

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
13 September 2001 (13.09.2001)

PCT

(10) International Publication Number
WO 01/66512 A1(51) International Patent Classification⁷: C07C 229/00

(21) International Application Number: PCT/IB01/00316

(22) International Filing Date: 7 March 2001 (07.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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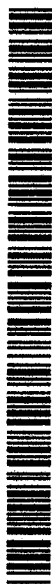
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Road East, Suite 2100, Princeton, NJ 08540 (US).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.



WO 01/66512 A1

(54) Title: ONE-POT SYNTHESIS OF ALKYL 3-CYCLOPROPYLAMINO-2-[2,4-DIBROMO-3-(DIFLUO-
ROMETHOXY)BENZOYL]-2-PROPENOATE AS A USEFUL INTERMEDIATE FOR ANTIBACTERIAL QUINOLONE
MEDICAMENTS(57) Abstract: The present invention relates to a new and industrially advantageous one-pot process for the preparation of alkyl
3-cyclopropyl amino-2-[2,4-dibromo-3-(difluoromethoxy) benzoyl]-2-propenoates of in which R represents methyl or ethyl, which
are valuable intermediates for the production of highly active antibacterial quinolone medicaments.

**ONE - POT SYNTHESIS OF ALKYL 3-CYCLOPROPYLAMINO-
2-[2,4-DIBROMO-3-(DIFLUOROMETHOXY) BENZOYL]-2-
PROPENOATE AS A USEFUL INTERMEDIATE FOR ANTIBACTERIAL
QUINOLONE MEDICAMENTS**

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FIELD OF THE INVENTION

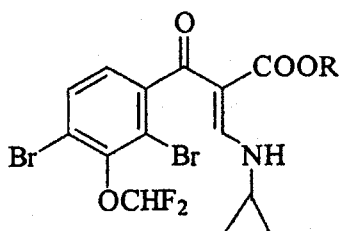
The present invention relates to a new and industrially advantageous one-pot process for the preparation of alkyl 3-cyclopropyl amino-2-[2,4-dibromo-3-(difluoromethoxy) benzoyl]-2-propenoates in which R represents methyl or ethyl, which are valuable intermediates for the production of highly active antibacterial quinolone medicaments.

10

BACKGROUND OF THE INVENTION

A previously known general method for the synthesis of intermediate, alkyl 3-cyclopropyl amino-2-[2,4-dibromo-3-(difluoromethoxy) benzoyl]-2-propenoate of the following formula:

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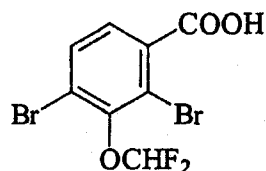
FORMULA I

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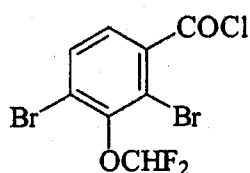
has been reported in US Patent No. 5,935,952 assigned to Toyama Chemical Company Ltd. The general method described in this patent includes, reaction of the compound of the following formula:

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**FORMULA II**

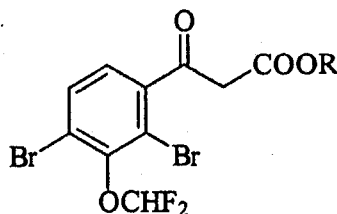
with a halogenating agent such as thionyl chloride to obtain acid chloride of
 5 the following formula:

**FORMULA III**

10 which on reaction with metal salt of malonic ester of the following formula:

**FORMULA IV**

wherein R is the same as defined above, in the presence of magnesium
 15 chloride at a temperature of about 45°C. Decarboxylation of Formula IV
 affords a compound of the following formula:

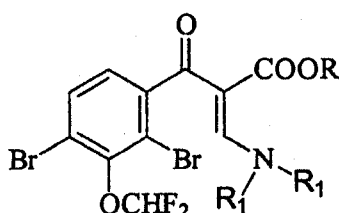


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FORMULA V

in which R is as defined above. Reaction of the compound of Formula V with an acetal such as N, N-dimethylformamide dimethyl acetal, N, N-dimethylformamide diethyl acetal to give a compound of the following formula:

5



FORMULA VI

wherein R₁ is methyl or ethyl, which on reaction with cyclopropylamine gives the intermediate, methyl/ethyl 3-cyclopropyl amino-2-[2,4-dibromo-3-(difluoromethoxy) benzoyl]-2-propenoate, of Formula I.

The above mentioned method described in the prior art for the manufacture of the compound of Formula I suffers from the following limitations and for various reasons stated below are not suitable for commercial purposes.

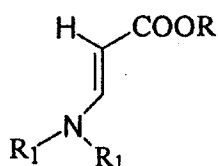
- The process is lengthy involving six steps.
- The process generates a lot of effluent waste and hence is not eco-friendly.

SUMMARY OF THE INVENTION

It is an object of the present invention to solve the problems associated with the prior art and to provide an efficient method.

According to one aspect of the present invention there is provided a one-pot process for the preparation of alkyl 3-cyclopropylamino-2-[2,4-dibromo-3-(difluoromethoxy)benzoyl]-2-propenoate of Formula I. The process provides obvious benefits with respect to economics and convenience to
 5 operate at a commercial scale.

More particularly, the present invention relates to a process for the preparation of alkyl 3-cyclopropylamino-2-[2,4-dibromo-3-difluoromethoxy) benzoyl]-2-propenoate of Formula I, wherein R is methyl or ethyl comprising reacting 2,4-dibromo-3-(difluoromethoxy)benzoic acid of Formula II, with a
 10 halogenating agent to get a corresponding acid chloride of Formula III, which on reaction with ester of 3,3-dialkyl amino acrylate of the following formula:



15

FORMULA VII

wherein R₁ is methyl or ethyl, in a suitable solvent in the presence of an organic base to give alkyl-3,3-dialkylamino-2[2,4-dibromo-3-difluoromethoxy) benzoyl]-2-propenoate of Formula VI wherein R and R₁ are methyl or ethyl
 20 which on treatment with cyclopropylamine affords the product of Formula I, and R is the same as defined above. More particularly, the compound of Formula II is reacted with thionyl chloride to provide an acid chloride of Formula III following a process known in the prior art. The acid chloride is

then reacted with methyl/ethyl ester of 3,3-dimethyl/diethylamino acrylate of Formula VI (R and R₁ are methyl or ethyl) in a suitable solvent in the presence of an organic base at a selected temperature within the range of 40-80°C, preferably, 50-70°C during a period of one to several hours. The suitable solvent is selected from the group comprising of aromatic solvents, chlorinated solvents ester solvents and mixture(s) thereof. Preferably, the solvents are selected from the group comprising benzene, toluene, xylenes, chloroform, dichloroethane, dichloromethane methyl acetate, butyl acetate, ethyl acetate or mixture(s) thereof. The suitable organic base is selected from the group comprising triethylamine, trimethyl amine, picolines, pyridine and pyridine derivatives. The reaction mixture is then cooled and poured into water. The organic layer contains the compound of Formula VI wherein R₁ is methyl or ethyl and is taken as such for reaction with cyclopropylamine at a selected temperature within the range of 0-30°C, preferably 5-10°C for 0.5 to several hours. The desired compound methyl/ethyl 3-cyclopropylamino-2-[2,4-dibromo-3-(difluoromethoxy) benzoyl]-2-propenoate of Formula I is isolated by conventional methods.

In the following section a preferred embodiment is described by way of an example to illustrate the process of this invention. However, this is not intended in any way to limit the scope of the present invention.

DETAILED DESCRIPTION OF THE INVENTION**EXAMPLE 1**

Preparation of Ethyl-3-cyclopropylamino-2-(2,4-dibromo-3-difluoromethoxy) benzoyl]-2-propenoate.

5 To a mixture of 2,4-dibromo-3-(difluoromethoxy) benzoic acid (10g) and thionyl chloride (4.38gm) was added a mixture of toluene (15ml) and N,N-dimethyl formamide (0.2ml). The reaction mixture was heated slowly to reflux and stirred at reflux for about 2.5 hours. The reaction mixture was then cooled to 35°C and added a solution of ethyl 3,3-dimethylaminoacrylate
10 (4.13gm), and triethylamine (3.79gm) in toluene (20ml) drop-wise during a period of about 1 hour maintaining a temperature of 35-40°C. After the addition was over, the reaction temperature was slowly increased to 60-65°C and stirred the reaction mixture for about 24 hours. Cooled the reaction mixture to 30°C, added water (20ml) and stirred for about 10 minutes. The
15 organic layer was separated, cooled to about 5°C and cyclopropylamine (1.82gm) was added to it drop-wise maintaining temperature at 8-10°C during a period of about 10 minutes. Stirred the reaction mixture for about 2 hours, solvent was removed under vacuum (~ 80% of the original amount) and cooled the reaction mixture to about 20°C. The solid separated was filtered
20 and dried to afford ethyl 3-cyclopropylamino-2-[2, 4-dibromo-3-(difluoromethoxy) benzoyl]-2-propenoate (10gm).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those

skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE 2

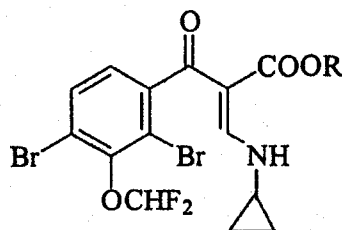
Preparation of ethyl 3-cyclopropylamino-2-[2,4-dibromo-3-

5 (difluoromethoxy)benzoyl]-2-propenoate

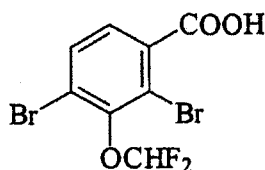
To a mixture of 2,4-dibromo-3-(difluoromethoxy)benzoic acid (50 g) in ethyl acetate (175mL) was added N,N-dimethyl formamide (1mL) and thionyl chloride (18.1g). The reaction mixture was heated to reflux and stirred at reflux for 1 hr. After evaporation of ethyl acetate, (125mL), triethylamine 10 (16.1g) and ethyl 3,3-dimethylaminoacrylate (20.7g) were added to the reaction mixture at room temperature. This reaction mixture was heated to reflux and stirred at reflux for 3 hrs. The mixture was then cooled to 25°C, water (100 mL) was added and the mixture was stirred for about 10 minutes. The organic layer was separated and cyclopropylamine (9.9 g) was added to 15 it and the reaction mixture was stirred at 25°C for 1 hr. The solvent of the reaction mixture was exchanged by isopropanol (200mL), maintaining the temperature about 68°C. The crystallization was achieved by cooling of the mixture, followed by filtration, washing with isopropanol and drying to afford ethyl3-cyclopropylamino-2-[2,4-dibromo-3-(difluoromethoxy)benzoyl]-2- 20 propenoate (58.6 g).

WE CLAIM:

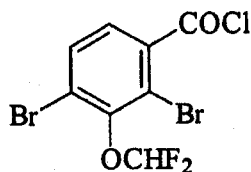
1. A process for the preparation of alkyl 3-cyclopropylamino-2-[2,4-dibromo-3-(difluoromethoxy) benzoyl]-2-propenoate of the following formula:

**FORMULA I**

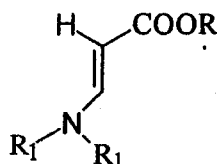
wherein R is methyl or ethyl, comprising reacting 2,4-dibromo-3-(difluoromethoxy) benzoic acid of the following formula:

**FORMULA II**

with a halogenating agent to get a corresponding acid chloride of the following formula:

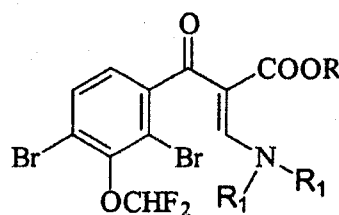
**FORMULA III**

which on reaction with alkyl ester of 3,3-dialkyl amino acrylate of the following formula:



FORMULA VII

wherein R₁ is methyl or ethyl in a suitable solvent in the presence of an organic base, to give alkyl 3, 3-dialkylamino-2-[2,4-dibromo-3-(difluoromethoxy) benzoyl]-2-propenoate of the following formula:



FORMULA VI

wherein R and R₁ are methyl or ethyl wherein R and R₁ are the same as defined above, which on treatment with cyclopropylamine affords the product of Formula I.

2. The process of claim 1 wherein the halogenating agent is thionyl chloride.
3. The process of claim 1 wherein the alkyl ester of 3,3-dialkylaminoacrylate is methyl ester of 3,3-dimethylaminoacrylate.

4. The process of claim 1 wherein the alkyl ester of 3,3-dialkylamino acrylate is ethyl ester of 3,3-diethylamino acrylate.
5. The process of claim 1 wherein the solvent is selected from a group comprising aromatic solvents, chlorinated solvents, ester solvents and mixture(s) thereof.
6. The process of claim 5 wherein a solvent is selected from the group comprising benzene, toluene, xylenes, chloroform, dichloromethane, dichloroethane methyl acetate, butyl acetate, ethyl acetate and mixture(s) thereof.
7. The process of claim 1 wherein the organic base is selected from the group comprising triethylamine, trimethylamine, picoline(s), pyridine and pyridine derivatives.
8. The process of claim 1 wherein the reaction temperature is in the range of 40-80°C.
9. The process of claim 8 wherein the reaction temperature is in the range of 50-70°C.
10. Use of the compound of Formula I prepared by the process of claim 1 for the synthesis of quinolone medicaments.