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(54) **METHOD FOR THE INDUSTRIAL PRODUCTION OF 2-HALO-4,6-DIALKOXY-1,3,5-TRIAZINES AND THEIR USE IN THE PRESENCE OF AMINES**

VERFAHREN ZUR INDUSTRIELLEN HERSTELLUNG VON 2-HALOGEN-4,6-DIALKOXY-1,3,5-TRIAZINEN UND DEREN VERWENDUNG IN GEGENWART VON AMINEN

PROCÉDÉ DE PRODUCTION INDUSTRIELLE DE 2-HALO-4,6-DIALKOXY-1,3,5-TRIAZINES ET LEUR UTILISATION EN PRÉSENCE D'AMINES

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EP 3 539 954 B1

Description

Field of application of the invention

[0001] The present invention relates to the sector of activating agents for condensation, crosslinking, grafting, and curing reactions that intervene in the processes of stabilization of collagen matrices, and for the condensation of natural and synthetic polymers.

[0002] In particular, the invention regards the process of synthesis, which can be implemented also on an industrial scale, of 2-halo-4,6-dialkoxy-1,3,5-triazines, which act as activating agents for condensation, crosslinking, grafting, and curing reactions, and for stabilization of collagen matrices, as well as for the condensation of polymers, and the multiple applications of said reagents in various industrial sectors, amongst which the tanning industry and the leather-processing industry.

Prior art

[0003] Commonly, amides, esters, and thioesters are formed from the reaction between an amine, alcohol, thioalcohol, and an "activated" carboxylic acid, i.e., obtained by formation of acyl chlorides, mixed anhydrides, or activated esters. These reactions underlie processes for production of a vast range of products in the most disparate sectors, such as those of pharmaceuticals, polymers, packaging, foodstuffs, tissues, etc.

[0004] In particular, carbodiimides are organic reagents widely used for the formation of amide bonds, ester bonds, thioester bonds, etc., in so far as they are able to react with carboxylic acids to form an active intermediate species, which, in the presence of an amine, alcohol, or thioalcohol, reacts to form the desired bond [A. El-Faham, Chem. Rev., 2011, 111, 6557-6602]. One of the carbodiimides most frequently used is dicyclohexylcarbodiimide (DCC); however, during the reaction, DCC leads to the formation of a toxic coproduct that must be carefully removed at the end of the reaction. Reactions in the presence of carbodiimides are prevalently carried out in organic solvent, since these molecules are not stable in aqueous solution, except for 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide chlorohydrate (EDC). EDC, however, calls for the combined use of equimolar amounts (or higher amounts) of N-hydroxysuccinimide (NHS), which is rather unstable and must be stored at low temperature (approximately -20°C) and is very expensive. Currently, this reagent is in any case one of the most widely used for the production of polyaminoacids and of other pharmaceutical derivatives with high added value, as well as for crosslinking of collagen, for the reconstruction of tendons and retinas, the production of hydrogels, etc. [US 8,691,279, US 2012/0009223 A1].

[0005] In the biotechnology sector, carbodiimides (for example, EDC/NHS) are widely used as alternatives to glutaraldehyde for crosslinking of collagen thanks to their lower toxicity. However, the properties of materials crosslinked with the exclusive use of carbodiimides, the gelatinization temperature (Tg), and the physico-mechanical properties are clearly inferior.

[0006] To obtain collagen matrices having characteristics comparable to those obtained with glutaraldehyde, acyl azides, and glycerol [E. Khor, Biomaterials, 1997, 18, 95-105], carbodiimides are normally used in the presence of crosslinking agents that remain permanently attached to the collagen tissue [X. Duan, Biomaterials, 2006, 27, 4608-4615].

[0007] It is known that the derivatives of 2-halo-4,6-dialkoxy-1,3,5-triazines, and in particular their quaternary ammonium salts, represent a valid alternative to carbodiimides and can be used, also in an aqueous environment, for the formation of amide bonds, ester bonds, and thioester bonds by means of reactions of crosslinking, grafting, curing, etc. in homogeneous and/or heterogeneous phase [US 6,458,948 B1, Z.J. Kaminski, J. Am. Chem. Soc., 2005, 127, 16912-16920]. In a large number of cases, these reagents are more efficient than other coupling agents known to date, such as DCC, EDC/NHS, PyBOP, HATU, HBTU, etc. An alternative, at present rarely employed, is to resort to the use of the quaternary ammonium salts of 2-halo-4,6-dialkoxy-1,3,5-triazines, and in particular 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (the only one commercially available), for stabilization of complex matrices for medical use, made up of collagen in combination with other natural and/or synthetic matrices [EP1748985 B1, US 2008/0234254 A1, US 2011/118265 A1, US 8,119,592, WO 2010/056778A].

[0008] The quaternary ammonium salts of 2-halo-4,6-dialkoxy-1,3,5-triazines do not present problems of toxicity in the end products since they are not withheld therein and can be easily eliminated at the end of the treatment/reaction. For these reasons, the scientific literature regarding DMTMM has undergone continuous growth in the last few years. For instance, the international patent application No. WO 2014/063102 presents the use of DMTMM for the preparation of artificial lubricants for cartilage. The derivatives of 2-halo-4,6-dialkoxy-1,3,5-triazines are, however, very sensitive to the solvent, and this constitutes a limit to their use. Up to the present day, the literature regarding the synthesis of derivatives of 2-halo-4,6-dialkoxy-1,3,5-triazines is rather limited and in all cases involves at least two steps: 1) synthesis of the triazine derivative from the corresponding 2-halo-4,6-dialkoxy-1,3,5-triazine in the presence of an amine in a given solvent, normally an organic one; 2) recovery and purification of the product before use [US 6,458,948B1; US 2003/0153785A1; EU174962B1/2006; WO2007/051496A1; S. S.A. Raw, Tetrah. Lett., 2009, 50, 946-948]. However,

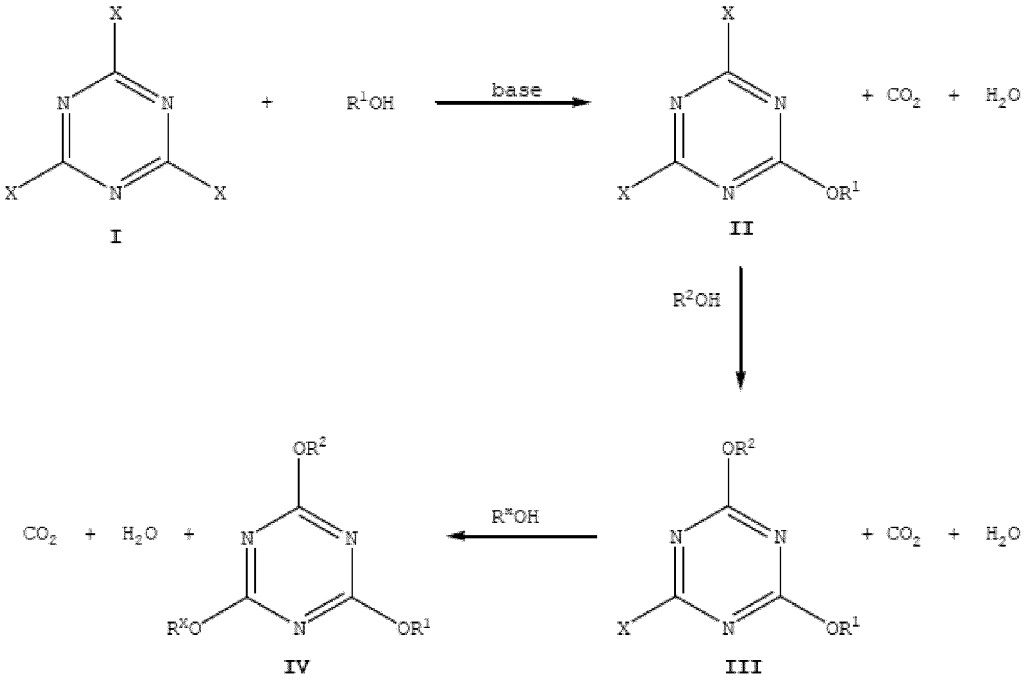
this protocol, which is generally used for the synthesis of organic compounds, also referred to as "Isolated-Product Protocol" (IPP), presents a certain number of critical features, above all from the standpoint of industrial production, in so far as it calls for complex reactors, large amounts of solvents, complicated purification steps, etc., which moreover reduce considerably the yield in the desired product, leading to an increase in the operating costs and hence sales prices.

[0009] M. Kunishima *et al.* have studied the mechanism of reaction of dehydrocondensations in the presence of quaternary ammonium salts of 2-halo-4,6-dialkoxy-1,3,5-triazines [Chem. Eur. J. 2012, 18, 15856-15867]. The authors give some examples of reactions conducted in CH_2Cl_2, a solvent in which the quaternary ammonium salts of 2-halo-4,6-dialkoxy-1,3,5-triazines are highly unstable, leading to rapid decomposition. To overcome this problem, the authors present some examples of reactions between a carboxylic acid and a primary amine, in the presence of CDMT and a tertiary amine, but probably on account of the solvent used (CH_2Cl_2) and the absence of buffers, auxiliaries, etc., in the majority of cases the main product obtained is the product of condensation between the triazine and the primary amine, instead of the desired amide. Currently, only 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), are commercially available, at very high prices, on account of the lack of an adequate process on an industrial scale for their production (in terms of kilograms per day or tonnes per day) .

[0010] In the recent literature, there have been described many examples of application that use DMTMM obtained by means of IPP, which, however, have some trouble in finding a use at an industrial level also on account of the problems linked to the use of DMTMM (high costs, low availability, instability over time, etc.) [US 2013/0123508 A1, EP 1992364 A1]. DMTMM has a cost that is over three hundred times the average cost of equivalent activating agents currently used for the synthesis of polymers, biomaterials, and leather. Furthermore, quaternary ammonium salts of 2-halo-4,6-dialkoxy-1,3,5-triazines are generally unstable at room temperature over long periods [US 2003/0153785 A1] and may be subject to partial or total decomposition if they are not shipped and stored in adequate conditions. To garantee conservation thereof, DMTMM must be shipped and stored at -20°C. The cost of DMTMM is directly linked to the cost and availability of CDMT from which it is synthesised.

[0011] The literature regarding synthesis of 2-halo-4,6-dialkoxy-1,3,5-triazines principally regards the preparation of CDMT. One of the fundamental aspects of the synthesis of CDMT, as likewise of 2-halo-4,6-dialkoxy-1,3,5-triazines in general, is the control of the course of the reaction in order to minimize or eliminate completely formation of secondary products.

[0012] Currently, the only protocol for the synthesis of 2-halo-4,6-dialkoxy-1,3,5-triazines is described in US 2002/0123628 and regards the synthesis on a scale of some grams carried out with normal laboratory equipment. The reaction is generally conducted starting from a cyanuric chloride in the presence of an alcohol, prevalently methanol, and a base, preferably $NaHCO_3$. During the reaction, water and CO_2 are formed. In the document No. US 2002/0123628, the authors pose as basic requisite for obtaining good selectivity and yields of 2-halo-4,6-dialkoxy-1,3,5-triazines that the amount of water present at the start and at the end of the reaction should always be less than 2.5 mol per mole of cyanuric halogenide (compound of formula I, hereinafter also referred to simply as "I", in the reaction sheme presented below). Consequently, since water is a byproduct of the reaction, to obtain high yields of CDMT according to the protocol described above, it is necessary for all the solvents to be distilled and anhydrified prior to use and possibly for the reactions to be conducted in an inert atmosphere. Furthermore, large amount of alcohol are required, used both as reagent and as solvent for reducing the viscosity of the system (ratio alcohol/I = 5-50 mol/mol). At the end of the reaction, the product must be recovered by extraction with water/organic solvents and then anhydrified, and the organic solvent evaporated. Presented in the scheme appearing below is the synthesis of 2-halo-4,6-dialkoxy-1,3,5-triazines, together with the secondary products that may form during the reaction.



where:

R^x is R^1 or R^2 ; R^1 and R^2 are chosen independently from: $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$; and X is Br^- or Cl^-.

[0013] According to Dudley [J. Am. Chem. Soc., 1951, 73, 2986-2990] the addition of variable amounts of water for the synthesis of CDMT improves the homogeneity of the system (ratio I/base/H_2O/MeOH=1/2/2/8). However, the author does not analyse the evolution of the kinetics of formation of the compound of formula IV as the rate of addition of the reagents varies. On the basis of our studies it has been found that, if the addition of the compound of formula I is too fast (exothermic) variable percentages of the compound of formula IV are formed (from 5 to 25%), with consequent higher consumption of methanol. Consequently, this procedure calls for large amounts of methanol, with yields of less than 74%. J. Cronin [Synth. Commun., 1996, 26, 3491-3494] in his work presents a methodology employed exclusively for the synthesis of CDMT, which, according to the author, can be used for up to a maximum of 20 kg. However, no detail as regards scale up is presented, and in effect, we have been unable to reproduce Cronin's protocol for amounts exceeding 50 g of CDMT, and complex mixtures containing compounds of formulas II, III, and IV were produced in variable percentages.

Summary of the invention

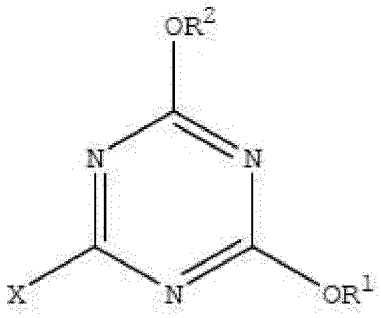
[0014] A purpose of the invention is to provide a method for the production of reagents to be used in the process of stabilization of collagen matrices and of condensation of natural and synthetic polymers, such as polyacrylic acid, polyethylene, cellulose, and/or modified celluloses, polysaccharides, starch, and lignin, by means of reactions of condensation, crosslinking, grafting, and curing.

[0015] In particular, the invention provides a method for the production of the active principle of one of the reagents that intervenes in the process of stabilization of collagen matrices and condensation of polymers, which also forms the subject of the invention. This active principle according to the invention is a 2-halo-4,6-dialkoxy-1,3,5-triazine, which in the presence of aliphatic, linear, branched, aromatic, cyclic, or heterocyclic tertiary amines activates reactions of condensation, crosslinking, grafting, and curing.

[0016] Forming the subject of the invention is also the method for the synthesis of 2-halo-4,6-dialkoxy-1,3,5-triazines that can be implemented on an industrial scale.

Detailed description of the invention

[0017] It has been found that compounds of formula III,



(III)

where: R^1 and R^2 are independently chosen from: $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$; and X is Cl^- or Br^- namely, 2-halo-4,6-dialkoxy-1,3,5-triazines, are able to act as agents for activating reactions of condensation, crosslinking, grafting, and curing and in processes of stabilization of collagen matrices, as well as of condensation of natural and synthetic polymers, such as cellulose, and/or modified celluloses, polysaccharides, starch, lignin, etc., and their application is very advantageous in terms of ease of use, economic convenience, and stability over time of these compounds.

[0018] Thus, it is possible to reduce the overall costs considerably as compared to the methods used for the same purpose in the prior art and reduce the environmental impact of the process, limiting the amount of solvents, energy, and time necessary for their preparation and implementation.

[0019] The method of stabilization of collagen matrices and of condensation of natural and synthetic polymers that forms the subject of the present invention hence presents as a methodology alternative to preparation using IPP.

[0020] In particular, the method of stabilization of collagen matrices and of condensation of polymers that forms the subject of the present invention is obtained from the reaction of two reagents, denoted, for the purposes of the present invention, as "first reagent", or "Reagent 1", and "second reagent", or "Reagent 2".

[0021] According to the present invention, Reagent 1 is a composition comprising:

a) at least one compound of formula III (2-halo-4,6-dialkoxy-1,3,5-triazine);
b) a buffer;
c) a salt;
d) a solvent.

[0022] According to the present invention, Reagent 2 is a composition comprising:

a) a tertiary amine;
b) a buffer;
c) a solvent.

[0023] Reagent 2 may further comprise an additive for the buffer.

[0024] Reagent 1 is a composition comprising as active principle one or more 2-halo-4,6-dialkoxy-1,3,5-triazines in a concentration ranging between 0.1M and 1.0M. The composition that constitutes Reagent 1 also comprises a buffer, preferably a Good buffer, chosen in the group: MES, ACES, BES, BIS-Tris, MOPS, TEA, TAPSO, POPSO, TAPS, formiate, phosphate, succinate. The composition that constitutes Reagent 1 comprises a base or a salt of formula X^+Y^-, where X^+ is Na^+, K^+, or Ag^+, and Y^- is: ClO_4^-, BF_4^-, PF_6^-, CO_3^{2-}, Cl^-, HCO_3^-.

[0025] The composition that constitutes Reagent 1 comprises a solvent chosen in the group of: aliphatic ethers, halogenates, alcohols, ketones, esters, aromatic or aliphatic hydrocarbons, amides, carbonates, DMSO, and water.

[0026] Reagent 2 is a composition comprising as active principle one or more linear, branched, cyclic, aromatic, heterocyclic tertiary amines, and/or their quaternary salts, in a concentration ranging between 0.1M and 1.0M. The composition that constitutes Reagent 2 also comprises a buffer, preferably a Good buffer, chosen in the group: HEPES, MOPS, TRIS, tri-Na-citrate, Tris-Cl, TAPS.

[0027] The composition that constitutes Reagent 2 comprises a solvent chosen in the group of: aliphatic ether, halogenate, alcohol, ketone, ester, aromatic or aliphatic hydrocarbon, amide, carbonate, DMSO, and water.

[0028] In some particularly preferred embodiments, Reagent 2 may further comprise additives for the buffer, which are chosen in the group: NaCl, Na_2HPO_4, NaOAc, KCl, SDS, glycine, boric acid, EDTA, and NaN_3.

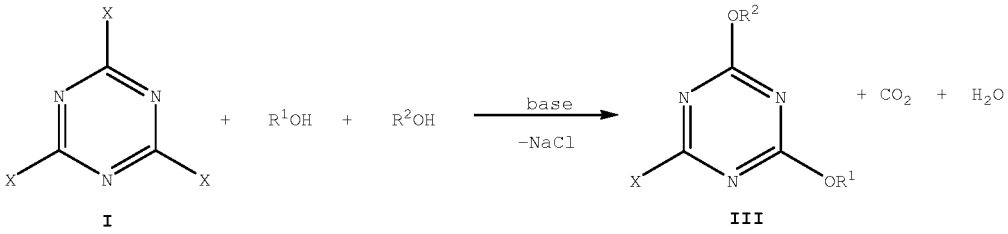
[0029] The present invention provides a method of production of 2-halo-4,6-dialkoxy-1,3,5-triazines that act as acti-

vating agents in the reactions of crosslinking, grafting, curing, and condensation of the processes of stabilization of natural matrices such as cellulose, and/or modified celluloses, and collagen matrices.

[0030] Object of the invention is the method for the production of 2-halo-4,6-dialkoxy-1,3,5-triazines, implemented on an industrial scale, in amounts of the order of kilograms or tonnes and optimization for the recovery or work up of the two products. Up to the present day, no batch or semi-batch process for the production of these compounds has been described.

[0031] Scale-up of the process of production is a fundamental practice for evaluating and solving the problems linked to passage from the production of a few grams (laboratory scale), to the production of kilograms or tonnes (industrial scale).

[0032] It has been shown that in the process of production of 2-halo-4,6-dialkoxy-1,3,5-triazines, by controlling the rate of addition of the reagents and the temperature of reaction it is possible to optimize the method considerably. This makes it possible to avoid the use of anhydros solvents, the need to operate in an inert atmosphere, etc. Furthermore, by controlling these parameters, a product with a high degree of purity is obtained, simply by washing with water, without the use of organic solvents, and/or other techniques of purification such as ricristallization. Consequently, this process for synthesis on an industrial scale of 2-halo-4,6-dialkoxy-1,3,5-triazines is obtained with considerably reduced costs as compared to current known processes, optimizing the operating parameters of the process of synthesis and recovery of the product in kilograms per day or tonnes per day.



I III

X: Br^-, Cl^-
R^1, R^2: CH_3, CH_2CH_3, $CH_2CH_2CH_3$, n-Bu, etc.
R^x: R^1 or R^2

[0033] The method for the synthesis of 2-halo-4,6-dialkoxy-1,3,5 triazines of formula III according to the invention, comprises the steps of:

- reaction of substitution between cyanhydric halogenide of formula I and linear or branched aliphatic alcohol, in single phase, in the presence of a base;
- quenching of the reaction by means of addition of water and stirring;
- filtration;
- drying.

[0034] The method hence envisages a reaction of substitution between a cyanuric halogenide (Cl^-, F^-, Br^-) of formula I and a linear or branched aliphatic alcohol in the presence of a base at a temperature ranging between 45°C and 130°C for a duration of 5-48 h according to the alcohol used.

[0035] The amount of water added is important since it affects: i) homogeneity of the reaction mixture; ii) control of heating. According to our results, the synthesis of 2-halo-4,6-dialkoxy-1,3,5-triazines is preferably carried out in the presence of 0-7 mol of water per mole of the compound of formula I, water which in effect favours the homogeneity of the reaction mixture providing high selectivity and purity in the compound of formula III. The presence of water enables reduction of the amount of alcohol used such that, for 1 mole of the compound of formula I moderate amounts of alcohol of between 1-5 Eq are sufficient.

[0036] The reaction may be conducted in the presence of any linear or branched aliphatic alcohol; for example, R^1, R^2: CH_3, CH_2CH_3, $CH(CH_3)_2$, $(CH_2)_2CH_3$, $(CH_2)_3CH_3$, where R^1 may be equal to or different from R^2, of any degree of purity commercially available without further purification (amounts of water variable in the range 0.03-0.5%) and without affecting in any way the selectivity or yield in the desired triazine. The base may be any carbonate; $NaHCO_3$ is preferably used. Normally, for the synthesis of 2-halo-4,6-dialkoxy-1,3,5-triazines the ratio between the reagents (compound of formula I, base, water, and solvent) is fixed in a very precise way. According to the invention it is possible to use ratios between the reagents I/base/water/solvent of between 1/1/0/4 and 1/5/7/12 obtaining, in all cases, compounds of formula III with yields and purities higher than 90%, guaranteeing a further versatility and reduction of the error margins for its application at an industrial level.

[0037] It is of fundamental importance for the addition of the reagents to be carried out at a certain rate, with a good control of the temperature and of stirring so as to prevent formation of non-desired products and intermediates, i.e., the compounds of formulas II and IV that are normally formed with the method according to the prior art [Dudley, 1951]. This has been obtained using auger dispensers and indicators for control of the temperature. When the addition of the compound of formula I is through, the reaction temperature gradually goes back to room temperature. This must be avoided, in so far as insufficient heating after the addition arrests the reaction with formation of high percentages of aspecific products.

[0038] Normally, the reaction is conducted at temperatures of between 45 and 130°C, according to the alcohol used. On the basis of the protocol described herein, there has been monitored over time by means of GLC formation of the aspecific products of reaction, respectively the compounds of formulas II, III, and IV of the Dudley method according the prior art, for the various 2-halo-4,6-dialkoxy-1,3,5,-triazines synthesized and, by way of example, the data for the synthesis of CDMT are plotted in the graph of Figure 1.

[0039] The reagents are added in the reactor where the reaction occurs in a specific order: first 1-5 Eq of base are introduced into the reactor together with 1-5 Eq of ROH (methanol, ethanol, isopropanol, butanol, etc.) and 0-7 Eq of water. Under vigorous stirring, 1 Eq of the compound of formula I is added in 0.5-3 h and, once addition of the compound of formula I is through, the mixture is heated at 45-130°C under stirring for 5-48 h. The amount of water reduces the viscosity of the reaction mixture; however, the system is heterogeneoous, so that it is necessary to have available an adequate stirring system able to mix a suspension having a viscosity ranging from low to medium. After 5-48 h the reaction mixture is stopped by adding 1-5 volumes of water and subsequently stirred for 0-480 min. The suspension is transferred into a filtering device, or Nutsche filter, separated from the solution, and dried. The method according to the invention enables recovery of 2-halo-4,6-dialkoxy-1,3,5-triazines with a yield higher than 90% and a purity of 92-97% (3-8% of water). After the reaction, the reactor is cleaned and is ready for another lot of reagents.

[0040] In a particularly preferred embodiment of the invention aimed at obtaining amounts of product of and order exceeding kilograms, the reaction is conducted in a batch reactor with ellipsoidal bottom, of adequate capacity, equipped with a system for addition of the reagents. The reaction between the compound of formula I and an alcohol, in the presence of a base, is initially an exothermic reaction with development of CO_2. The heat developed enables the reaction to proceed for the duration of the additions. The temperature must be effectively controlled in such a way that within the reactor the relation 10 C< T <45°C is satisfied. This is performed via control of the temperature using reactors with an external/internal cooling system. To determine the dimensions of the reactor, also the amount of water used for stopping the reaction and purifying the products must be taken into account. For this reason, the total internal volume must be at least 1.5-2.0 times the total volume of the reagents. For instance, for a production of 10 kg, the volume of the reactor must be comprised between 0.2 and 1 m^3.

[0041] The reactors selected are normal pressurized containers, reinforced, and lined with steel. Particular linings with high resistence to corrosion may be used when necessary. The reactors used have an external and/or internal coil system with appropriate heat-exchange properties for heating or cooling the reaction and condensing the solvent vapours, with possible recycling of the condensed vapours. The reactors must moreover have a blade stirrer, inlets, and outlets that connect it to other equipment, sensors for detecting temperature, pressure, pH, and viscosity, bypass loops to monitor the reaction over time (GLC). The products are recovered by filtration, washing, and drying. Typically, the products are present in the reaction mixture as suspended solids. After cooling and purification or work-up, the reaction mixture is transferred into a filtering device or Nutsche filter for drying and recovery of the product. The volume of the filter may be configured for receiving an entire load from the reactor. The main flow of the reaction, containing the solvent, may be collected separataly from the purification solvent (water) and recycled in the batch reactor (further fresh alcohol is added to obtain the required stoichiometry).

[0042] The availablility of a reagent having low or zero toxicity, which is able to crosslink the collagen supplying highly stable matrices, i.e., highly stable to temperature (Tg) and hence highly resistance to degradation over time, constitutes an important result for a wide range of applications in pharmaceutical, biomedical field, etc.

Experimental part

[0043] The invention will be described in what follows by way of non-limiting illustration, with particular reference to some examples.

[0044] In the examples presented hereinafter for non-limiting illustrative purposes, Reagents 1 and 2 according to the invention are identified and represented with the codes AaBbCcDdEe and FfGgHhEe, where a, b, c, d, ... = 0, 1, 2, 3, 4, ... n.

[0045] In particular, for Reagent 1:

A identifies 2,4-dialkoxy-1,3,5-triazines; for example, A_1: 2-chloro-4,6-dimethoxy-1,3,5-triazine; A_2: 2-chloro-4,6-diethoxy-1,3,5-triazine; A_3: 2-chloro-4methyl-6-ethyl-1,3,5-triazine, etc.

B identifies the buffer, preferably a Good buffer; for example, B_1: MES; B_2: ACES; B_3: BES, B_4: POPSO; B_5: TRIS;

B_6: HEPPSO; B_7: TAPS; B_8: Tris-NaCitrate.
C identifies the cation of an inorganic salt X^+; for example, C_1: Na^+; C_2: K^+; C_3: Ag^+.
D identifies the anion of an inorganic salt Y^-; for example, D_1: ClO_4^-; D_2: BF_4^-; D_3: Cl^-; etc.
E identifies the solvent; for example, E_1: aliphatic ether; E_2: alcohol; E_3: water; E_4: acetone; E_5: THF; etc.

[0046] For Reagent 2:

F identifies the aliphatic, linear, branched, cyclic, aromatic, heterocyclic, amine and/or its quaternary salts, for example, F_1: TMA (trimethylamine); F_2: TEA (triethylamine), F_3: DEMA (diethylmethylamine); F_4: NMM (N-methylmorpholine); F_5: NEM (N-ethylmorpholine); F_6: MPD (methylpyrrolidine); F_7: MP (methylpiperidine); etc.
G identifies the buffer, preferably a Good buffer; for example, G_1: BES; G_2: MOPS; G_3: TRIS; G_4: POPSO, G_5: TAPS; G_6: Tris-NaCitrate; etc.
H identifies the additives for the buffer; for example, H_1: NaCl; H_2: Na_2HPO_4; H_3: NaOAc; H_4: KCl; H_5: SDS; etc.
E identifies the solvent; for example, E_1: aliphatic ether; E_2: alcohol; E_3: water; E_4: acetone; E_5: THF; etc.

[0047] All the analyses presented herein were carried out with a gas chromatograph Agilent Technologies 6850, using a flame-ionization detector, equipped with an HP5 capillary column (5% methylphenylsilicone; conditions of analysis: 50°C for 4 min, then 20°C/min up to 250°C). The ^1H and ^{13}C NMR spectra were recorded with a spectrometer Bruker Avance 300 operating at 300.11 MHz for the proton spectrum and at 75.03 MHz for the carbon spectrum. The FT-IR spectra (KBr tablet) were obtained with a spectrophotometer Perkin Elmer "Spectrum One". The DSC analyses were determined with DSC Netzsch STA 409 PC, melting point Buchi 535. The enantiomeric excesses were measured by means of chiral HPLC using a CHIRALCEL OD-H (250 mm x 4.6 mm) with an Agilent 1100 HPLC equipped with a 254-nm UV detector.

Example -1. General procedure for the synthesis of 2-halo-4,6-dialkoxy-1,3,5-triazines

[0048] In a reactor as described previously, there were introduced by means of an auger dispenser and/or a dispenser for liquids, 1-5 Eq of base, 4-12 Eq of ROH (methanol, ethanol, isopropanol, butanol, etc.), and 0-7 Eq of water. Under stirring 1 Eq of cyanuric halogenide was added through an auger dispenser (time of additions 0.5-3 h), and then the mixture was heated at 45-130°C for 5-48 h. At the end of the reaction work-up was carried out by adding 1-5 volumes of water with subsequent stirring for 0-480 min. The suspension was filtered, and the product collected and dried in a vacuum. 2-halo-4,6-dialkoxy-1,3,5-triazines were recovered with a yield of 85-90% and a purity of 92-97% (3-8% of water) . This method was used up to 150 kg of 2-halo-4,6-dialkoxy-1,3,5-triazines. For larger production volumes, it is recommended to arrange a number of reactors side by side in parallel.

Example 2. Synthesis of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)

[0049] CDMT was synthesized using the general procedure described above (Example 1) : in a reactor as described previously, there were introduced by means of an auger dispenser and/or a dispenser for liquids, 36 kg of $NaHCO_3$, 9.0 L of methanol, and 7.5 L of water. Then, there were introduced under stirring by means of an auger dispenser 10 kg of cyanuric chloride in approx. 2-3 h and then the mixture was heated at 100°C for 36 h. At the end of the reaction, the work-up was carried out by adding 1-5 volumes of water (9-45 L) with subsequent stirring for 480 min. The suspension was filtered, and the product collected and dried in a vacuum. An amount of 8.5 kg (48.3 mol) was recovered with a yield of 89.5% and a purity of 96.7% (3.3% of water). This method was used up to 150 kg of CDMT. For larger production volumes, it is recommended to arrange a number of reactors side by side in parallel.
^1H NMR ($CDCl_3$, 300 MHz, ppm) δ_H: 4.07; ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ_C: 172.72, 172.54, 56.04. FT-IR: 1540, 928, 806 cm^{-1}
m.p.: 75.2°C

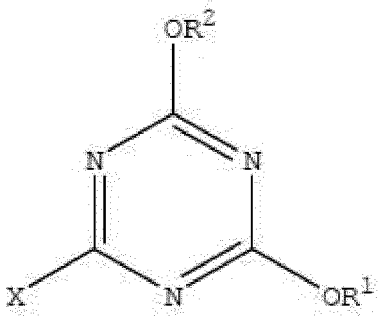
Example 3. Synthesis of 2-chloro-4,6-diethoxy-1,3,5-triazine (CDET)

[0050] The CDET was synthesized using the general procedure described above (Example 1): in a reactor as described previously, there were introduced by means of an auger dispenser and/or dispenser for liquids, 32.4 kg of $KHCO_3$, 12.6 L of ethanol, and 9.7 L of water. Then, there were introduced under stirring by means of an auger dispenser 10 kg of cyanuric chloride in approximately 2-3 h, and then the mixture was heated at 120°C for 48 h. At the end of the reaction work-up was carried out by adding 1-5 volumes of water (9-45 L) with subsequent stirring for 480 min. The suspension was filtered, and the product was collected and dried in a vacuum. An amount of 10.0 kg (49.4 mol) was recovered with a yield of 91.5% and a purity of 96.8% (3.2% of water) . This method was used up to 150 kg of CDET. For larger production

volumes, it is recommended to set a number of reactors side by side in parallel.
^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H: 4.47 (q, 4H), 1.40 (t, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ_C:. 172.7, 172.1, 65.5, 14.2.
IR: 1554, 1325, 809 cm^{-1}
m.p.: 145°C

Claims

1. A method for the synthesis of 2-halo-4,6-dialkoxy-1,3,5-triazines of formula III



(III)

Where:

R^1 and R^2 are independently chosen from: $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, and X is Cl^- or Br^-; performed in the presence of water,comprising the steps of:

- reaction of substitution between the corresponding cyanuric trihalogenide $C_3N_3X_3$ where X is Br^- or Cl^- (compound of formula I) and linear or branched aliphatic alcohols, in single phase, in the presence of a base;
- quenching of the reaction by addition of water and stirring;
- filtration;
- drying,

wherein the ratio between the reagents: compound of formula I/base/water/alcohol is comprised between 1/6/7.7/4 and 1/7.9/10/4.1.

2. The method according to Claim 1, wherein the substitution reaction is conducted at a temperature of between 45°C and 135°C for a time comprised between 5 h and 48 h.

3. The method according to Claims 1 and 2, wherein quenching of the reaction by means of addition of water and stirring have a duration ranging between 0 min and 480 min.

4. The method according to Claims 1 to 3, wherein the reagents are added in the reactor in which the reaction is carried out in the following order:

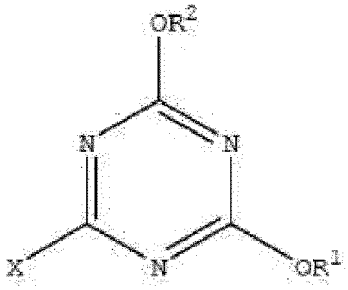
- 6-7.9 Eq of base together with 4-4.1 Eq of alcohol and 7.7-10 Eq of water;
- 1 Eq of cyanuric trihalogenide $C_3N_3X_3$, where X is Br^- or Cl^- (compound of formula I) over 0.5-3 h under vigorous stirring.

5. The method according to any one of the preceding claims, wherein the aliphatic alcohol (R_1 and R_2) is methanol, ethanol, isopropanol, or butanol.

6. The method according to any one of Claims 1 to 5, conducted on an industrial scale in a batch reactor with ellipsoidal bottom, pressure resistant, reinforced and lined with steel, equipped with means for the addition of reagents, stirring means, and means for temperature control.

Patentansprüche

1. Verfahren zur Synthese von 2-Halo-4,6-dialkoxy-1,3,5-triazinen der Formel III



(III)

wobei:

R^1 und R^2 unabhängig voneinander ausgewählt sind aus: $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)$, $-(CH_2)_2CH_3$, $(CH_2)_3CH_3$, und
X Cl^- oder Br^- ist; in der Anwesenheit von Wasser durchgeführt wird, umfassend die Schritte:

- Substitutionsreaktion zwischen dem korrespondierenden Cyanurtrihalogenid $C_3N_3X_3$ wobei X Br^- oder Cl^- ist (Verbindung der Formel I) und linear oder verzweigten aliphatischen Alkoholen, in einer Phase, in Anwesenheit einer Base;
- Abschrecken der Reaktion durch Hinzugeben von Wasser und Rühren;
- Filtrieren;
- Trocknen,

wobei das Verhältnis zwischen den Reagenzien: Verbindung der Formel I/Base/Wasser/Alkohol zwischen 1/6/7,7/4 und 1/7,9/10/4,1 vorgesehen ist.

2. Verfahren nach Anspruch 1, wobei die Substitutionsreaktion bei einer Temperatur zwischen 45°C und 135°C für eine Zeit zwischen 5 h und 48 h durchgeführt wird.

3. Verfahren nach den Ansprüchen 1 und 2, wobei das Abschrecken der Reaktion durch Zugabe von Wasser und Rühren eine Dauer zwischen 0 min und 480 min hat.

4. Verfahren nach den Ansprüchen 1 bis 3, wobei die Reagenzien in folgender Reihenfolge in den Reaktor, in dem die Reaktion durchgeführt wird, gegeben werden:

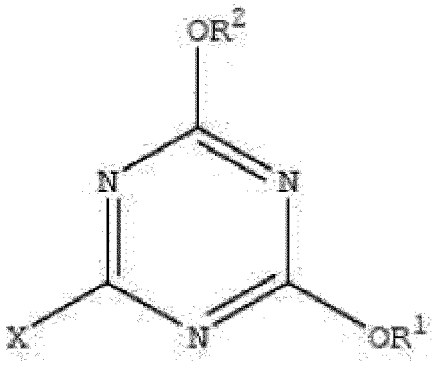
- 6-7,9 Äq. Base zusammen mit 4-4,1 Äq. Alkohol und 7,7-10 Äq. Wasser;
- 1 Äq. Cyanurtrihalogenid $C_3N_3X_3$, wobei X Br^- oder Cl^- ist (Verbindung der Formel I) in 0,5-3 h unter starkem Rühren.

5. Verfahren nach einem der vorstehenden Ansprüche, wobei der aliphatische Alkohol (R_1 und R_2) Methanol, Ethanol, Isopropanol oder Butanol ist.

6. Verfahren nach einem der Ansprüche 1 bis 5, durchgeführt im industriellen Maßstab in einem Batchreaktor mit ellipsodialem Boden, druckfest, verstärkt und mit Stahl ausgekleidet, ausgestattet mit Vorrichtungen zur Zugabe von Reagenzien, Rührmitteln und Vorrichtungen zur Temperaturkontrolle.

Revendications

1. Procédé pour la synthèse de 2-halo-4,6-dialcoxy-1,3,5-triazines de formule III



(III)

dans laquelle :

R^1 et R^2 sont choisis indépendamment parmi : $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, et X est Cl^- ou Br^- ; mis en œuvre en présence d'eau, comprenant les étapes suivantes :

- une réaction de substitution entre le trihalogénure cyanurique $C_3N_3X_3$ correspondant où X est Br^- ou Cl^- (composé de formule I) et des alcools aliphatiques linéaires ou ramifiés, dans une unique phase, en présence d'une base ;
- la désactivation de la réaction par ajout d'eau et une agitation ;
- une filtration ;
- un séchage,

dans lequel le rapport entre les réactifs : composé de formule I/base/eau/alcool est compris entre 1/6/7,7/4 et 1/7,9/10/4,1.

2. Procédé selon la revendication 1, dans lequel la réaction de substitution est menée à une température située entre 45 °C et 135 °C pendant une durée comprise entre 5 h et 48 h.

3. Procédé selon les revendications 1 et 2, dans lequel la désactivation de la réaction par ajout d'eau et l'agitation ont une durée de 0 min et 480 min.

4. Procédé selon les revendications 1 à 3, dans lequel les réactifs sont ajoutés dans le réacteur dans lequel la réaction est effectuée dans l'ordre suivant :

- 6 à 7,9 éq de base conjointement avec 4 à 4,1 éq d'un alcool et 7,7 à 10 éq d'eau ;
- 1 éq de trihalogénure cyanurique $C_3N_3X_3$, où X est Br^- ou Cl^- (composé de formule I) en 0,5 à 3 h sous agitation vigoureuse.

5. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'alcool aliphatique (R_1 et R_2) est le méthanol, l'éthanol, l'isopropanol ou le butanol.

6. Procédé selon l'une quelconque des revendications 1 à 5, mis en œuvre à l'échelle industrielle dans un réacteur discontinu à fond ellipsoïdal, résistant à la pression, renforcé et revêtu d'acier, équipé de moyens pour l'ajout de réactifs, de moyens d'agitation et de moyens de régulation de la température.

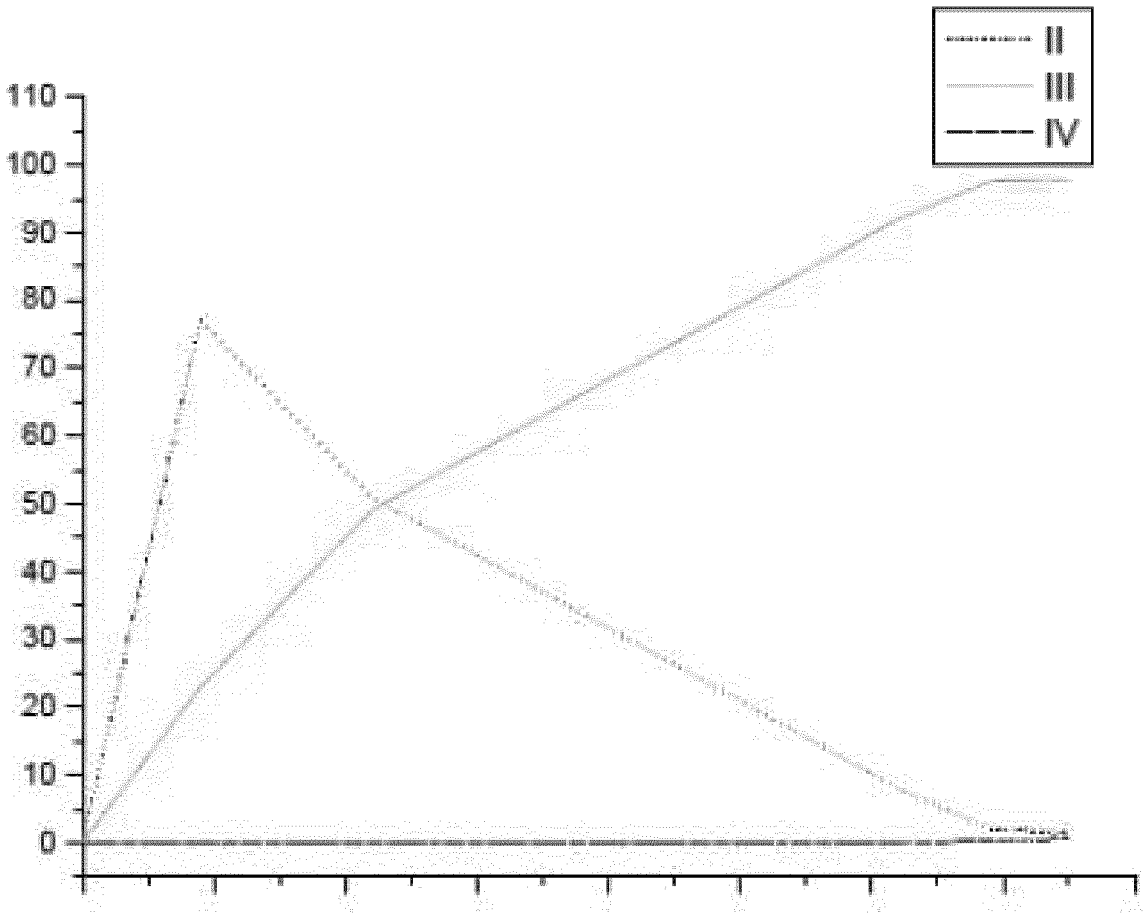


Figure 1

REFERENCES CITED IN THE DESCRIPTION

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