alkali metal or alkaline earth metal thionite, alkali metal or alkaline earth metal dithionite or alkali metal or alkaline earth metal thiosulfate.

Especially preferred as sulfur-containing salts are the respective sodium salts, i.e., the sulfur-containing salt is selected from the group consisting of sodium bisulfite, sodium sulfite, sodium thionite, sodium dithionite, and sodium thiosulfate.

The sulfur-containing salts that are most preferred are sodium bisulfite or sodium sulfite, and a mixture of both can also be used.

If sodium bisulfite is used as a sulfur-containing salt, water is the preferred polar solvent, since this combination of reagent and solvent leads to very high yields.

It is preferred to add 2 to 3 equivalents of the sulfur-containing salt to the reaction mixture.

It is particularly preferred to add 2 to 2.5 equivalents of the sulfur-containing salt to the reaction mixture.

A further preferred embodiment envisages the reaction mixture being heated to a temperature which lies within a range whose lower limit is 40°C and whose upper limit corresponds to the reflux temperature of the solvent.

Particularly preferred, however, is the version of the process at a reaction temperature which corresponds approximately to the boiling temperature of the solvent respectively used. In this case the reaction may also be carried out under elevated pressure, in order to attain a temperature which lies up to 15°C above the boiling point of the respective solvent under atmospheric pressure. A reaction temperature increased by up to 15°C makes it possible, advantageously, for the reaction time to be shortened.

In one preferred embodiment the heating of the reaction mixture takes place with stirring for a duration of 1 to 48 hours.

Particularly preferred is the heating of the reaction mixture with stirring for a duration of 1 to 24 hours, and a reaction time of 2 to 12 hours is most preferred.

It is within the scope of the invention to add a defoamer or a mixture of different defoamers to the reaction mixture before the boiling temperature of the solvent respectively used has been reached. Examples of suitable defoamers include Fluowet PL 80 and Korasilon LP-Si E 1051.

The defoamer preferably is added before the beginning of the heating of the reaction mixture. It is likewise within the scope of the invention for, prior to the isolation of the reaction product, a precipitant to be added to the reaction mixture, the precipitant being selected from the group of polar solvents consisting of water, a (C_1-C_4) alcohol or a mixture of water and a (C_1-C_4) alcohol. The addition of the precipitant has the advantage, in particular, that the yield is increased on isolation by filtration.

Alternatively to isolation by filtration, the reaction product of formula (I) may also be used further without isolation, in the form, for example, of a suspension or solution, in the synthesis of fine chemicals and active ingredients in pharmacy and/or agriculture.

A further aspect, accordingly, concerns the use of a compound of the formula (I) for preparing fine chemicals and active ingredients with pharmaceutical or herbicidal activity.

The use of a compound of the formula (I) for preparing active ingredients with insecticidal or fungicidal activity additionally.

The examples below elucidate the invention in more detail.

EXAMPLES

Example 1:
Preparation of 7-fluoro-1,3-dihydro-2*H*-indol-2-one
7-Fluoro-3-(methylsulfanyl)-1,3-dihydro-2*H*-indol-2-one (270.5 g) was dissolved in water (2000 g) and admixed with sodium bisulfite (300 g). The mixture was heated to reflux, in the course of which it was vigorously stirred. After 2.25 h, the mixture was cooled to 25°C and isolated by filtration on a suction filter. It was washed twice with water (500 g each time) and then dried under reduced pressure (<50 mbar, 50°C). This gave 7-fluoro-1,3-dihydro-2*H*-indol-2-one as a white solid (206.3 g, 95% yield).

LC-MS: M+H = 152 (100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.59 (s, 2H), 6.94-7.04 (m, 3H), 8.22 (s, broad, H).

Example 2:
Preparation of 5-fluoro-1,3-dihydro-2*H*-indol-2-one
5-Fluoro-3-(methylsulfanyl)-1,3-dihydro-2*H*-indol-2-one (20 g) was reacted in the same way as in Example 1. This gave 5-fluoro-1,3-dihydro-2*H*-indol-2-one as a solid (13.5 g, 93% yield).

LC-MS: M+H = 152 (100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.55 (s, 2H), 6.78 (dd, I H), 6.89-7.00 (m, 2H), 8.32 (s, broad, H).

Example 3:
Preparation of 7-chloro-1,3-dihydro-2*H*-indol-2-one
7-Chloro-3-(methylsulfanyl)-1,3-dihydro-2*H*-indol-2-one (20 g) was reacted in the same way as in Example 1. This gave 7-chloro-1,3-dihydro-2H-indol-2-one as a solid (15.6 g, 99% yield).

LC-MS: M+H = 168 (100%), 170 (60%).

^{1}H-NMR (400 MHz, $CDCI_3$): δ (ppm) = 3.62 (s, 2H), 6.96 (t, 1H), 7.13 (d, I H), 7.22 (d, IH), 8.17 (s, broad, H).

Example 4:
Preparation of 5,7-difluoro-1,3-dihydro-2*H*-indol-2-one
5,7-Difluoro-3-(methylsulfanyl)-1,3-dihydro-2H-indol-2-one (4.25 g) was reacted in the same way as in Example 1. This gave the title compound as a solid (3.04 g, 91% yield).

LC-MS: M+H = 170 (100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.58 (s, 2H), 6.76-6.84 (m, 2H), 7.91 (s, broad, 1H).

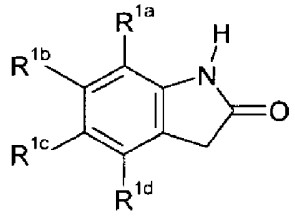
Example 5:
Preparation of 7-methoxy-1,3-dihydro-2*H*-indol-2-one
7-Methoxy-3-(methylsulfanyl)-1,3-dihydro-2H-indol-2-one (1.86 g) was reacted in the same way as in Example 1. This gave the title compound as a solid (1.43 g, 95% yield).

LC-MS: M+H = 164

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.55 (s, 2H), 3.87 (s, 3H), 6.83 (dd, 2H), 6.98 (t, 1H), 7.83 (s, broad, 1H).

Patentkrav

1. Fremgangsmåde til fremstilling af en forbindelse med formel (I)



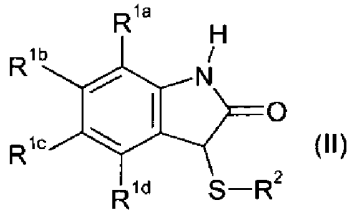
(I)

,

hvor

R^{1a} til R^{1d} er udvalgt uafhængigt af hinanden fra gruppen bestående af hydrogen, fluor, chlor, brom og trifluormethyl, (C_1-C_6)-alkyl, idet alkylgruppen er usubstitueret eller er substitueret med en eller flere substituenter udvalgt af gruppen, der består af (C_1-C_4)-alkoxy eller (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl, idet cycloalkylgruppen er usubstitueret eller er substitueret med en eller flere substituenter udvalgt af gruppen bestående af (C_1-C_4)-alkyl eller (C_3-C_7)-cycloalkyl eller (C_1-C_4)-alkoxy, (C_1-C_6)-alkoxy, idet alkoxygruppen forgrenet eller uforgrenet er usubstitueret eller er substitueret med en eller flere substituenter udvalgt af gruppen bestående af (C_1-C_4)-alkoxy eller (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkoxy, idet cycloalkoxygruppen er usubstitueret eller er substitueret med en eller flere substituenter udvalgt af gruppen bestående af (C_1-C_4)-alkyl eller (C_1-C_4)-alkoxy, (C_1-C_6)-alkylthio, idet alkylthiogruppen forgrenet eller uforgrenet er usubstitueret eller er substitueret med en eller flere substituenter udvalgt af gruppen bestående af (C_1-C_4)-alkyl eller (C_1-C_4)-alkoxy,
(C_3-C_7)-cycloalkylthio, idet cycloalkylthiogruppen er usubstitueret eller er substitueret med en eller flere substituenter udvalgt af gruppen bestående af (C_1-C_4)-alkyl eller (C_1-C_4)-alkoxy, og phenyl eller 1-naphthyl eller 2-naphthyl eller en fem- eller seksleddet heteroaromatisk ring med 1 til 2 heteroatomer, idet heteroatomerne er udvalgt uafhængigt af hinanden fra gruppen bestående af O eller N, og idet aryl- eller heteroarylgruppen er usubstitueret eller er

substitueret med en eller flere substituenter udvalgt af gruppen bestående af (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy eller (C_3-C_7)-cycloalkyl eller (C_1-C_4)-alkylthio, idet der gås ud fra en forbindelse med formel (II)



(II)

,

hvor

R^{1a} til R^{1d} er defineret som i formel (I), og R^2 er en usubstitueret eller substitueret (C_1-C_{14})-alkyl, (C_3-C_7)-cycloalkyl, benzyl eller en CH_2-C(O)O-(C_1-C_6)-alkyl,

kendetegnet ved, at

a) en forbindelse med formel (II) opløses eller suspenderes i et polært opløsningsmiddel,

b) der til opløsningen eller suspensionen tilsættes et svovlholdigt salt, og

c) reaktionsblandingen under reflux opvarmes ved en temperatur, som svarer til maksimalt kogetemperaturen for det polære opløsningsmiddel.

2. Fremgangsmåde til fremstilling af forbindelser med formel (I) ifølge krav 1, kendetegnet ved, at R^{1a} til R^{1d} er udvalgt uafhængigt af hinanden fra gruppen bestående af hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, fluor, chlor, brom og trifluormethyl.

3. Fremgangsmåde til fremstilling af forbindelser med formel (I) ifølge krav 1 eller 2, kendetegnet ved, at R^{1a} til R^{1d} er udvalgt uafhængigt af hinanden fra gruppen bestående af hydrogen, methoxy, fluor og chlor.

4. Fremgangsmåde til fremstilling af forbindelser med formel (I) ifølge et af kravene 1 til 3, kendetegnet ved, at R^2 er en usubstitueret eller substitueret (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, benzyl eller CH_2-C(O)O-(C_1-C_6)-alkyl, idet

substituenterne er udvalgt uafhængigt af hinanden fra gruppen bestående af hydrogen, (C_1-C_6)-alkyl eller (C_3-C_7)-cycloalkyl.

5. Fremgangsmåde til fremstilling af forbindelser med formel (I) ifølge et af kravene 1 til 4, kendetegnet ved, at det polære opløsningsmiddel er vand, en (C_1-C_4)-alkohol eller en blanding af vand og en (C_1-C_4)-alkohol.

6. Fremgangsmåde til fremstilling af forbindelser med formel (I) ifølge et af kravene 1 til 5, kendetegnet ved, at det svovlholdige salt er et alkali- eller jordalkalisulfit, alkali- eller jordalkalibisulfit, alkali- eller jordalkalithionit, alkali- eller jordalkalidithionit eller alkali- eller jordalkalithiosulfat.

7. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge krav 6, kendetegnet ved, at det svovlholdige salt er udvalgt af gruppen bestående af natriumbisulfit, natriumsulfit, natriumthionit, natriumdithionit og natriumthiosulfat.

8. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge krav 7, kendetegnet ved, at det svovlholdige salt er natriumsulfit, natriumbisulfit eller en blanding af begge dele.

9. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge et af kravene 6 til 8, kendetegnet ved, at der til reaktionsblandingen tilsættes 2 til 3 ækvivalenter af det svovlholdige salt.

10. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge krav 9, kendetegnet ved, at der til reaktionsblandingen tilsættes 2 til 2,5 ækvivalenter af det svovlholdige salt.

11. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge et af kravene 1 til 10, kendetegnet ved, at

reaktionsblandingen opvarmes til en temperatur, som ligger mellem 40 °C og reflux-temperaturen for det pågældende opløsningsmiddel.

12. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge krav 11, kendetegnet ved, at reaktionstemperaturen svarer til reflux-temperaturen på det pågældende anvendte opløsningsmiddel.

13. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge et af de foregående krav, kendetegnet ved, at opvarmningen af reaktionsblandingen sker under omrøring i en periode på 1 til 48 timer.

14. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge krav 13, kendetegnet ved, at opvarmningen af reaktionsblandingen sker under omrøring i en periode på 1 til 24 timer, fortrinsvis i en periode på 2 til 12 timer.

15. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge et af de foregående krav, kendetegnet ved, at der til reaktionsblandingen tilsættes et antiskummiddel eller en blanding af forskellige antiskummidler.

16. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge et af de foregående krav, kendetegnet ved, at der til reaktionsblandingen inden isoleringen af reaktionsproduktet ifølge formel (I) ved hjælp af filtrering tilsættes et fældningsmiddel, idet fældningsmidlet er udvalgt af gruppen af de polærer opløsningsmidler bestående af vand, en (C_1-C_4)-alkohol eller en blanding af vand og en (C_1-C_4)-alkohol.

17. Fremgangsmåde til fremstilling af en forbindelse med formel (I) ifølge et af de foregående krav, kendetegnet ved, at reaktionsproduktet isoleres efter afslutning af reaktionen ved hjælp af filtrering.