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

(57) Abrégé/Abstract:
N-[3-(3-Dimethylamino-acryloyl)-phenyl]-N-ethyl-acetamide is reacted with 5-amino- lH-pyrazol-4-carbonitrile in a medium comprising a solution of hydrochloric or hydrobromic acid in a C1-C5 alcohol, or in a C4-C6 aliphatic or cyclic ether, or in a C2-C5 alkoxyalcohol, or in a 5- to 6-membered aromatic heterocyclic solvent, containing 1-2 oxygen atoms, or in mixtures thereof with water, thus forming ZALEPLON.

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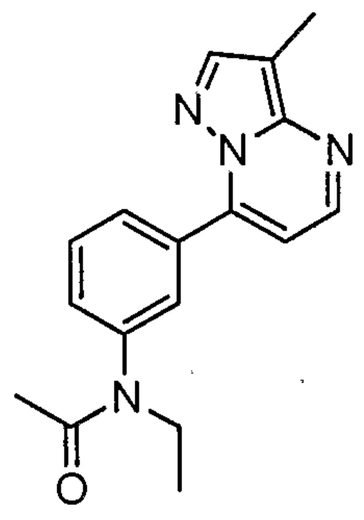
(54) Title: PROCESS FOR THE PREPARATION OF ZALEPLON

(57) Abstract: *N*-[3-(3-Dimethylamino-acryloyl)-phenyl]-*N*-ethyl-acetamide is reacted with 5-amino- 1*H*-pyrazol-4-carbonitrile in a medium comprising a solution of hydrochloric or hydrobromic acid in a C1-C5 alcohol, or in a C4-C6 aliphatic or cyclic ether, or in a C2-C5 alkoxyalcohol, or in a 5- to 6-membered aromatic heterocyclic solvent, containing 1-2 oxygen atoms, or in mixtures thereof with water, thus forming ZALEPLON.

PROCESS FOR THE PREPARATION OF ZALEPLON

## Technical Field

The invention concerns a new method of production of *N*-ethyl-*N*-[3-(3-methyl-pyrazolo[1,5-*a*]pyrimidin-7-yl)-phenyl]-acetamide, known under the INN (International Non-Proprietary Name) zaleplon, of formula I

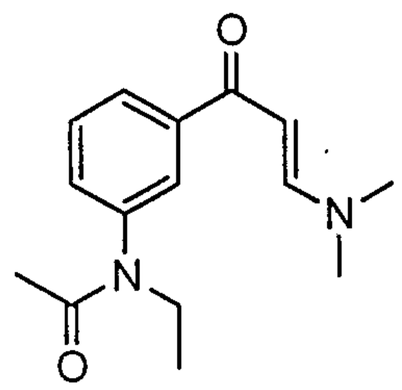


(I)

The aforesaid drug is an important representative of CNS chemotherapeutics, wherein it is used mainly as an anxiolytic, antiepileptic, or sedative/hypnotic drug.

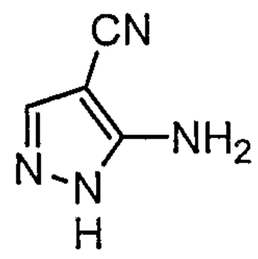
## Background Art

Zaleplon is produced according to published US patents Nos. 4,626,538 and 5,714,607 via reaction of *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-ethyl-acetamide of formula II



(II)

with 5-amino-1*H*-pyrazol-4-carbonitrile of formula III



(III)

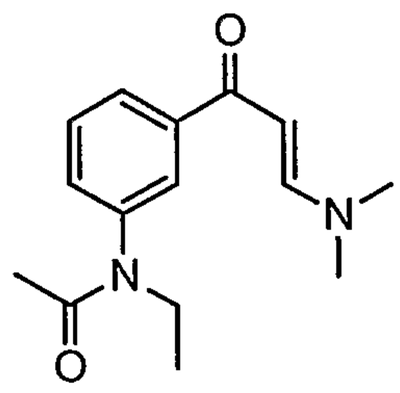
The reaction was performed in the original US patent No. 4,626,538 in anhydrous acetic acid. Later, it was discovered that the reaction is faster and the resulting product is purer if the reaction is carried out in aqueous acetic acid. This procedure is described in US patent No. 5,714,607.

This invention describes a new, improved method of production of *N*-ethyl-*N*-[3-(3-methyl-pyrazolo[1,5-*a*]pyrimidin-7-yl)-phenyl]-acetamide (zaleplon).

Disclosure of Invention

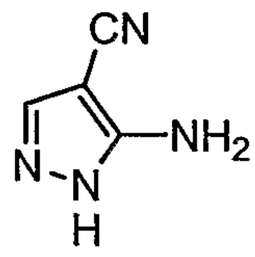
The subject matter of the invention is a new, improved method of production of *N*-ethyl-*N*-[3-(3-methyl-pyrazolo[1,5-*a*]pyrimidin-7-yl)-phenyl]-acetamide (zaleplon). The whole procedure is based on the surprising finding that it is advantageous to perform the reaction of *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-ethyl-acetamide (II) with 5-amino-1*H*-pyrazol-4-carbonitrile (III) in numerous organic solvents or alternatively in their mixtures with water with a number of organic and inorganic acids being used as catalysts.

The essence of the invention consists in reacting *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-ethyl-acetamide of formula II



**(II)**

with 5-amino-1*H*-pyrazol-4-carbonitrile of formula III



**(III)**

in a medium comprising a solution of hydrochloric or hydrobromic acid in a C1-C5 alcohol, or in a C4-C6 aliphatic or cyclic ether, or in a C2-C5 alkoxyalcohol, or in a 5- to 6-membered aromatic heterocyclic solvent, containing 1-2 oxygen atoms, or in a mixture thereof with water.

It has been shown that likewise as when aqueous acetic acid or aqueous formic acid are used, the reaction time gets significantly shorter when the above solvents and the above acidic catalysts are used. Moreover, in some cases, better yields and/or higher purity of the crude product were achieved.

In an usual embodiment, the two starting substances were mixed with a suitable solvent at laboratory temperature. The quantity of the used solvent can be selected from a wide range so that after the reaction is complete and cooled down, crystals of the product fall out in high yields. The reaction mixture was either a homogenous solution or a suspension. A suitable acidic catalyst was added to the mixture created in this way and the mixture was stirred at a temperature from 25 °C to the boiling point of the used solvent. After the reaction was completed, the mixture was cooled down; after crystals fell out, the mixture was left to sit for several hours at 5 up to 10 °C and, subsequently, the crude product was sucked off. In some cases, the reaction mixture was mixed with a suitable co-solvent after it cooled down and the product was sucked off after cooling down.

A number of solvents turned out to be suitable. The use of methanol, ethanol, propanol or 2-propanol turned out to be especially advantageous as high yields of highly pure crude product were obtained. The crude product provided a product with high HPLC purity, usually higher than 99.5% (read from areas of individual peaks) after a single crystallization from a suitable solvent. However, the reaction is not limited only to the environment of hydroxylated solvents; it can be performed in a number of other solvents, for example tetrahydrofuran, dioxane, dimethoxyethane, etc.; these can be used either alone or in admixtures with the above-mentioned hydroxylated solvents, or in their mixtures with water. Presence of 20 to 80 % of water is preferable.

In order for the reaction to proceed successfully, presence of acidic catalysts is necessary. Instead of aqueous acids, solutions of acids in suitable solvents can be used, for example, solutions of hydrogen chloride or hydrogen bromide in various solvents, C1-C5 alcohols being preferable.

The invention is explained in more detail in the following examples. The examples, which illustrate preferred alternatives of production of zaleplon according to the invention, have a purely illustrative character and do not limit the extent of the invention in any respect.

Examples

Example 1

A mixture of compound II (2.6 g, 10 mmol) and nitrile III (1.1 g, 10.2 mmol) in ethanol (30 ml) was dissolved at lab temperature and then, a saturated solution of hydrogen chloride in ethanol (1 ml) was added. The resulting mixture was boiled for 2 hours using a reflux condenser and, then, cooled down to 5 to 10 °C and the precipitated crystals were sucked off, washed with water and air dried. 2.6 g of crude product (85%), m.p. 184-188 °C were obtained. After crystallization, 2.4 g (79%) of crystals were obtained with m.p. 187-188 °C.

Example 2

Following the procedure described in Example 1 wherein the reaction mixture was stirred for 2 days at lab temperature, a similar amount of a product was obtained with m.p. 182-186 °C. After crystallization from methanol, 72% of crystals were obtained with m.p. 185-187 °C.

Example 3

A mixture of compound II (2.6 g, 10 mmol) and nitrile III (1.1 g, 10.2 mmol) in methanol (30 ml) is dissolved at lab temperature and, subsequently, concentrated hydrochloric acid was added (1 ml). The resulting mixture was boiled for 5 hours using a reflux condenser and, then, water was added (50 ml) and the mixture was cooled down to 5 to 10 °C. Crystals that fell out were sucked off, washed with water and air dried. 2.8 g of crude product were obtained (92%), m.p. 185-188 °C.

Example 4

Following the procedure described in Example 1 wherein propanol was used as the solvent instead of ethanol, 86% of the product was obtained with m.p. 185-188 °C.

Example 5

Following the procedure described in Example 1 wherein 2-propanol was used as the solvent instead of ethanol, 91% of the product was obtained with m.p. 184-187 °C.

Example 6

Following the procedure described in Example 1 wherein 2-methoxyethanol was used as the solvent instead of ethanol, 76% of the product was obtained with m.p. 184-187 °C.

Example 7

Following the procedure described in Example 1 wherein 2-ethoxyethanol was used as the solvent instead of ethanol, 79% of the product was obtained with m.p. 184-187 °C.

Example 8

Following the procedure described in Example 1 wherein 70% of aqueous ethanol was used as the solvent instead of ethanol, 87% of the product was obtained with m.p. 185-188 °C.

Example 9

Following the procedure described in Example 1 wherein 50% of aqueous ethanol was used as the solvent instead of ethanol, 69% of the product was obtained with m.p. 184-187 °C.

Example 10

Following the procedure described in Example 1 wherein 30% of aqueous ethanol was used as the solvent instead of ethanol, 72% of the product was obtained with m.p. 184-188 °C.

Example 11

A mixture of compound II (0.26 g, 1 mmol) and nitrile III (0.11 g, 1.0 mmol) in tetrahydrofuran (3 ml) was dissolved at lab temperature and, subsequently, concentrated hydrochloric acid was added (1 ml). The resulting mixture was boiled for 2 hours using a reflux condenser and, then, water was added (5 ml) and the mixture was cooled down to 5 to 10 °C. Crystals that fell out were sucked off, washed with water and air dried. 0.25 g of crude product were obtained (82%), m.p. 184-187 °C.

Example 12

Following the procedure described in Example 11 wherein dioxane was used as the solvent instead of tetrahydrofuran and hexane was added instead of water after the reaction was completed, 86% of the product was obtained with m.p. 183-187 °C

Example 13

Following the procedure described in Example 1 wherein hydrobromic acid was used as the catalyst instead of hydrochloric acid, 81% of the product was obtained with m.p. 184-188 °C.

Example 14

Following the procedure described in Example 1 wherein 10% of sulfuric acid was used as the catalyst instead of hydrochloric acid, 82% of the product was obtained after thorough washing with water and drying with m.p. 184-187 °C.

Example 15

Following the procedure described in Example 1 wherein 10% of orthophosphoric acid was used as the catalyst instead of hydrochloric acid and reaction time was increased to 8 hours, 65% of the product was obtained after thorough washing with water and drying with m.p. 182-186 °C.

Example 16

Following the procedure described in Example 1 wherein perchloric acid was used as the catalyst instead of hydrochloric acid, 69% of the product was obtained after thorough washing with water and drying with m.p. 184-187 °C.

Example 17

A mixture of compound II (0.26 g, 1 mmol) and nitrile III (0.11 g, 1.0 mmol) in ethanol (3 ml) was dissolved at lab temperature and, subsequently, acetic acid was added (1 ml). The resulting mixture was boiled for 3 hours using a reflux condenser and, then, it was cooled down to 5 to 10 °C. Crystals that fell out were sucked off, washed with water and air dried. 0.26 g of crude product were obtained (85%), m.p. 184-187 °C.

Example 18

A mixture of compound II (0.26 g, 1 mmol) and nitrile III (0.11 g, 1.0 mmol) in methanol (3 ml) was dissolved at lab temperature and, subsequently, trifluoroacetic acid was added (0.1 ml). The resulting mixture was boiled for 1 hours using a reflux condenser and, then, it was cooled down to 5 to 10 °C. Crystals that fell out were sucked off, washed with water and air dried. 0.24 g of crude product were obtained (79%), m.p. 184-187 °C.

Example 19

Following the procedure described in Example 1 wherein methanesulfonic acid was used as the catalyst instead of hydrochloric acid, 83% of the product was obtained after thorough washing with water and drying with m.p. 183-186 °C.

Example 20

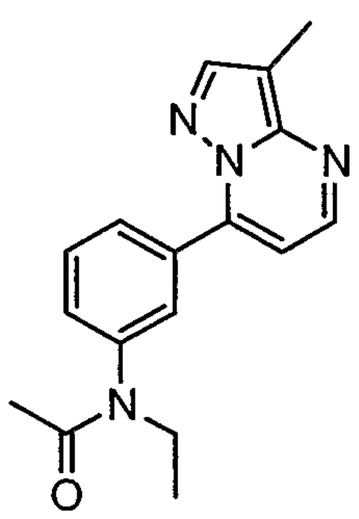
Following the procedure described in Example 1 wherein benzenesulfonic acid was used as the catalyst instead of hydrochloric acid, 66% of the product was obtained after thorough washing with water and drying with m.p. 183-186 °C.

Example 21

Following the procedure described in Example 1 wherein 4-toluenesulfonic acid was used as the catalyst instead of hydrochloric acid, 59% of the product was obtained after thorough washing with water and drying with m.p. 184-187 °C.

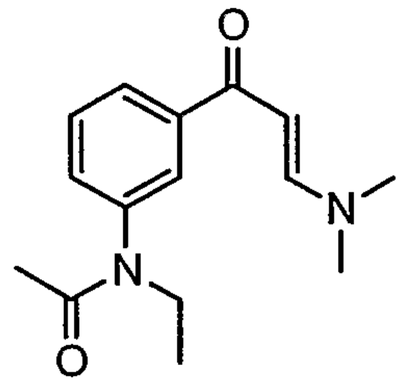
# CLAIMS

1. A method of production of *N*-ethyl-*N*-[3-(3-methyl-pyrazolo[1,5-*a*]pyrimidin-7-yl)-phenyl]-acetamide, known under the INN name zaleplon, of formula I



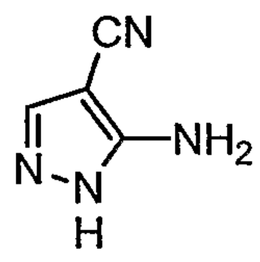
(I)

**characterized in that** *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-ethyl-acetamide of formula II



(II)

is reacted with 5-amino-1*H*-pyrazol-4-carbonitrile of formula III



(III)

in a medium comprising a solution of hydrochloric or hydrobromic acid in a C1-C5 alcohol, or in a C4-C6 aliphatic or cyclic ether, or in a C2-C5 alkoxyalcohol, or in a 5- to 6-membered aromatic heterocyclic solvent, containing 1-2 oxygen atoms, or in a mixture thereof with water.

2. The method according to claim 1 **characterized in that** ethanol is used as the solvent.

3. The method according to claim 1 **characterized in that** methanol is used as the solvent.

4. The method according to claim 1 **characterized in that** propanol is used as the solvent.

5. The method according to claim 1 **characterized in that** 2-propanol is used as the solvent.

6. The method according to claim 1 **characterized in that** 2-methoxyethanol is used as the solvent.

7. The method according to claim 1 **characterized in that** 2-ethoxyethanol is used as the solvent.

8. The method according to claim 1 **characterized in that** tetrahydrofuran is used as the solvent.

9. The method according to claim 1 **characterized in that** dioxane is used as the solvent.

10. The method according to any of the preceding claims **characterized in that** a mixture of a solvent mentioned in claims 1 through 9 with water is used as the solvent, preferably mixtures containing 20 to 80% of water being used.