

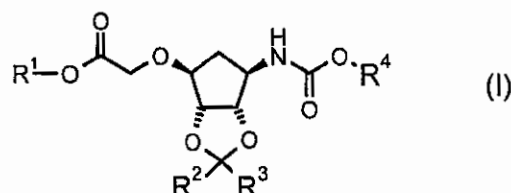
CHEMICAL PROCESS

The present invention concerns a process for the preparation of alkoxy carbonyl methoxy cyclopentanes which are useful intermediates in the preparation of pharmaceutically active triazolo[4,5-*d*]pyrimidine cyclopentanes.

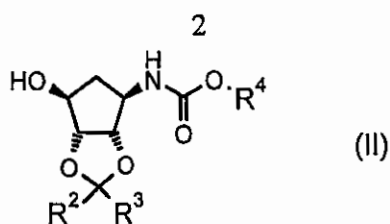
The compound [1*S*-(1 α , 2 α , 3 β (1*S**, 2*R**), 5 β)]-3-[7-[2-(3,4-difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol (Compound A), and similar such compounds, are disclosed in WO 00/34283 and WO 99/05143. These compounds are disclosed as P_{2T} (which is now usually referred to as P_{2Y12}) receptor antagonists. Such antagonists can be used as, *inter alia*, inhibitors of platelet activation, aggregation or degranulation.

Compounds of formula (I) (see below) are useful in the preparation of Compound A (see example 1 of WO 01/92263). The preparation of a compound of formula (I) is disclosed in example 1 of WO 01/92263 and in that example the process was conducted at 0°C. It has been found that when scaling up the process of example 1 of WO 01/92263 (say to more than 0.2 mole scale) and keeping the temperature at 0°C, competing side-reactions lead to a significant increase in the level of impurities, an increase in the reagent requirement, and a resulting reduction in the percentage yield of compound of formula (I). This is clearly a problem as it makes the process more costly and less efficient. We have now unexpectedly found that when the process is operated on a 0.2 mole scale or more, the use of a lower temperature allows the compound of formula (I) to be produced in good yield and minimizes the products of the unwanted side reactions.

The present invention provides a process for the preparation of a compound of formula (I):



wherein R¹ is C₁₋₆ alkyl; R² and R³ are, independently, C₁₋₆ alkyl; and R⁴ is C₁₋₆ alkyl (such as *tert*-butyl) or benzyl (wherein the phenyl ring of benzyl is optionally substituted by nitro, S(O)₂(C₁₋₄ alkyl), cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)(C₁₋₄ alkyl), N(C₁₋₆ alkyl)₂, CF₃ or OCF₃); the process comprising reacting a compound of formula (II):



wherein R², R³ and R⁴ are as defined above, with a suitable base; and reacting the product so formed with R¹OC(O)CH₂X, wherein R¹ is as defined above and X is chloro, bromo or iodo; wherein the process is carried out in a suitable solvent at a temperature in the range
 5 -40°C to -5°C; and wherein at least 0.2 moles of the compound of formula (II) are used in the process.

Alkyl groups and moieties are straight or branched chain and comprise, for example, 1 to 6 (such as 1 to 4) carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

10 In one particular aspect the present invention provides a process wherein R¹ is C₁₋₄ alkyl (for example ethyl).

In another aspect the present invention provides a process wherein R² and R³ are, independently, C₁₋₄ alkyl; for example R² and R³ are both methyl.

In a further aspect of the invention R⁴ is benzyl (wherein the phenyl ring of benzyl is
 15 optionally substituted by C₁₋₄ alkyl); for example R⁴ is unsubstituted benzyl.

In a still further aspect the present invention provides a process wherein X is bromo.

Suitable bases include an alkali metal C₁₋₆ alkoxide (for example potassium tert-butoxide).

In another aspect of the invention the molar ratio of suitable base: R¹O₂CCH₂X :
 20 compound of formula (II) is (1 to 1.3):(1 to 1.3):1, for example (1.1 to 1.3):(1.1 to 1.3):1, such as about 1.2:1.2:1.

Suitable solvents include cyclic and aliphatic ethers (such as tetrahydrofuran, diethyl ether, diisopropyl ether or methyl tert-butyl ether) and aromatic solvents (such as benzene, toluene or a xylene). The solvent can be a mixture of two or more solvents (for example a
 25 mixture of an ether and an aromatic solvent, as exemplified above). In another aspect the invention provides a process wherein an ether, as exemplified above, is used as solvent.

In yet another aspect of the invention the temperature is in the range -30°C to -10°C, for example -25°C to -15°C.

In a further aspect the process of the present invention comprises adding a solution of
 30 suitable base to a solution of a compound of formula (II) at -15 to -25°C, and then adding to

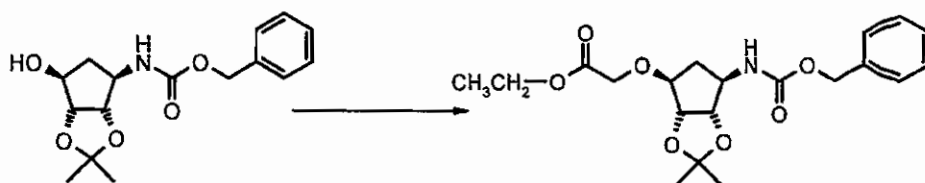
this mixture a solution of $R^1OC(O)CH_2X$ at -15 to -25°C , a suitable ether being used as solvent.

A compound of formula (II) can be prepared by a method, or a method analogous to a method, disclosed in the literature (for example WO 01/92263).

5 The following Example illustrates the invention.

EXAMPLE 1

This Example illustrates a process for the preparation of [3aS-(3 α ,4 α ,6 α ,6 α)]-[2,2-dimethyl-6-((ethoxycarbonyl)methoxy)-tetrahydro-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester.



A solution (Solution A) of [3aS-(3 α ,4 α ,6 α ,6 α)]-[tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester (80g, 260 mmol) in THF (160ml), under a nitrogen atmosphere, was cooled to -22°C . A solution of potassium tert-butoxide (36.1g, 312 mmol) in THF was prepared and added to the cooled Solution A over a period of 30 minutes, while maintaining the reaction temperature at about -20°C . This provided a reaction mixture.

A pre-made solution of ethyl bromoacetate (53.2g, 312 mmol) in THF was then added to the reaction mixture over a period of 30 minutes while maintaining the reaction temperature at about -20°C . The resulting mixture was stirred for approximately an hour at -22°C . HPLC analysis showed that there was a 98% conversion to the desired product.

Table below shows variations on this process.

Ex	Mole ratios of reagents to (II)		<u>t-BuOK</u> Addition		<u>EtBrAc</u> Addition		<u>Hold time</u> (min.)
	t-BuOK	EtBrAc	<u>Time</u> (min.)	<u>Temp.</u> ($^\circ\text{C}$)	<u>Time</u> (min.)	<u>Temp.</u> ($^\circ\text{C}$)	
2	1.40	1.46	13	-20	34	-20	23
3	1.15	1.15	22	-22	42	-22	20

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Ex	Mole ratios of reagents to (II)		<u>t-BuOK</u> <u>Addition</u>		<u>EtBrAc</u> <u>Addition</u>		<u>Hold time</u> <u>(min.)</u>
	t-BuOK	EtBrAc	<u>Time</u> <u>(min.)</u>	<u>Temp.</u> <u>(°C)</u>	<u>Time</u> <u>(min.)</u>	<u>Temp.</u> <u>(°C)</u>	
4	1.20	1.20	30	-20	45	-20	15
5	1.10	1.10	20	-30	30	-30	20
6	1.20	1.20	20	-22	30	-22	20
7	1.10	1.10	20	-10	30	-10	20
8*	1.20	1.20	20	-22	30	-22	20
9	1.20	1.20	30	-22	180	-22	150
10	1.20	1.20	25	-21	45	-21	10
11	1.20	1.20	30	-22	40	-20	10
12	1.2	1.2	13	-23/-28	10	-22/-28	30
13	1.15	1.15	12	-20/-22	15	-19/-24	30

Ex = Example number

(II) = [3aS-(3α,4α,6α,6α)]-[tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester

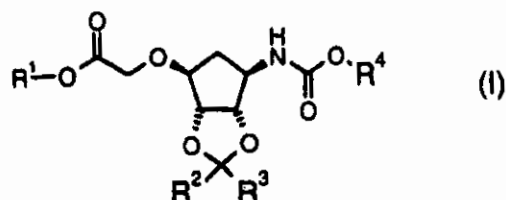
5 t-BuOK = potassium tert-butoxide

EtBrAc = ethyl bromoacetate

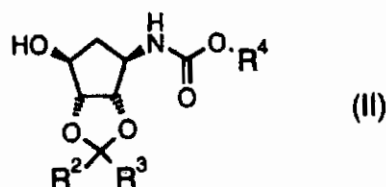
* = Both the THF solution of compound of formula (II) and potassium *tert*-butoxide were filtered before use

Claims

1. A process for the preparation of a compound of formula (I):



wherein R^1 is C_{1-6} alkyl; R^2 and R^3 are, independently, C_{1-6} alkyl; and R^4 is C_{1-6} alkyl or benzyl (wherein the phenyl ring of benzyl is optionally substituted by nitro, $S(O)_2(C_{1-4}$ alkyl), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)(C_{1-4}$ alkyl), $N(C_{1-6}$ alkyl) $_2$, CF_3 or OCF_3); the process comprising reacting a compound of formula (II):



wherein R^2 , R^3 and R^4 are as defined above, with a suitable base; and reacting the product so formed with $R^1OC(O)CH_2X$, wherein R^1 is as defined above and X is chloro, bromo or iodo; wherein the process is carried out in a suitable solvent at a temperature in the range $-40^\circ C$ to $-5^\circ C$; and wherein at least 0.2 moles of the compound of formula (II) are used in the process.

2. A process as claimed in claim 1 wherein R^1 , R^2 and R^3 are independently selected from C_{1-4} alkyl.
3. A process as claimed in claim 1 or 2 wherein R^1 is ethyl.
4. A process as claimed in claim 1, 2 or 3 wherein R^2 and R^3 are methyl.
5. A process as claimed in claim 1, 2, 3 or 4 wherein R^4 is benzyl optionally substituted by C_{1-4} alkyl.

6. A process as claimed in claim 1, 2, 3, 4 or 5 wherein R^4 is unsubstituted benzyl.
7. A process as claimed in any one of claims 1 to 6 wherein X is bromo.
8. A process as claimed in any one of claims 1 to 7 wherein the base is an alkali metal C_{1-6} alkoxide.
9. A process as claimed in any one of claims 1 to 8 wherein the base is potassium tert-butoxide.
10. A process as claimed in any one of claims 1 to 9 wherein the molar ratio of suitable base: $R^1O_2CCH_2X$: compound of formula (II) is (1 to 1.3):(1 to 1.3):1.
11. A process as claimed in any one of claims 1 to 10 wherein the molar ratio of suitable base: $R^1O_2CCH_2X$: compound of formula (II) is (1.1 to 1.3):(1.1 to 1.3):1.
12. A process as claimed in any one of claims 1 to 11 wherein the molar ratio of suitable base: $R^1O_2CCH_2X$: compound of formula (II) is 1.2:1.2:1.
13. A process as claimed in any one of claims 1 to 12 wherein the solvent is selected from a cyclic ether, an aliphatic ethers and an aromatic solvent.
14. A process as claimed in any one of claims 1 to 13 wherein the solvent is selected from tetrahydrofuran, diethyl ether, diisopropyl ether, methyl tert-butyl ether, benzene, toluene and xylene; and a mixture of two or more of said solvents.
15. A process as claimed in any one of claims 1 to 14 wherein the solvent is tetrahydrofuran.
16. A process as claimed in any one of claims 1 to 15 wherein the temperature is in the range -30°C to -10°C .
17. A process as claimed in any one of claims 1 to 16 wherein the temperature is in the range -25°C to -15°C .