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(54) Title: PROCESS FOR THE PRODUCTION OF ESTERS OF NITRIC ACID

(57) Abstract: Organic nitrates are prepared from mono-, di- or polyhydric alcohols by (i) simultaneously feeding a first continuous-flow microreactor unit with (a) concentrated nitric acid, (b) acetic anhydride, (c) optionally, a catalytic amount of a strong inorganic acid other than nitric acid, and (d) optionally, a solvent, to obtain a solution of acetyl nitrate, and (ii) simultaneously feeding a second continuous-flow microreactor with the solution of acetyl nitrate obtained in step (i) and said mono-, di- or polyhydric alcohol in liquid form or dissolved in a solvent to obtain a solution of said organic nitrate, and (iii) optionally, isolating said organic nitrate from the solution obtained in step (ii). The process of the invention is particularly suited for mono-nitration of dihydric alcohols such as 1,4-butanediol.



Process for the Production of Esters of Nitric Acid

The invention relates to a process for the production of organic nitrates (i.e., esters of nitric acid with organic hydroxy compounds). In addition to their well known applications as explosives and propellants, some organic nitrates are useful as pharmaceutically active substances (e.g. glycerol trinitrate) or intermediates in the syntheses of pharmaceutically active substances. For example, 4-nitrooxybutan-1-ol (4-nitryloxybutan-1-ol, 1,4-butylene glycol mononitrate) is an intermediate in the synthesis of naproxcinod (nitronaproxen; WO 01/10814 A1).

The classical method for preparing organic nitrates comprises reacting hydroxy compounds with a mixture of nitric acid and sulfuric acid. While this method has been optimized for decades in the production of explosives such as glycerol trinitrate, ethylene glycol dinitrate or pentaerythritol tetranitrate, it is not satisfactory in the preparation of mononitrates derived from dihydric or polyhydric alcohols, because the mixture of nitric acid and sulfuric acid is highly reactive which makes it difficult to control the reaction in a way that allows to obtain the mononitrate as main product. Therefore one known approach for the preparation of mononitrates from diols is to first prepare the dinitrate and then hydrolyze one nitrate moiety to obtain the mononitrate. Another possibility is to protect one hydroxy group, e.g. by acylation, before the remaining hydroxy group is reacted with nitric acid and the protective group is cleaved in a subsequent step (see e.g. WO 2009/000723 A1 or WO 2009/046992 A1). Both ways are tedious and require at least one additional reaction step.

Attempts were made to obtain and isolate the mononitrate of 1,4-butanediol by using "stabilized" nitric acid in large excess in order to obtain a reasonable reaction rate and conversion, and monitoring the progress of the nitrate formation before quenching the reaction (WO 2004/043897 A1), or carefully selecting the residence time and flow regime in a capillary reactor (WO 2009/080755 A1). However, the large excess of nitric acid required by these methods (WO 2004/043897 A1: ca. 13 mol HNO₃ per mol of 1,4-butanediol; WO 2009/080755 A1: ca. 8 to 15 mol HNO₃ per mol of 1,4-butanediol) has to be neutralized and eventually disposed of, which gives rise to large amounts of waste. Moreover, in spite of the careful monitoring of the nitrate formation there is a considerable amount (WO 2004/043897 A1: ca. 33 wt.%) of the unwanted dinitrate being formed.

Therefore, it was an object of the present invention to provide a process for the safe production of nitric acid esters of mono-, di- or polyhydric alcohols that does not

require a substantial excess of nitric acid or another nitrate source that would result in large amounts of waste being generated during the work-up procedure, that can be operated continuously, and that allows to produce the mononitrates of dihydric alcohol without formation of substantial amounts of the corresponding dinitrates or other unwanted byproducts.

According to the invention, an organic nitrate is prepared from a mono-, di- or polyhydric alcohol by a process comprising the steps of

- (i) simultaneously feeding a first continuous-flow microreactor unit comprising at least two reactive fluid inlet ports, at least one mixing zone, at least one reaction zone and a reactive fluid outlet port with
 - (a) concentrated nitric acid,
 - (b) acetic anhydride,
 - (c) optionally, a catalytic amount of a strong inorganic acid other than nitric acid, and
 - (d) optionally, a solvent,to obtain a solution of acetyl nitrate,
- (ii) simultaneously feeding a second continuous-flow microreactor unit comprising at least two reactive fluid inlet ports, at least one mixing zone, at least one reaction zone and a reactive fluid outlet port with the solution of acetyl nitrate obtained in step (i) and said mono-, di- or polyhydric alcohol in liquid form or dissolved in a solvent to obtain a solution of said organic nitrate, and
- (iii) optionally, isolating said organic nitrate from the solution obtained in step (ii).

It has been known that acetyl nitrate is a potent nitrating agent that can be used in stoichiometric amounts to nitrate e.g. aromatic compounds. However, acetyl nitrate is highly explosive and cannot be safely handled in an industrial scale. According to the invention, acetyl nitrate is prepared continuously in a microreactor unit and then continuously reacted in another microreactor unit so that at any given point in time only small amounts are present in the process equipment.

The continuous-flow microreactor units to be used in the process of the invention may be those known in the art, for example as described in WO 2007/112945 A1. They can be made of any material that is not attacked or corroded by the starting materials and products of the process. A preferred material is Hastelloy® C which is corrosion resistant and has a sufficient thermal conductivity.

Herein, the expression "microreactor unit" is to be understood to mean a functional unit comprising the recited elements, irrespective of their actual mechanical configuration. In fact, the microreactor units in steps (i) and (ii) of the process of the invention may be in separate assemblies or in the same assembly, in particular if a modular system as described in WO 2007/112945 A1 is used. When the microreactor units are in the same assembly, they may be in separate modules or in the same module. If they are in the same assembly but in separate modules, the reactive fluid outlet port of the first microreactor unit is externally connected to one of the reactive fluid inlet ports of the second microreactor unit.

In a preferred embodiment, both microreactor units are combined in one module so that the reactive fluid outlet port of the first microreactor unit is internally connected to one of the reactive fluid inlet ports of the second microreactor and the whole module outwardly appears to have (at least) three reactive fluid inlet ports and has two or more mixing zones and a reaction zone between each pair of subsequent mixing zones, for example between the first and the second mixing zone. Since step (i), namely, the formation of acetyl nitrate, requires more time (typically about one minute) than step (ii), which typically requires as few seconds or even less, the reaction zone of the first microreactor unit is advantageously substantially larger than the reaction zone of the second microreactor unit.

The concentrated nitric acid may be the "concentrated nitric acid" of commerce, which is a 65–70 wt.% aqueous nitric acid having a concentration that is approximately equal to that of the $\text{HNO}_3/\text{H}_2\text{O}$ binary azeotrope, or the so-called "strong" or "white fuming" nitric acid having a concentration of about 90 wt.% or more. Preferably the concentrated nitric acid is pure anhydrous nitric acid having a concentration of 99 wt.% or more.

In steps (i) and (ii), the reactants are fed simultaneously and continuously into the respective microreactor units, in a way that the molar ratio of the reactants being fed into the microreactor units remains essentially constant throughout the operating time of the process.

Depending on the intended use of the organic nitrate, the product discharged from the second microreactor unit may be utilized as is, or isolated and/or purified in a subsequent step (iii).

In a preferred embodiment, the product solution obtained in step (ii) that is discharged from the second microreactor unit is quenched with water or an aqueous base, such as

sodium or potassium hydroxide, to stop the reaction, in particular if the starting alcohol is a di- or polyhydric alcohol and one or more hydroxy groups of said di- or polyhydric alcohol shall remain intact, and/or to prevent the acetic acid formed as byproduct in step (i) from causing unwanted side reactions such as acetylation of said remaining hydroxy groups of a di- or polyhydric alcohol. The quenching is preferably carried out with an aqueous base which is also useful for hydrolyzing any acetylated byproducts. The base is advantageously used in a stoichiometric amount, i.e., 2 mol per mol of acetic anhydride used as starting material, or in a slight excess. This quenching step may be conducted semi-continuously by introducing and collecting the product solution in a large volume of water or aqueous base.

In a more preferred embodiment, the quenching is carried out continuously in a third microreactor unit that is fed with said product solution and with water or an aqueous base as defined above.

Said third microreactor unit may be in a separate assembly, or in the same assembly as the second microreactor unit. If it is in the same assembly, it may be in a separate module or in the same module as the second microreactor unit. If it is in the same assembly but in a separate module, the reactive fluid outlet port of the second microreactor unit is externally connected to one of the reactive fluid inlet ports of the third microreactor unit.

The further isolation and purification of the products of the process of the invention can be conducted by methods known in the art for the respective compounds. Due to the inherent instability of organic nitrates it may be advantageous to abstain from isolating the products in pure form and to store and ship them as a solution in a suitable solvent.

A strong inorganic acid other than nitric acid may be used to catalyze the formation of acetyl nitrate from acetic anhydride and nitric acid. In a preferred embodiment, the strong inorganic acid other than nitric acid is sulfuric acid. The sulfuric acid is advantageously used in an amount (based on nitric acid) of 0.1 to 5.0 mol%, preferably 0.2 to 2.0 mol%, more preferably 0.5 to 1.0 mol%.

The first reaction step, i.e., the formation of acetyl nitrate, is advantageously conducted at a temperature of 0–50 °C, preferably at 0–40 °C, more preferably at 20–40 °C, most preferably 20–30 °C. The required reaction time depends on the reaction temperature and the concentrations of the reactants and is typically 0.5 to 20 minutes, or generally a few minutes.

Acetic anhydride and nitric acid are advantageously used in approximately equimolar amounts, the molar ratio of acetic anhydride and nitric acid being from 1:1.5 to 1.5:1, preferably from 1:1.2 to 1.2:1, more preferably from 1:1.1 to 1.1:1.

- 5 The second reaction step, i.e., the formation of the nitrate ester of the mono-, di- or polyhydric alcohol, is advantageously conducted at a temperature of 0–40 °C, preferably at 10–35 °C, more preferably 10–20 °C. The reaction is typically very fast and takes place almost immediately in the mixing zone of the second microreactor unit and to a less extent in the reaction zone. The total reaction time depends on the reaction
10 temperature and the concentrations of the reactants and is typically one or a few seconds or even less.

- The third step, i.e., the quench and hydrolysis of the acetylated byproducts, is advantageously conducted at a temperature of –5 to +50 °C, preferably at 0–30 °C. The
15 required reaction time depends on the reaction temperature and the concentrations of the reactants and is typically 2 minutes to about 1 hour.

- The reaction temperatures in steps (i) and (ii) are advantageously controlled in a suitable manner, for example by using heat exchange modules as described in
20 WO 2007/112945 A1.

- The solvents in steps (i) and (ii), if present, may be the same or different and may be any solvent(s) being essentially inert under the reaction conditions and being able to dissolve and/or dilute the starting materials and products.

- 25 In a preferred embodiment, the solvent in step (i) is dichloromethane.

- The acetic anhydride, the nitric acid, the optional strong inorganic acid other than nitric acid, and the optional solvent in step (i) may be fed separately into the first continuous-
30 flow microreactor unit, provided that said microreactor unit has an appropriate number of reactive fluid inlet ports. Two or three of these starting materials may also be premixed, with the proviso that acetic anhydride and nitric acid must not come into contact with each other before they are fed into the microreactor unit.

- 35 In a preferred embodiment, step (i) is conducted in a way where the acetic anhydride, the strong inorganic acid other than nitric acid and the optional solvent are admixed before they are fed into said first continuous-flow microreactor unit. This admixture is then fed into one reactive fluid inlet port while the concentrated nitric acid is fed

simultaneously into another reactive fluid inlet port and mixed with said admixture in the mixing zone.

The process of the invention is preferably carried out with a stoichiometric amount or a slight excess of nitric acid, i.e., with 1.0 to 1.5, more preferably 1.0 to 1.2, and most preferably 1.0 to 1.1 mol nitric acid per equivalent of mono-, di- or polyhydric alcohol to be esterified. One equivalent of mono-, di- or polyhydric alcohol means one mol divided by the number of hydroxy groups per molecule that are to be esterified.

10 In a preferred embodiment, the organic nitrate has the formula



wherein

15 R^1 is selected from the group consisting of hydrogen, $HO-$, O_2N-O- , R^2O- , optionally substituted aryl, and optionally substituted heteroaryl,

R^2 is C_{2-6} alkanoyl or aroyl,

and Q is linear, branched or cyclic alkanediyl, said alkanediyl optionally being substituted with one or more R^1 moieties as defined above, and said mono-, di- or

20 polyhydric alcohol has the formula



wherein Q is as defined above and R^1' is the same as R^1 , with the proviso that, if any
25 of the R^1 moieties in formula I is O_2N-O- , the corresponding R^1' moiety in formula II can be $HO-$.

Here and hereinbelow, "aryl" means any carbocyclic moiety comprising at least one aromatic system, such as phenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl,
30 biphenyl or pyrenyl. Accordingly, "heteroaryl" means any heterocyclic moiety comprising at least one aromatic system, such as pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl and the like.

The expression " C_{2-6} alkanoyl" is to be understood to mean any acyl group derived
35 from an alkanic acid having 2 to 6 carbon atoms, such as acetyl, propionyl, butyryl, isobutyryl, valeryl (pentanoyl), isovaleryl (3-methylbutyryl), caproyl (hexanoyl) and the like.

The expression "aroyl" is to be understood to mean any acyl group derived from an aromatic monocarboxylic acid, such as benzoyl or naphthoyl.

The expression "linear, branched or cyclic alkanediyl" is to be understood to mean any divalent moiety derived from a linear, branched or cyclic alkane by removing two hydrogens from the same or different (adjacent or non-adjacent) carbon atoms, such as methylene, ethylidene, 1,2-ethanediyl, 1,2-propanediyl, 1,3-propanediyl, 1,2-butanediyl, 1,3-butanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl, 2-methyl-1,3-propanediyl, 2,2-dimethyl-1,3-propanediyl, 1,2-cyclopentanediyl, 1,3-cyclopentanediyl, 1,2-cyclohexanediyl, 1,3-cyclohexanediyl, 1,4-cyclohexanediyl and the like.

More preferably, Q is C₂₋₈ alkanediyl, R¹ is HO- or O₂N-O-, and R^{1'} is HO-; or Q is C₂₋₈ alkanediyl and R¹ and R^{1'} are C₂₋₆ alkanoyloxy.

Most preferably, R¹ and R^{1'} are HO- and Q is 1,4-butanediyl.

The following non-limiting examples are intended to illustrate the process of the invention.

Example 1

4-Nitrooxybutan-1-ol (I; R¹ = HO-, Q = -(CH₂)₄-)

A first microreactor unit made of Hastelloy® C, essentially as described in WO 2007/112945 A1, with an arrangement of meander channel mixing and reaction zones as depicted in Fig. 8A and in item e) of Fig. 10 of WO 2010/130811 A2 was continuously and simultaneously fed during 4 min with a mixture of dichloromethane (325 g), acetic anhydride (49.58 g, 486 mmol) and sulfuric acid (0.46 g, 5 mmol), and with nitric acid (99.5%, 30.85 g, 490 mmol). The dimensions of the microreactor were as follows: hydraulic diameter of the mixing zone: 0.95 mm, length of the mixing zone: 0.29 m (cross section 0.7×1.5 mm², 18 meanders), total channel length: 2.6 m, total volume: 10.9 mL. The temperature of the microreactor unit was kept at about 20 °C using heat exchange modules and an external thermostat and the residence time was 1.0 min. The effluent of the first microreactor unit was found to be a solution essentially consisting of acetyl nitrate (theoretical concentration, assuming 100% yield: 12.6 wt.%) in dichloromethane, which was immediately fed into a second microreactor unit in a module made of Hastelloy® C that formed part of another modular microreactor assembly, as described in WO 2007/112945 A1, simultaneously with neat

1,4-butanediol (40 g, 444 mmol). The dimensions of said second microreactor unit were as follows: meander channel mixing zone, hydraulic diameter of the mixing zone: 0.71 mm, length of the mixing zone: 0.21 m (cross section 0.5×1.1 mm², 14 meanders), total channel length: 1.0 m, total volume: 2.76 mL. The temperature of the second microreactor module was kept at 20 °C as described above and the residence time was 7 seconds. The effluent of the second microreactor unit, which was found to contain 7.4 wt.% of 4-nitrooxybutan-1-ol, corresponding to a yield of 55% (based on 1,4-butanediol), was quenched by collecting it in a flask charged with water (281 g) at 20 °C. The resulting two-phase system was separated and the organic phase was analyzed with GC. 4-Nitrooxybutan-1-ol was found to be the main product (12.1 area%), along with some 1,4-bis(nitrooxy)butane (ca. 3.8 area%), 4-nitrooxybutyl acetate (ca. 0.6 area%) and 4-hydroxybutyl acetate (ca. 0.4 area%). The organic phase was washed 10 times with the same volume of water at 20 °C to extract the 4-nitrooxybutan-1-ol from the organic phase while the 1,4-bis(nitrooxy)-butane formed as byproduct remained in the organic phase due to its poor solubility in water. The product was then extracted with dichloromethane (5×40 mL) from the combined aqueous phases to obtain a solution of 4-nitrooxybutan-1-ol that was essentially free of 1,4-bis(nitrooxy)butane and was subsequently concentrated under reduced pressure to obtain a solution of 15 wt.% 4-nitrooxybutan-1-ol in dichloromethane.

Example 2

4-Nitrooxybutan-1-ol (I; R¹ = HO-, Q = -(CH₂)₄-)

A first microreactor unit made of Hastelloy® C, as described in Example 1 was continuously and simultaneously fed during 7 min with a mixture of dichloromethane (2.005 kg), acetic anhydride (504.0 g, 4.93 mol) and sulfuric acid (2.63 g, 26 mmol), and with nitric acid (99.5%, 312.8 g, 4.93 mol). The temperature of the microreactor unit was kept at 30 °C using heat exchange modules and an external thermostat and the residence time was 0.8 min. The effluent of the first microreactor was found to be a solution essentially consisting of acetyl nitrate (theoretical concentration, assuming 100% yield: 18.1 wt.%) in dichloromethane, which was immediately fed into the first mixing zone of a second microreactor module made of Hastelloy® C that formed part of another modular microreactor assembly, as described in Example 1. Neat 1,4-butanediol (404 g, 4.48 mol) was fed simultaneously into the second mixing zone. The temperature of the second microreactor unit was kept at 30 °C and the residence time was 4 seconds.

The effluent of the second microreactor unit, which was found to contain 10.5 wt.% of 4-nitrooxybutan-1-ol, corresponding to a yield of 55%, based on 1,4-butanediol, was precooled to a temperature of 5 °C. Then the precooled solution was quenched by feeding it to a third microreactor unit in a separate modular system as described in
5 WO 2007/112945 A1, made of Hastelloy® C, simultaneously with a 13 wt.% aqueous sodium hydroxide solution (3.921 kg, 12.7 mol). The quench temperature was 5 °C at a residence time of 0.1 min. The resulting product emulsion was stirred for additional 10 min at 20–30 °C to achieve hydrolysis of traces of acetylated byproducts. The resulting two-phase system was separated and the organic phase was analyzed with GC.
10 4-Nitrooxybutan-1-ol was found to be the main product (23.8 area%), along with some 1,4-bis(nitrooxy)butane (ca. 5.6 area%) and 4-nitrooxybutyl acetate (ca. 0.7 area%). 4-Hydroxybutyl acetate could not be detected (<0.1 area%).

The organic phase washed with water (17.143 kg) at 5–20 °C in an extraction column (e.g. Kueni column) to extract the 4-nitrooxybutan-1-ol from the organic phase while
15 the 1,4-bis(nitrooxy)butane formed as byproduct remained in the organic phase due to its poor solubility in water. The product was then extracted with 5.300 kg of dichloromethane in a second extraction column from the combined aqueous phases to obtain a solution of 4-nitrooxybutan-1-ol that was essentially free of 1,4-bis(nitrooxy)butane and was subsequently concentrated under reduced pressure to obtain a solution of
20 15 wt.% (24.0 area% in GC) 4-nitrooxybutan-1-ol in dichloromethane. GC analysis revealed some 1,4-bis(nitrooxy)butane (5.6 area%) and traces of 4-nitrooxybutyl acetate (0.7 area%) as byproducts. The obtained yield was 38–42%.

25 Example 3

4-Nitrooxybutan-1-ol (I; R¹ = HO–, Q = –(CH₂)₄–)

A first microreactor unit made of Hastelloy® C, as described in Example 1, was continuously and simultaneously fed during approx. 50 min (the collection for product
30 isolation was 42.8 min) with a mixture of dichloromethane (1866.0 g), acetic anhydride (469.0 g, 4.59 mol) and sulfuric acid (2.45 g, 24 mmol), and with nitric acid (99.2 wt.%, 291.6 g, 4.59 mol, 1.00 eq), corresponding to flow rates of 54.60 g/min for the first feed and 6.80 g/min for the second feed. The temperature of the microreactor unit was kept at 30 °C using heat exchange modules and an external thermostat and the residence
35 time was 0.8 min. The effluent of the first microreactor unit was fed into a Hastelloy® C capillary tube (3.15 mm inner diameter, 1.4 m length) to increase the residence time and the effluent of said capillary tube, which was found to be a solution essentially consisting of acetyl nitrate (theoretical concentration, assuming 100% yield: 18 wt.%)

in dichloromethane, was immediately fed into a second microreactor unit in a module made of Hastelloy® C in another modular microreactor assembly, as described in Example 1, simultaneously with neat 1,4-butanediol (377.6 g, 4.19 mol); flow rate 8.82 g/min = 8.69 ml/min, according to a molar ratio of acetyl nitrate to butanediol of 1.1 (assumed 100% conversion of acetic anhydride). The temperature of the second microreactor unit was kept at 30 °C and the residence time was 4 seconds.

The effluent of the second microreactor unit was fed into a second Hastelloy® C capillary tube (1.6 mm inner diameter, 4.0 m length) to increase the residence time and the effluent of said second capillary tube, which was found to contain 10.5 wt.% of 4-nitrooxybutan-1-ol, corresponding to a yield of 57%, based on 1,4-butanediol, was precooled to a temperature of 5 °C. Then the precooled solution was quenched by feeding it to a third microreactor unit made of Hastelloy® C, simultaneously with a 13 wt.% aqueous sodium hydroxide solution (3.690 kg, 11.99 mol). The dimensions of the third microreactor which comprised 12 tangential mixing chambers as depicted in item c) of Fig. 10 of WO 2010/130811 A2 were as follows: hydraulic diameter of the mixing zone: 2.66 mm, length of the mixing zone: 0.15 m, total channel length: 1.5 m, total volume: 11.65 mL. The quench temperature was 5 °C at a residence time of 0.1 min. The resulting product emulsion was heated up in an additional residence time module (a stainless steel capillary tube of 3.15 mm inner diameter and 2.0 m length) to a temperature of 25–30 °C for 1 min, then the emulsion was stirred for another 10 min at 25–30 °C to achieve hydrolysis of traces of acetylated byproducts (pH ca. 13). The resulting two-phase system was separated and the organic phase was analyzed with GC. 4-Nitrooxybutan-1-ol was found to be the main product (23.1 area%), along with some 1,4-bis(nitrooxy)butane (ca. 5.4 area%) and 4-nitrooxybutyl acetate (ca. 0.6 area%). 4-Hydroxybutyl acetate could not be detected (<0.1 area%).

The organic phase was washed with water (13.87 kg) at 5–20 °C in an extraction column to extract the 4-nitrooxybutan-1-ol from the organic phase while the 1,4-bis(nitrooxy)butane formed as byproduct remained in the organic phase due to its poor solubility in water. The product was then extracted with 4.311 kg of dichloromethane in a second extraction column from the combined aqueous phases to obtain a solution of 4-nitrooxybutan-1-ol that was essentially free of 1,4-bis(nitrooxy)butane and was subsequently concentrated under reduced pressure to obtain a solution of 15 wt.% BDMN (4 nitrooxybutan-1-ol) in dichloromethane. The obtained yield was 38–42%.

Example 4**4-Nitrooxybutan-1-ol (I; $R^1 = \text{HO}-$, $Q = -(\text{CH}_2)_4-$)**

A first microreactor unit as described in Example 1 made of Hastelloy® C, essentially as described in WO 2007/112945 A1, with an arrangement of meander channel mixing and reaction zones as depicted in Fig. 8A and in item e) of Fig. 10 of WO 2010/130811 A2 was continuously and simultaneously fed during 38 min (the collection time for product isolation was 8 min) with a mixture of dichloromethane (1656.0 g), acetic anhydride (252.0 g, 2.47 mol) and sulfuric acid (2.34 g, 23 mmol), and with nitric acid (99.5%, 157.0 g, 2.48 mol). The temperature of the microreactor unit was kept at 30 °C (the reactor temperature was controlled with a thermostat) and the residence time was 1.2 min. The effluent of the first microreactor was found to be a solution essentially consisting of acetyl nitrate in dichloromethane (theoretical concentration, assuming 100% yield: 12.6 wt.%), which was immediately fed into one inlet of the first mixing zone of a second microreactor module comprising four interconnected microreactor units, each of them consisting of a mixing zone made up of a series of 12 tangential mixing chambers as depicted in item c) of Figure 10 of WO 2010/130811 A2, and a reaction zone. In particular, the dimensions of said four microreactor units were as follows: hydraulic diameter of the mixing zones: 2.01 mm, length of each mixing zone: 0.06 m, channel length of each unit: 0.6 m, total volume: 11.2 mL. The outlet of each of the first three units was directly connected to one of the two inlets of the mixing zone of the next unit.

The second inlet of the first mixing zone was closed, so that the first unit of said second module was only used to increase the residence time. Neat 1,4-butanediol (203.7 g, 2.25 mol) was simultaneously fed into the second mixing zone of said second microreactor module. The temperature of the second microreactor module was kept at 30 °C and the residence time was 3.3 seconds. The effluent of the second microreactor unit was found to contain 7.5 wt.% of 4-nitrooxybutan-1-ol corresponding to a yield of 55%, based on 1,4-butanediol. It was quenched by feeding water (362 g, 20.1 mol) to the third mixing zone of the same microreactor module. The quench temperature was 30 °C at a residence time of 6 seconds. The resulting two-phase system was separated and the organic phase was analyzed with GC. 4-Nitrooxybutan-1-ol was found to be the main product (10.98 area%), along with some 1,4-bis-(nitrooxy)butane (ca. 4.0 area%), 4-nitrooxybutyl acetate (ca. 0.4 area%) and 4-hydroxybutyl acetate (ca. 0.4 area%).

Example 5**4-Nitrooxybutan-1-ol (I; R¹ = HO-, Q = -(CH₂)₄-)**

Example 4 was repeated using a higher concentration of acetic anhydride (20.0 wt.% instead of 13 wt.%, corresponding to a theoretical concentration of acetyl nitrate of 18.2 wt.%) and less sulfuric acid (0.6 mol%, based on 1,4-butanediol). The second microreactor unit was as described in Example 1 (residence time: 7 second). The effluent of the second microreactor unit was quenched in a large amount of water and the resulting two-phase system was separated. The organic phase was analyzed with GC and 4-nitrooxybutan-1-ol was found to be the main product (21.1 area%), along with some 1,4-bis(nitrooxy)butane (ca. 5.4 area%), 4-nitrooxybutyl acetate (ca. 0.7 area%) and 4-hydroxybutyl acetate (ca. 0.9 area%).

Comparative Example 1 (batch process)**1,4-Bis(nitrooxy)butane (I; R¹ = O₂N-O-, Q = -(CH₂)₄-)**

To a mixture of dichloromethane (18.7 mL), acetic anhydride (6.24 g, 61 mmol) and 96 wt.% sulfuric acid (0.04 g, 0.33 mmol) at -10 °C, nitric acid (3.9 g, 61 mmol) and a previously prepared solution of 1,4-butanediol (5 g, 55 mmol) in dichloromethane (1.5 mL) were added. After stirring the reaction mixture at -10 °C for 30 min, a 13 wt.% aqueous solution of sodium hydroxide (48.1 g solution, 156 mmol) was added. The mixture was allowed to warm up to room temperature and the resulting two phases were separated. The organic phase was analyzed by GC and 1,4-bis(nitrooxy)butane was found to be the main product (18.81 area%) along with traces of 4-nitrooxybutan-1-ol (ca. 0.2 area%) and 1,4-butylene diacetate (ca. 0.1 area%).

Comparative Example 2 (batch process, reverse addition)**4-Nitrooxybutan-1-ol (I; R¹ = HO-, Q = -(CH₂)₄-)**

To a mixture of dichloromethane (37.5 mL), acetic anhydride (12.5 g, 122 mmol) and 96 wt.% sulfuric acid (0.07 g, 0.7 mmol) at -10 °C, nitric acid (7.7 g, 122 mmol) was added. The resulting mixture was warmed up to 20 °C and a previously prepared solution of 1,4-butanediol (10 g, 111 mmol) in dichloromethane (3.0 mL) was added. The reaction mixture was cooled to 0 °C and a 13 wt.% aqueous solution of sodium hydroxide (96.3 g solution, 313 mmol) was added. The mixture was allowed to warm up to room temperature and the resulting two phases were separated. The organic

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phase was analyzed by GC and 4-nitrooxybutan-1-ol was found to be the main product (14.38 area%), along with some 1,4-bis(nitrooxy)butane (ca. 4.5 area%), 4-nitrooxybutyl acetate (ca. 3.6 area%) and traces of 1,4-butylene diacetate (ca. 0.8 area%) and 4-hydroxybutyl acetate (ca. 0.1 area%).

Claims

1. A process for the production of an organic nitrate from a mono-, di- or polyhydric alcohol, comprising the steps of
 - (i) simultaneously feeding a first continuous-flow microreactor unit comprising at least two reactive fluid inlet ports, at least one mixing zone, at least one reaction zone and a reactive fluid outlet port with
 - (a) concentrated nitric acid,
 - (b) acetic anhydride,
 - (c) optionally, a catalytic amount of a strong inorganic acid other than nitric acid, and
 - (d) optionally, a solvent,to obtain a solution of acetyl nitrate,
 - (ii) simultaneously feeding a second continuous-flow microreactor unit comprising at least two reactive fluid inlet ports, at least one mixing zone, at least one reaction zone and a reactive fluid outlet port with the solution of acetyl nitrate obtained in step (i) and with said alcohol in liquid form or dissolved in a solvent, to obtain a solution of said organic nitrate, and
 - (iii) optionally, isolating said organic nitrate from the solution obtained in step (ii).
2. The process of claim 1, wherein said first and second continuous-flow microreactor unit are combined into one microreactor module so that the reactive fluid outlet port of the first microreactor unit forms one of the reactive fluid inlet ports of the second microreactor unit.
3. The process of claim 1 or 2, wherein the isolation step (iii) comprises a quenching with water or an aqueous base.
4. The process of claim 3, wherein said quenching with water or an aqueous base is conducted in a third microreactor unit.
5. The process of any of claims 1 to 4, wherein the strong inorganic acid other than nitric acid is sulfuric acid.
6. The process of any of claim 1 to 5, wherein the solvent in step (i) is dichloromethane.

7. The process of any of claims 1 to 6, wherein in step (i) the acetic anhydride, the strong inorganic acid other than nitric acid and/or the solvent are admixed before they are fed into said first continuous-flow microreactor unit.

- 5 8. The process of any of claims 1 to 7, wherein said organic nitrate has the formula



wherein

- 10 R^1 is selected from the group consisting of hydrogen, $HO-$, O_2N-O- , R^2O- , optionally substituted aryl, and optionally substituted heteroaryl,
 R^2 is C_{2-6} alkanoyl or aroyl,
and Q is linear, branched or cyclic alkanediyl, said alkanediyl optionally being substituted with one or more R^1 moieties as defined above, and said mono-, di- or
15 polyhydric alcohol has the formula



- 20 wherein Q is as defined above and $R^{1'}$ is the same as R^1 , with the proviso that, if any of the R^1 moieties in formula I is O_2N-O- , the corresponding $R^{1'}$ moiety in formula II can also be $HO-$.

9. The process of claim 8, wherein Q is C_{2-8} alkanediyl, R^1 is $HO-$ or O_2N-O- and $R^{1'}$ is $HO-$.

- 25 10. The process of claim 8, wherein Q is C_{2-8} alkanediyl and R^1 and $R^{1'}$ are C_{2-6} alkanoyloxy.

11. The process of claim 9 or 10, wherein Q is 1,4-butanediyl.

- 30 12. The process of any of claims 1 to 11, wherein the concentrated nitric acid is used in an amount of 1.0 to 1.5 mol nitric acid per equivalent of mono-, di- or polyhydric alcohol to be esterified.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/001615

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C201/02 C07C203/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 98/25918 A1 (HOECHST MARION ROUSSEL INC [FR]; DROUX SERGE [FR]; GIGLIOTTI GIUSEPPE) 18 June 1998 (1998-06-18) page 9, line 11 - line 21 page 12, line 18 - page 13, line 29 ----- -/-	1-12



Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/001615

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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