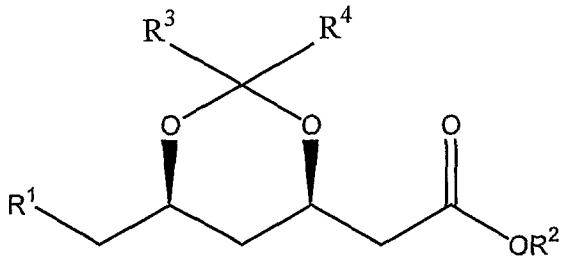
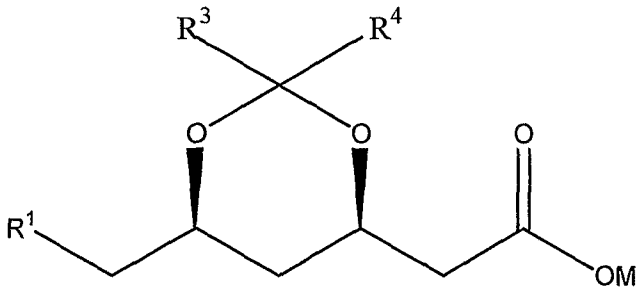
PROCESS FOR THE PREPARATION OF DIOXANE ACETIC ACID ESTERS

The invention relates to a process for the preparation of an ester of formula (1)



(1)

wherein R^1 represents a leaving group, CN, OH or a $COOR^5$ group, R^3 and R^4 each independently represent a C1-3 alkyl group and R^2 and R^5 each independently represent an ester residue, wherein the corresponding salt with formula (2)



(2)

wherein M represents H or an alkali (earth) metal in an inert solvent is contacted with an acid chloride forming agent to form the corresponding acid chloride, and the acid chloride is contacted with an alcohol with formula R^2OH in the presence of N-methyl morpholine (NMM).

Many processes for the preparation of esters are known in the art, for instance the preparation of esters via the formation of the acid chloride. It was, however, to be expected that such processes would not lead to high yields due to the lack of stability of the present compound under acidic conditions.

It is the object of the invention to provide a process for the

preparation of esters with high yield in a robust process, even at large scale and with relatively high concentrations.

Surprisingly it has been found that even sterically hindered esters that are difficult to obtain in esterifications like t-butyl esters of the acid unstable molecules of formula (1), can be obtained in high yield in an easily reproducible process.

With the process according to the invention esters with formula (1) that are unstable under acidic conditions, for instance with pH < 4, can be prepared in high yield.

R^1 represents a leaving group, CN, OH or a $COOR^5$ group wherein R^5 represents an ester residue, for example an alkyl group with for instance 1-6 C-atoms, or an aryl group with for instance 6-12 C-atoms. A leaving group by definition is a group that can easily be replaced, for example a halogen, for instance Cl, Br or I; a tosylate group; a mesylate group; an acyloxy group, with, for instance, 1-6 C-atoms in particular an acetoxy group; a phenacetyloxy group; an alkoxy group with, for instance, 1-6 C-atoms or an (hetero) aryloxy group with, for instance, 6-12 C-atoms . Preferably R^1 represents Cl.

R^2 represents an ester residue, preferably an alkyl group, for instance an alkyl group with 1-6 C-atoms or an aryl group, for instance an aryl group with 6-12 C-atoms, in particular a methyl, ethyl, propyl, isobutyl or t.butyl group. An important group of esters that can be prepared with the process according to the invention are t.butyl esters.

R^3 and R^4 each independently represent a C1-C3 alkyl group, for instance a methyl or ethyl group. Preferably R^3 and R^4 both represent methyl.

M in formula (2) can be chosen from the group of H, alkali metals, for instance lithium, sodium, potassium and alkali earth metals, for instance magnesium or calcium. Preferably M represents sodium or potassium.

The acid chloride forming agent can be chosen from the group of reagents that is generally known as such. Suitable examples of acid chloride forming agents are oxalyl chloride, thionyl chloride, PCl_3, PCl_5, and $POCl_3$. Preferably the acid chloride forming agent is used in an excess relative to the amount the salt with formula (2), for instance between 1 and 3 equivalents, more preferably between 1.2 and 1.8 equivalents.

If desired, in the acid chloride formation also a catalyst may be present. The amount of catalyst may for instance vary from 0-1, preferably 0-0.5 equivalents, calculated with respect to the amount of salt with formula (2). Higher

amounts of catalyst are also possible, but will normally have no extra advantageous effect. Preferably the amount of catalyst, if any, will be between 0.05 and 0.2 equivalents calculated with respect to the salt with formula (2).Suitable catalysts are the catalysts generally know to accelerate acid chloride formation, for instance dimethylformamide (DMF) and N-methylpyrrolidone (NMP).

The conversion of the acid chloride into the ester with formula (1) is carried out in the presence of an alcohol with formula R^2OH. The amount of alcohol with formula R^2OH is not very critical and preferably is between 1 and 15 equivalent calculated with respect to the amount of salt with formula (2), more preferably between 2 and 13, most preferably between 3 and 6. Surprisingly it has been found that even t.-butyl esters can be prepared with high yield using a relatively low amount of t.-butyl alcohol.

The conversion of the acid chloride into the ester with formula (1) is carried out in the presence of NMM. In practice a small amount of NMM, efficient to catch eventually remaining free HCl, for instance 1.5 to 2.5, preferably 1.8 to 2.0 equivalents calculated with respect to the amount of salt with formula (2) is applied. When a large excess of acid chloride forming agent is used, preferably higher amounts of NMM are used, and when a lower excess of acid chloride forming agent is used, preferably lower amounts of NMM are used.

The acid chloride formation reaction preferably is carried out at a temperature between -30° and 60°C, more preferably between 20 and 50°C. The conversion of the acid chloride into the ester with formula (1) preferably is carried out at a temperature between 20 and 80°C, more preferably between 20 and 50°C.

The process of the present invention may be carried out in one step. Preferably first the salt with formula (2) is converted into the corresponding acid chloride, and subsequently the acid chloride is contacted with the alcohol with formula R^2OH and NMM. In a particularly preferred embodiment the acid chloride formed is quenched with NMM and the alcohol with formula R^2OH.

The product with formula 1, wherein R^1 represents a leaving group may subsequently be converted into the corresponding compound wherein R^1 represents an acyloxy group. This can be achieved in a manner known per se, for instance by reaction with an acyloxylating agent for instance a carboxylic or sulphonic acid, a quaternary ammonium or phosphonium salt, a carboxylic or sulphonic acid quaternary ammonium or phosphonium salt or a combination thereof. Preferably a combination of a quaternary phosphonium salt and a carboxylic or sulphonic acid salt is used as the acyloxylating agent.

Subsequently the compound with formula 1, wherein R^1 represents an acyloxy group can be converted in the corresponding compound wherein R^1 represents a hydroxy group, for instance by subjecting it to solvolysis in the presence of a base. Suitable bases are, for instance, alkali (earth) metal hydroxides or carbonates or organic bases, for instance alkali (earth) metal carboxylic acids, for instance acetates, ammonia, pyridines, amines, for instance triethylamine and the like.

The invention will be elucidated by the following examples.

Example I

1864 g of an aqueous solution of the (4R-cis)-(6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetic acid, sodium salt (3.31 moles) and 4.8 L of toluene were mixed and water was removed by azeotropic distillation under reduced pressure. Subsequently, 870 g of fresh toluene were added and removed by distillation. To the obtained suspension was added 33.4g of NMP. Then 588 g of oxalyl chloride were added while maintaining the temperature at 20 °C. The resulting mixture was stirred for 6 hours at 20-25 °C and then slowly added to a mixture of 979 g of t.-butanol and 836 g of *N*-methyl morpholine. After stirring for 1 hour, 3966 g of an 8% (w/w) aqueous NaOH solution was added and the resulting mixture stirred for 1.5 hours at 40 °C. After washing the organic phase with 3300 g of water, 3064 g of a toluene solution of the desired t.-butyl ester was obtained, corresponding to 751 g (81%) of product.

Example II

In a 100 ml HEL Vessel with 4 blade stirrer 8.0 g (4R-cis)-(6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetic acid, sodium salt (92.4%; 30 mmol) was suspended in 41 g toluene and 0.3 g NMP (3 mmol). In 1h 4.5 g (36 mmol) oxalylchloride was dosed at a temperature of 15-20°C. The reaction mixture (50 g) was stirred for 2.5 hours. The reaction mixture was split into 2 parts: Part A (23.83 g) and part B (24.25 g). Part A of the reaction mixture was dosed during 1 h. to a mixture of 22.2 g (20 eq.) t.-butanol and 3.0 g (2 eq.) NMM at 25°C. The reaction mixture was stirred overnight and analyzed by GC. The yield of the t.-butyl ester was 88%.

Examples III-V

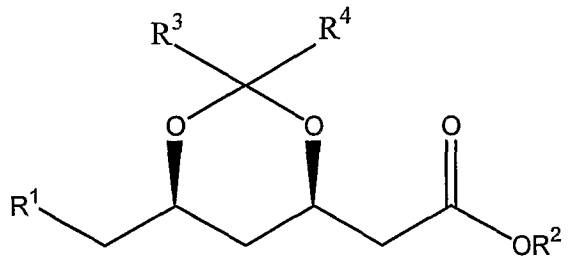
Following the same procedure as described in Example I, the ethyl, isopropyl and n-hexyl esters, respectively, are prepared wherein instead of 4 eq. butanol, now 4 eq. ethanol, 4 eq. isopropanol and 4 eq. n-hexanol, respectively is used. The yield of the desired ethyl, isopropyl and n-hexyl ester was 89 mol%, 88 mol% and 84 mol% respectively, calculated with respect to the sodium salt starting material.

Example VI

A mixture of 35.0 g of t-butyl (4R-cis)-(6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetate, 14.8 g of tetrabutyl phosphonium bromide, 16.0 g of potassium acetate and 5.9 g of toluene were heated to 105 °C under reduced pressure. After 22 hours at this temperature the reaction mixture was cooled to ambient temperature after which 400 g of heptane and 350 g of water were added. The organic phase was washed with 150 g of water and subsequently treated with 3.0 g of activated carbon. After filtration of the carbon, the solution was concentrated and subsequently cooled to -10 °C after which crystallised product was isolated by means of filtration. Yield 24.9 g (76%) of a white crystalline material

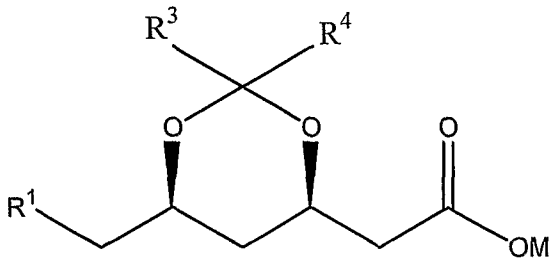
CLAIMS

1. Process for the preparation of an ester of formula (1),



(1)

wherein R^1 represents a leaving group, CN, OH or a $COOR^5$ group, R^3 and R^4 each independently represent a 1-3 C alkyl group, and R^2 and R^5 each independently represent an ester residue, wherein the corresponding salt with formula (2),



(2)

wherein M represents H or an alkali (earth) metal in an inert solvent is contacted with an acid chloride forming agent to form the corresponding acid chloride, and the acid chloride is contacted with an alcohol with formula R^2OH in the presence of N-methyl-morpholine.

2. Process according to claim 1, wherein M represents an alkali metal.
3. Process according to claim 1 or 2, wherein R^2 represents an alkyl group.
4. Process according to claim 3, wherein R^2 represents a t.-butyl group.
5. Process according to any one of claims 1-4, wherein the acid chloride forming agent is oxalylchloride.
6. Process according to any one of claims 1-5, wherein the acid chloride formation is performed in the presence of a catalyst.
7. Process according to any one of claims 1-6, wherein the amount of alcohol

with formula R^2OH is between 3 and 6 equivalents calculated with respect to the amount of salt with formula (2).

8. Process according to any one of claims 1-7, wherein first the salt with formula (2) is converted into the corresponding acid chloride and subsequently the acid chloride is contacted with the alcohol with formula R^2OH and N-methyl-morpholine.
9. Process according to claim 8, wherein the acid chloride is quenched with the alcohol with formula R^2OH and N-methyl-morpholine.
10. Process according to any one of claims 1-9, wherein R^1 represents a leaving group, and wherein the ester of formula 1 wherein R^1 represents a leaving group is subsequently converted into the corresponding ester with formula 1 wherein R1 represents an acyloxy group.
11. Process according to claim 10, wherein first an ester of formula 1 wherein R^1 represents an acyloxy group is prepared and subsequently the ester of formula 1 is converted into the corresponding compound with formula 1 wherein R^1 represents OH.