(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 3 237 390 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
08.05.2019 Bulletin 2019/19

(21) Application number: **15830862.7**

(22) Date of filing: **22.12.2015**

(51) Int Cl.:
C07D 251/46 *(2006.01)*

(86) International application number:
PCT/IB2015/059892

(87) International publication number:
WO 2016/103185 (30.06.2016 Gazette 2016/26)

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

VERFAHREN ZUR INDUSTRIELLEN HERSTELLUNG VON 2-HALO-4,6-DIALKOXY-1,3,5-TRIAZINEN UND VERWENDUNG DAVON IN ANWESENHEIT VON AMINEN

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

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Validation States:
MA

(30) Priority: **23.12.2014 IT VE20140070**
23.12.2014 IT VE20140071

(43) Date of publication of application:
01.11.2017 Bulletin 2017/44

(60) Divisional application:
19165931.7
19165938.2

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(56) References cited:
US-A- 4 076 538
US-A1- 2002 123 628
US-A1- 2013 219 634
US-B2- 8 679 196

- **CRONIN J S ET AL: "AN IMPROVED PROCEDURE FOR THE LARGE SCALE PREPARATION OF 2-CHLORO-4,6-DIMETHOXY-1,3,5-TRIAZINE", SYNTHETIC COMMUNICATIONS, TAYLOR & FRANCIS INC, PHILADELPHIA, PA; US, vol. 26, no. 18, 1 January 1996 (1996-01-01), pages 3491-3494, XP002944723, ISSN: 0039-7911, DOI: 10.1080/00397919608003754**
- **BOWES J H ET AL: "Crosslinking of Collagen", JOURNAL OF APPLIED CHEMISTRY, WILEY, US, vol. 15, no. 7, 1 July 1965 (1965-07-01), pages 296-304, XP002750889, ISSN: 0021-8871, DOI: 10.1002/JCTB.5010150702 [retrieved on 2007-05-04] cited in the application**

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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 which uses 2-halo-4,6-dialkoxy-1,3,5-triazines 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

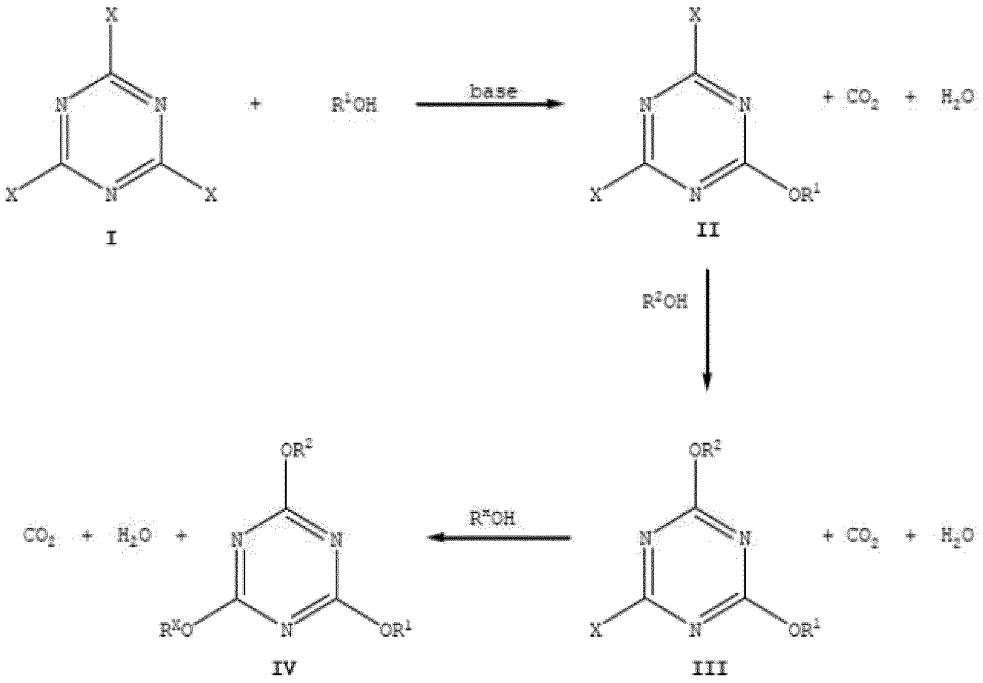
Protocol" (IPP), presents a certain number of critical features, above all from the standpoint of industrial production, in so far as it calls for complex reactors, large amounts of solvents, complicated purification steps, etc., which moreover reduce considerably the yield in the desired product, leading 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.

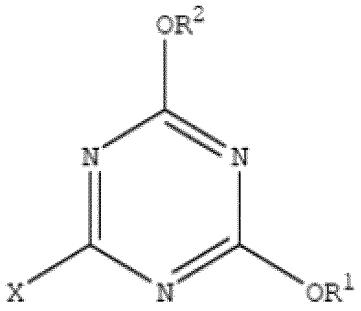
Summary of the invention

[0014] It is an object of the invention is the use of said 2-halo-4,6-dialkoxy-1,3,5-triazines and of the compositions that include them as agents for activating reactions of condensation, crosslinking, grafting, and curing.

[0015] Also falling within the scope of the present invention is the use of 2-halo-4,6-dialkoxy-1,3,5-triazines in processes for tanning hides, where their application is particularly advantageous. In this particular form of reaction, the invention envisages that stabilization of the hide is obtained by means of reaction with two reagents, in succession or previously mixed, one of which comprises one or more 2-halo-4,6-dialkoxy-1,3,5-triazines, and the other comprises one or more linear, branched, aromatic, cyclic, heterocyclic alkyl tertiary amines.

Detailed description of the invention

[0016] 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.

[0017] Thus, through a specific method that uses them, which forms the subject of the invention described herein, 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.

[0018] 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.

[0019] 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".

[0020] 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.

[0021] According to the present invention, Reagent 2 is a composition comprising:

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

[0022] Reagent 2 may further comprise an additive for the buffer.

[0023] Hence, the compositions of the aforesaid two reagents, Reagent 1 and Reagent 2, are essential for implementation of the method according to the invention.

[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.

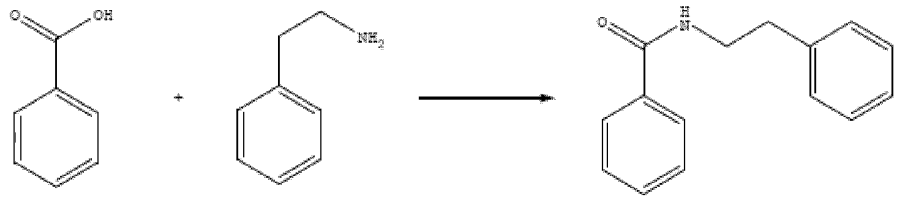
[0028] In some particularly preferred embodiments, Reagent 2 may further comprise additives for the buffer, which are chosen in the group: NaCl, Na_2HPO_4, NaOAc, KCl, SDS, glycine, boric acid, EDTA, and NaN_3.

[0029] The process of stabilization of the collagen matrices according to the invention finds application in multiple contexts of considerable technological and industrial interest.

[0030] Up to the present day, there does not exist any protocol that uses 2-halo-4,6-dialkoxytriazines in the presence of amines for stabilization of collagen. The present applicant has conducted tests that demonstrate that the method forming the subject of the invention enables crosslinking of powdered collagen dispersed in water by adding one after the other the two reagents, Reagent 1 and Reagent 2, as described in the examples provided hereinafter. From the results of the experimentation, it emerges clearly that the procedure adopted for crosslinking the collagen according to the invention conducted in the presence of Reagents 1 and 2, is notably superior to the one obtained with IPP. In particular, Reagents 1 and 2 have proved to present a better performance than aldehydes, glycerol, synthetic/natural crosslinking agents, carbodiimides, EDC/NHS, and quaternary ammonium salts of 2-halo-4,6-dialkoxy-1,3,5-triazines, which are currently used for stabilization of collagens according to the prior art, where normally the gelatinization temperature (Tg) does not exceed 80°C.

[0031] The above result is particularly important for the production of collagen tissues and materials with high thermal stability and their conservation in time for medical use and use in biotechnology (collagen, leather, tissues, corneas, etc.). On the basis of the results obtained for the reaction of crosslinking of collagen between phenethylamine and benzoic acid it may be pointed out that:

i) the IPP procedure presents limits of application in so far as not all the quaternary ammonium salts of 2-halo-4,6-dialkoxy-1,3,5-triazines can be synthesised, isolated, and used as activating agents;
ii) Reagents 1 and 2 enable the above difficulties to be overcome in the majority of the cases with the use of the procedure disclosed;
iii) in all comparable cases, 1,3,5-triazines provide conversions, performance, and characteristics that are equal or superior to those obtained with the corresponding IPP;
iv) the protocol of use of Reagents 1 and 2 may be formulated in the presence of various amines, and hence, according to the application, it is possible to choose the one available at the most advantageous market price;
v) Reagents 1 and 2 that do not present problems of activity linked to the nature of the solvent may moreover be used also in aqueous solvent;
vi) the protocol presented herein may be scaled up without substantial modifications from grams to kilograms and beyond; the effectiveness of the method according to the invention has moreover been verified for the reaction of condensation between benzoic acid and phenethylamine, presented in the scheme represented below as possible non-limiting example of condensation between a generic acid and a generic amine.



[0032] The effectiveness of the procedure according to the invention has moreover been verified in condensation reactions conducted on powdered bovine collagen, used as standard substrate for verifying the activity of the reagents of reactions of crosslinking, grafting, condensation, and curing, supplying data that are reproducible on collagen in other forms (liquid collagen, hydrolysed collagen, collagen fibres, solid matrix, etc.). It has been demonstrated that the use of additional crosslinking agents, such as formaldehyde, glutaraldehyde, glycerol, etc., is not necessary. The values of Tg obtained refer to stabilization of the collagen matrix obtained by exclusive crosslinking of the collagen with itself by the action of 2-halo-4,6-dialkoxy-1,3,5-triazines in the presence of amines and various additives.

[0033] It has moreover been found (Example 3) that the method, if conducted in the presence of chiral reagents, maintains enantioselectivity in the products. This characteristic is of fundamental importance for the synthesis of drugs, fragrances, active principles with high added value, etc.

[0034] In one embodiment, the present invention provides a method for stabilization of natural matrices, such as cellulose and/or modified celluloses. For instance, using Reagents 1 and 2, as specified in Example 5 of the experimental

section, carboxymethylcellulose (CMC), which is commonly used for the production of biodegradable hydrogels [C. Demitri, International J. Polymer Science, 2013, 1-6] can be converted into a material that is not soluble in water, is biodegradable, and presents totally innovative characteristics. From a markedly hydrophilic matrix a highly hydrophobic material is obtained thanks to the high degree of crosslinking due to reaction of the acid and alcohol groups present in CMC, with formation of ester groups.

[0035] In another embodiment of the present invention, described in Example 6, the use of Reagents 1 and 2 is performed by grafting of natural polymers and synthetic polymers, to form polyamides, polyesters, and polythioesters (Example 6). In this embodiment, the procedure represents a valid alternative for the production of polyamides, polyesters, etc. In this way, the preparation of the polymers, instead of being conducted specifically for each polymer, enables synthesis of an aspecific base polymer, which, thanks to the subsequent derivatization or grafting, assumes specific characteristics. Consequently, in this way, starting from one and the same matrix and in a single step, it is possible to obtain a vast range of known and unknown polymeric products.

[0036] In a further, particularly preferred, embodiment, the method of stabilization of collagen according to the invention finds application in the sector of the tanning industry and of processing of animal skins, to enable their conservation and subsequent further processing. The method enables the pelts obtained according to the standard preliminary procedures to be treated in a single step with the two tanning reagents, namely, the first reagent, or Reagent 1, and the second reagent, or Reagent 2, described previously, where for both of the reagents the solvent is water, to obtain a collagen derivative with high thermal stability (Tg $\geq$80 °C), as shown in Examples 7-17.

[0037] The two reagents in aqueous solution are essential for implementation of the tanning method according to the invention.

[0038] The method for tanning leather according to the present invention is suitable for obtaining leather from the skins of common slaughter animals, such as cattle, sheep, goats, and horses. The method is totally innovative and extremely simple to use, and moreover provides gelatinization temperatures (Tg) even higher than 100°C, which had never been obtained previously with alternative systems according to the prior art.

[0039] The method according to the invention envisages treatment of pelts, i.e., defleshed skin stripped of hair and ready for tanning, according to what is envisaged by the standard procedures used also for preparation of skin that is to be tanned with chromium (III) salts.

[0040] The pelt is then suspended in water.

[0041] Reagents 1 and 2, as defined previously, are added in the water bath containing the pelt in a concentration ranging between 3 and 22 wt% with respect to the weight of pelt set to react.

[0042] Reagents 1 and 2 can be added to the bath simultaneously, or in succession, in the order Reagent 1 and then Reagent 2. To obtain high Tg values, it is preferable for the addition of the two reagents to be carried out in two successive stages. Alternatively, the two reagents may be premixed in a homogenizer/reactor under stirring and with control of the temperature (10°C < T < 45°C), and then used for tanning.

[0043] In the presence of Reagents 1 and 2, the pH of the tanning environment does not call for pre-acidification or neutralization since the treatment reaches its maximum effectiveness in a range of values of pH of between 5.5 and 8.5. Consequently, the specimens of pelt subjected to the tanning procedure according to the present invention do not need to undergo the prior pickling step, i.e., the preparatory step envisaged prior to chromium tanning, which is carried out by treating the pelts in a solution of salt and acid, more frequently formic acid and sulphuric acid, nor the subsequent basification.

[0044] At the end of the step of tanning conducted in the presence of 2-halo-4,6-dialkoxy-1,3,5-triazines and amines, the spent bath is emptied out of the drum or reactor used, and the latter is washed with 150-200 wt% of water, and the skins thus obtained are sent on to the subsequent processing steps.

[0045] Consequently, the process of tanning of the hide carried out with Reagents 1 and 2 of the present invention comprises the steps of:

a) suspension of pelts in water in a reactor;
b) addition of the two tanning reagents in water in a concentration ranging between 3 and 22 wt% with respect to the weight of the pelt set to react; and
c) removal of the spent bath from the reactor and flushing of the reactor with water.

[0046] Furthermore, the leather obtained with the method according to the invention is suitable for undergoing the subsequent processes, such as neutralization, retanning, greasing, dyeing, etc.

[0047] The procedure described herein is totally metal-free, i.e., it is obtained without the use of any metal such as for example chromium, aluminium, iron, zirconium, titanium salts, etc., and does not undergo any contamination from formaldehyde or phenol, because it does not use these reagents or their derivatives in any way. Furthermore, by using 2-halo-4,6-dialkoxy-1,3,5-triazines, no acid treatment of the skins prior to the tanning process is required, thus also enabling omission of the subsequent basification step. In this way, the tanning process is obtained in a single step.

[0048] The tanning agents used in the method according to the invention, deriving from 2-halo-4,6-dialkoxy-1,3,5-triazines in the presence of amines, and buffer, as per the formulation of Reagents 1 and 2, are not equivalent to synthetic tannins since they are not withheld within the matrix, but act exclusively as crosslinking activators, in this way tanning the leather. The use of triazine derivatives according to the invention enables high Tg values to be to obtained in 1-4 h. However, the treatment can, for any type of particular need, be protracted also for longer times, without altering in any way the quality of the finished product. This technical feature represents an advantage over the classic processes of chromium tanning, the total duration of which varies, according to the type of leather treated, up to a maximum of 20-24 h.

[0049] The method according to the present invention, which uses as Reagent 2 a formulation containing a mixture of two or more amines, makes it possible to obtain a crosslinking agent having controlled action, which can be modulated in order to obtain leather with different characteristics.

[0050] The effectiveness of the method that uses Reagents 1 and 2 forming the subject of the invention has been demonstrated by means of specific crosslinking or tanning tests, conducted with the reagents on specimens of powdered bovine collagen. Experimentation with this substrate provides reproducible data on the effectiveness of the two reagents and of the corresponding method on solid collagen, i.e., on skins. In all cases, the Tg values obtained with the pelt specimens are similar to those obtained with powdered collagen and in any case comprised between 71°C and 105°C.

[0051] The effectiveness of Reagents 1 and 2, formulated according to what has been described above, has been verified also on specimens of bovine skins previously softened, stripped of hair, delimed, macerated, and defleshed (pelt) according to standard procedures used for the preparation of leather tanned with chromium (III) salts.

[0052] The methodology disclosed according to the present invention is free from problems due to the presence of substances harmful for health in the finished product since it is known that 2-halo-4,6-dialkoxy-1,3,5-triazines do not remain englobed in the matrix and/or reagents used and are eliminated during the washing cycles at the end of the reaction. The effectiveness of the method according to the invention is widely demonstrated in the examples presented in the experimental section of the present description. The experimental data have shown that, using different embodiments of Reagent 1 and Reagent 2 according to the invention, Tg values of up to 105°C were obtained, with excellent dyeability due to the perfectly white colour that characterizes all the specimens of skins treated with these 2-halo-4,6-dialkoxy-1,3,5-triazine derivatives.

[0053] From the present description it hence appears evident that falling within the scope of the invention is also the use of 2-halo-4,6-dialkoxy-1,3,5-triazines and of the compositions that comprise them as activating agents for reactions of crosslinking, grafting, curing, and condensation, in particular in the processes of collagen stabilization and of condensation of natural and synthetic polymers, such as for example polyacrylic acid, polyethylene, cellulose, and/or modified celluloses, polysaccharides, starch, and lignin.

Experimental part

[0054] The invention will be described in what follows by way of non-limiting illustration, with particular reference to some examples.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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 ^{1}H 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. Condensation between benzoic acid and phenethylamine (Test 2 of Table 1) by means of a procedure that uses Reagent 1 ($A_1B_1C_2D_3E_3$) and Reagent 2 ($F_6G_2H_2E_3$)

[0059] In a flask provided with magnetic stirring there were dissolved 293.1 mg (2.4 mmol) of benzoic acid in 15 mL of methanol. To the solution there were added 300 μL (2.4 mmol) 2 of phenethylamine and 2.4 mL of Reagent 1. Finally, there were added 2.4 mL of Reagent 2. After 2h a sample was taken for monitoring conversion, which was found to be 60%; then, the solvent was evaporated using a rotary evaporator. The solid residue was dissolved in diethyl ether (30 mL), and subsequently washed with a saturated solution of Na_2CO_3, water, a 1N solution of HCl, and a saturated solution of NaCl, anhydrified with $MgSO_4$, and filtered. The solution was dried off to obtain the product in the form of a white solid (450.6 mg, 2 mmol, yield 83%).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H: 7,72-7.31 (m, 2H), 7.52- 7.23 (m, 8H), 6.26 (br s, 1H), 3.73 (m, 2H), 2.95 (t, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ_c: . 167.43, 138.86, 134.60, 131.33, 128.75, 128.65, 128.43, 126.76, 126.52, 41.10, 35.67.

[0060] Formulation of Reagent 1 ($A_1B_1C_2D_3E_3$): 1.0M solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine, and of 10 wt% of MES, 0.5 wt% of KCl, and water.

[0061] Formulation of Reagent 2 ($F_6G_2H_2E_3$): 1.0M solution of MPD, 0.5-0.8 wt% of MOPS, 0.5-1.5 wt% of Na_2HPO_4, and water.

Example 1 - comparative test. Reaction of condensation between benzoic acid and phenethylamine (Test 1 of Table 1) with DMT-MPD with IPP method

Synthesis of DMT-MPD

[0062] In a flask provided with magnetic stirring there were introduced 500 mg (2.85 mmol) of CDMT dissolved in 10 mL of THF to which there were added drop by drop 300 μL (2.85 mmol) of MPD. After 10 min a white precipitate was obtained, which was recovered by filtration. The NMR analyses, in various solvents, highlighted that the product was not stable in solution, and hence it was not possible to carry out coupling with this reagent.

Table 1. Coupling reaction of benzoic acid and phenethylamine in the presence of triazine quaternary ammonium salts obtained with IPP and with the method that uses Reagent 1 and Reagent 2

Test	Activator	t(h)	Conv. (%) [a]
1	DMT-MPD[b]	-	-
2	$A_1B_1C_2D_3E_3/F_6G_2H_2E_3$	1 h	60
3	DET-EM[b]	-	-
4	$A_2B_2C_2D_1E_1/F_5G_4H_1E_1$	24 h	60
5	DET-TMA[b]	-	-
6	$A_2B_2C_2D_1E_3/F_1G_4H_1E_3$	1 h	100
7	DMT-MP	2 h	81
8	$A_1B_3C_2D_1E_4/F_7G_4H_1E_4$	2 h	90
9	DET-TMA	2 h	98
10	$A_1B_1C_2D_2E_5/F_1G_4H_1E_5$	2 h	100
11	DET-MM[b]	-	-
12	$A_2B_2C_2D_1E_3/F_4G_3H_1E_3$	2 h	70

(continued)

Test	Activator	t(h)	Conv. (%) [a]
13	DMT-MM[c]	2 h	96
14	$A_1B_4C_2D_2E_5/F_4G_3H_1E_5$	2 h	100
15	DET-EM	24 h	76
16	$A_1B_0C_2D_2E_4/F_5G_4H_1E_4$	24 h	82

Conditions of reaction: benzoic acid (1 Eq), phenethylamine (1 Eq), condensing agent (1 Eq).
[a] Conversion calculated by means of GLC with 156 mg (1 mmol) of n-undecane as internal standard.
[b] It was not possible to isolate the quaternary ammonium salt according to IPP.
[c] Commercially available.

Example 2 - comparative test. Condensation between benzoic acid and phenethylamine (Test 7 of Table 1) by means of IPP

[0063] In a flask provided with magnetic stirring there were dissolved 293.1 mg (2.4 mmol) of benzoic acid in 15 mL of methanol. To the solution there were added 300 μL (2.4 mmol) of phenethylamine and 692 mg (2.4 mmol) of DMT-MP obtained with IPP. After 2 h a sample was taken for monitoring conversion, which was found to be 81%; then, the solvent was evaporated using a rotary evaporator. The solid residue was dissolved in diethyl ether (30 mL), and subsequently washed with a saturated solution of Na_2CO_3, water, a 1N solution of HCl, and a saturated solution of NaCl and then anhydrified in $MgSO_4$, and filtered. The solution was dried off to obtain the product as white solid (405.5 mg, 1.8 mmol, yield 75%).
^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H: 7.72-7.31 (m, 2H), 7.52-7.23 (m, 8H), 6.26 (br s, 1H), 3.73 (m, 2H), 2.95 (t, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ_c: 167.43, 138.86, 134.60, 131.33, 128.75, 128.65, 128.43, 126.76, 126.52, 41.10, 35.67.

Example 3. Production of chiral amides with the method that uses Reagent 1 ($A_2B_3C_1D_1E_3$) and Reagent 2 ($F_4G_3H_1E_3$)

[0064] In a flask provided with magnetic stirring there were dissolved 200 mg (0.51 mmol) of 2-methyl-3-p-anisyl propanoic acid in 15 mL of methanol. To the solution there were added 55 μL (0.6 mmol) of aniline, 0.5 mL of Reagent 1 and, finally, 0.5 mL of Reagent 2. After 24 h the solvent was evaporated using a rotary evaporator. The solid residue was dissolved in ethyl ether (30 mL), and subsequently washed with a saturated solution of Na_2CO_3, water, a 1N solution of HCl, and a saturated solution of NaCl, and then anhydrified with $MgSO_4$, and filtered. The solution was then dried off to obtain the product in the form of a yellow liquid with a yield of 75% (101 mg, 0.375 mmol).
^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ_H: 7.33-7.26 (m, 2H), 7.24-7.14 (m, 2H), 7.07-7.01 (m, 2H),7.01-6.95 (m, 1H), 6.75 (d, 2H), 3.69 (s, 3H), 2.95-2.80 (m, 1H), 2.70-2.56 (m, 1H), 2.55-2.35 (m, 1H), 1.19 (d, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ_c: 172.95, 157.17, 136.68, 130.66, 128.89, 127.85, 123.18, 118.96, 112.91, 54.23, 44.02, 38.71, 16.67; HPLC: and.and. 96%, CHIRACEL OD-H column, n-hexane/isopropanol 92/8, 0.8 mL/min, t_R = 17.15 min (lower) and t_R =21.2 min (upper).
[0065] Formulation of Reagent 1 ($A_2B_3C_1D_1E_3$): 1.0M solution of 2-chloro-4,6-diethoxy-1,3,5-triazine, and of 0-6 wt% of BES, 0.5 wt% of $NaClO_4$, and water.
[0066] Formulation of Reagent 2 ($F_4G_3H_1E_3$): 0.5M solution of NMM, 0.1-0.8 wt% of Tris, 0.5-2.5 wt% of NaCl, and water.

Example 4. Funtionalization with aniline of polyacrylic acid with the method that uses Reagent 1 ($A_1B_4C_2D_1E_3$) and Reagent 2 ($F_4G_6H_2E_3$)

[0067] In a flask provided with magnetic stirring there were dissolved 60 mg (1.3×10^{-4} mmol) of PAA (MW = 450000) and 190 μL (2.1 mmol) of aniline in 35 mL of methanol.
[0068] To the solution there were then added 2.1 mL of Reagent 1 and 2.1 mL of Reagent 2. The solution was left under stirring for 24 h and then the solid was filtered, washed, dried, and analysed by means of ^{1}H NMR.
Formulation of Reagent 1 ($A_1B_4C_2D_1E_3$): 0.7M solution of 2-chloro-4,6,dimethoxy-1,3,5-triazine, and of 0-6 wt% of POPSO, 0.5-1.0 wt% of $KClO_4$, and water.
[0069] Formulation of Reagent 2 ($F_4G_6H_2E_3$): 0.7M solution of NMM, 0.1-5 wt% of Tris NaCitrate, 0.7-2.3 wt% of Na_2HPO_4, and water.

Example 5. Crosslinking of CMC with the method that uses Reagent 1 ($A_1B_4C_2D_1E_3$) and Reagent 2 ($F_4G_6H_2E_3$)

[0070] In a flask provided with magnetic stirring there were dissolved 279 mg of CMC (carboxymethylcellulose with carboxylation degree of 0.7) in 25 mL of water. To the solution there were then added 3 mL of Reagent 1 and 3 mL of Reagent 2. The solution was left under stirring for 24 h, and then the aqueous phase was evaporated by means of a high-vacuum pump. The solid obtained was washed with water and characterized by means of FT-IR.
FT-IR: 3200, 1750-1735, 1602, 1020 cm^{-1}

[0071] Formulation of Reagent 1 ($A_1B_4C_2D_1E_3$): 0.5M solution of 2-chloro-4,6,dimethoxy-1,3,5-triazine, and of 0-6 wt% of POPSO, 0.5-1.0 wt% of $KClO_4$, and water.

[0072] Formulation of Reagent 2 ($F_4G_6H_2E_3$): 0.5M solution of NMM, and of 0.1-5 wt% of Tris NaCitrate, 0.7-2.3 wt% of Na_2HPO_4, and water.

Example 6. Funtionalization with methanol of polyacrylic acid with the method that uses Reagent 1 ($A_2B_4C_2D_1E_3$) and Reagent 2 ($F_4G_6H_2E_3$)

[0073] In a flask provided with magnetic stirring there were dissolved 1.65 g (3.8×10^{-2}mmol) of an aqueous solution at 35% of sodium salt of polyacrylic acid (PAANa, MW = 15000) and 2 mL of methanol in 60 mL of water. To the solution there were then added 5 mL of Reagent 1 and 5 mL of Reagent 2. The solution was left under stirring for 24 h, and washed with etyl ether. The aqueous phase was concentrated using a high-vacuum pump, and the solid obtained was analysed by means of ^1H NMR.
^1H NMR (D_2O, 300 MHz, ppm) δ_H: 2.94 (s, 0.48H), 2.47 (br s, 1H), 1.66 (m, 2H).

Formulation of Reagent 1 ($A_2B_4C_2D_1E_3$): 0.2M solution of 2-chloro-4,6-diethoxy-1,3,5-triazine, and of 0-6 wt% of POPSO, 0.5-1.0 wt% of $KClO_4$, and water.
Formulation of Reagent 2 ($F_4G_6H_2E_3$): 0.2M solution of NMM, 0.1-5 wt% of Tris NaCitrate, 0.7-2.3 wt% of Na_2HPO_4, and water.

Table 2. Crosslinking of powdered collagen with triazine quaternary ammonium salts obtained with IPP or with Reagent 1 and Reagent 2.

Test	Activator	Tg (°C) [(a)]
1	DMT-MPD[(b)]	-
2	$A_1B_1C_2D_3/F_6G_2H_2$	101
3	DET-MM[(b)]	-
4	$A_2B_3C_1D_1/F_4G_3H_1$	85
5	DET-EM[(b)]	-
6	$A_2B_2C_2D_1/F_5G_4H_3$	103
7	DET-TMA[(b)]	-
8	$A_2B_2C_2D_1/F_1F_6G_4H_1$	89
9	DMT-MP	87
10	$A_1B_3C_2D_1/F_7G_6H_5$	89
11	DTM-EM	93
12	$A_1B_5C_2D_1/F_5G_5H_1$	104
13	DMT-EP	92
14	$A_1B_3C_2D_1/F_8G_2H_2$	95
15	DMT-TEA	-
16	$A_1B_3C_2D_1/F_2G_2H_3$	101
17	DET-TMA	89
18	$A_2B_3C_2D_1/F_1G_5H_1$	87

(continued)

Test	Activator	Tg (°C) [a]
19	DMT-MM	87
20	$A_1B_4C_2D_1/F_4G_4H_2$	95
Conditions of reaction: powdered collagen; solvent: water; time of reaction: 4 h; T(°C): 25°C. [a]Tg determined by means of DSC analysis. [b]It was not possible to isolate the quaternary ammonium salt according to IPP.		

Example 7. Tanning of powdered collagen with Reagent 1 ($A_1B_1C_2D_3$) and Reagent 2 ($F_6G_2H_2$), Test 2 of Table 2

[0074] In a 50-ml beaker there were added 500 mg of collagen, 25 mL of distilled water, and 0.6-12 mL of Reagent 1 and subsequently 0.6-12 mL of Reagent 2. The system was set under stirring at room temperature and the pH monitored every 60 min. After 4 h the suspension was filtred with a Buchner filter and washed with 50 ml of distilled water. The collagen treated was then analysed by means of DSC, to provide a Tg value of 85-101°C as the concentration of reagents used varies.

Formulation of Reagent 1 ($A_1B_1C_2D_3$): 0.5M solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine, and of 10 wt% of MES, 0.5 wt% of KCl, and water.
Formulation of Reagent 2 ($F_6G_2H_2$): 0.5M solution of MPD, 0.5-0.8% of MOPS, 0.5-1.5% of Na_2HPO_4, and water.

Example 8. Tanning of leather with Reagent 1 ($A_1B_1C_2D_3$) and Reagent 2 ($F_6G_2H_2$)

[0075] A piece of skin of approximately 100 g softened, limed/delimed, macerated, and defleshed (pelt) according to the normal industrial procedures, was treated as described in what follows. A piece of pelt of approximately 100 g was put in a drum in the presence of 100 mL of water at room temperature. The system was set in rotation and subsequently there were added Reagent 1 and Reagent 2 (in concentrations ranging from 3.0% to 22%). After 4 h the bath was poured off, and the system washed twice with abundant water. Tg = 83°C-103°C as the concentration of Reagents 1 and 2 used varies.

Example 9. Tanning of powdered collagen with Reagent 1 ($A_2B_3C_1D_1$) and Reagent 2 ($F_4G_3H_1$), Test 4, Table 2

[0076] The test was conducted in a way similar to what is described in Example 10.

Formulation of Reagent 1 ($A_2B_3C_1D_1$): 1.0M solution of 2-chloro-4,6-diethoxy-1,3,5-triazine, and of the 0-6 wt% of BES, 0.5 wt% of $NaClO_4$, and water
Formulation of Reagent 2 ($F_4G_3H_1$): 0.5M solution of NMM, 0.1-0.8 wt% of Tris, 0.5-1.5 wt% of NaCl, and water.
Tg = 73°C-85°C as the concentration of Reagents 1 and 2 used varies.

Example 10. Tanning of leather with Reagent 1 ($A_2B_3C_1D_1$) and Reagent 2 ($F_4G_3H_1$)

[0077] The test was conducted in a way similar to what is described in Example 11, where Reagent 1 and Reagent 2 were formulated in a way similar to what is described in Example 12.
Tg = 71°C-87°C as the concentration of Reagents 1 and 2 used varies.

Example 11. Tanning of powdered collagen with Reagent 1 ($A_2B_2C_2D_1$) and Reagent 2 ($F_5G_4H_3$), Test 6 of Table 2

[0078] The test was conducted in a way similar to what is described in Example 10.

Formulation of Reagent 1 ($A_2B_2C_2D_1$): 0.7M solution of 2-chloro-4,6-diethoxy-1,3,5-triazine, and of 0-6 wt% of ACES, 0.5-1.0 wt% of $KClO_4$, and water;
Formulation of Reagent 2 ($F_5G_4H_3$):0.7M solution of NEM, 0.1-0.8wt% of POPSO, 0.5-2.5 wt% of NaOAc, and water. Tg=93 °C-103°C as the concentration of Reagents 1 and 2 used varies.

Example 12. Tanning of leather with Reagent 1 ($A_2B_2C_2D_1$) and Reagent 2 ($F_5G_4H_3$)

[0079] The test was conducted in a way similar to what is described in Example 11, where Reagent 1 and Reagent 2 are formulated in a way similar to what is described in Example 14.

[0080] Tg=90°C-105°C as the concentration of Reagents 1 and 2 used varies.

Example 13. Tanning of powdered collagen with Reagent 1 ($A_2B_2C_2D_1$) and Reagent 2 ($F_6F_1G_4H_1$), Test 8 of Table 2

[0081] The test was conducted in a way similar to what is described in Example 10.

Formulation of Reagent 1 ($A_2B_2C_2D_1$): 0.8M solution of 2-chloro-4,6-diethoxy-1,3,5-triazine, and of 0-6 wt% of ACES, 0.5-1.0 wt% of $KClO_4$, and water.
Formulation of Reagent 2 ($F_6F_1G_4H_1$):0.7M solution of MPD, 0.3 M of TMA, 0.1-0.8 wt% of POPSO, 0.5-2.5 wt% of NaCl, and water.
Tg = 83°C-89°C as the concentration of Reagents 1 and 2 used varies.

Example 14. Tanning of leather with Reagent 1 ($A_2B_2C_2D_1$) and Reagent 2 ($F_6F_1G_4H_1$)

[0082] The test was conducted in a way similar to what is described in Example 11, where Reagent 1 and Reagent 2 are formulated in a way similar to what is described in Example 16.
Tg = 81°C-90°C as the concentration of Reagents 1 and 2 used varies.

Example 15. Crosslinking of powdered collagen with DMT-MP with IPP (Test 9 of Table 2)

I) Synthesis of DMT-MP

[0083] In a flask provided with magnetic stirring there were introduced 500 mg (2.85 mmol) of CDMT dissloved in 10 mL of THF to which there were added drop by drop 350 μL (2.85 mmol) of MP. After 2 h there was obtained a white precipitate that was recovered by filtration (yield of 60%) .
^1H NMR (D_2O, 300 MHz, ppm) δ_H: 4.42 (d, 2H), 4.06 (s, 6H), 3.54 (m, 2H),3.32 (s, 3H), 2.0-1.4 (m, 6H); ^{13}C NMR (D20, 75 MHz, ppm) δ_c: 174.38, 171.24, 62.44, 57.44, 21.54, 20.30; m.p. 71.0°C.
ii) In a beaker provided with magnetic stirring there were suspended 500 mg of powdered collagen in 50 mL of water. To the mixture there were then added 82.5 mg (0.3 mmol) of DMT-MP. The mixture was left under stirring for 4 h at room temperature and subsequently the solid was filtered, washed with water, and analysed by means of DSC. (Tg = 87°C)

Example 16. Tanning of powdered collagen with Reagent 1 ($A_1B_3C_2D_1$) and Reagent 2 ($F_7G_6H_5$), Test 10 of Table 2

[0084] The test was conducted in a way similar to what is presented in Example 10.

[0085] Formulation of Reagent 1 ($A_1B_3C_2D_1$) : 0.6M solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine, and of 0-6 wt% of BES, 0.5-1.0 wt% of $KClO_4$, and water.
Formulation of Reagent 2 ($F_7G_6H_5$): 0.3M solution of MP, 0.1-0.8% of Tris NaCitrate, H_5: SDS, and water.
Tg = 83°C-89°C as the concentration of Reagents 1 and 2 used varies.

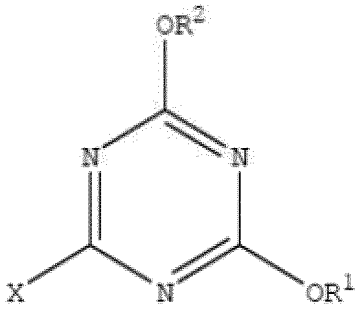
Example 17. Tanning of leather with Reagent 1 ($A_1B_3C_2D_1$) and Reagent 2 ($F_7G_6H_5$)

[0086] The test was conducted in a way similar to what is presented in Example 11, where Reagent 1 and Reagent 2 are formulated in a way similar to what is presented in Example 19.
Tg = 82°C-90°C as the concentration of Reagents 1 and 2 used varies.

[0087] Finally, it should be emphasized that, even though the present invention has been described purely by way of non-limiting illustration, according to its preferred embodiments, variations and/or modifications may be made by persons skilled in the branch, without thereby departing from the corresponding sphere of protection, as defined by the annexed claims.

Claims

1. Use of the compound of formula III (2-halo-4,6-dialkoxy-1,3,5-triazine)



(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^-, as active principle of a reagent involved in a method for the stabilization of collagen matrices and for the condensation of natural and synthetic polymers.

2. Use according to Claim 1, wherein the method of stabilization of collagen matrices and of condensation of polymers is implemented through reactions of condensation, crosslinking, grafting, and curing.

3. Use according to Claim 2, wherein the polymers are polyacrylic acid, polyethylene, cellulose, modified cellulose, polysaccharides, starch, and lignin.

4. Use according to Claims 1 to 3 in a process of stabilization of collagen deriving from waste of the foodstuffs industry.

5. A method for stabilization of collagen matrices and for condensation of natural and synthetic polymers, comprising the single-step reaction with a pair of reagents, wherein a first reagent is a composition comprising:

a) at least one compound of formula III (2-halo-4,6-dialkoxy-1,3,5-triazine)
where R^1 and R^2 are independently chosen from: $-CH_3$,$-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$;
X and is Cl^- or Br^-;
b) a buffer;
c) an inorganic salt;
d) a solvent, and

a second reagent is a composition comprising:

a) a tertiary amine, and/or a quaternary salt thereof;
b) a buffer; and
c) a solvent.

6. The method according to Claim 5, wherein the first reagent comprises as active principle one or more 2-halo-4,6-dialkoxy-1,3,5-triazines of formula III in a concentration ranging between 0.1 and 1.0 M.

7. The method according to Claims 5 and 6, wherein the first reagent comprises a buffer, chosen in the group of: MES, ACES, BES, BIS-Tris, MOPS, TEA, TAPSO, POPSO, TAPS, formiate, phosphate, and succinate; and a base or a salt of formula X^+Y^-, where X^+ is chosen from Na^+, K^+, Ag^+, and Y^- is chosen from: ClO_4^-, BF_4^-, PF_6, CO_3^- , Cl^-, and HCO_3^-.

8. The method according to any one of Claims 5 to 7, wherein the solvent of Reagent 1 is chosen in the group of: aliphatic ether, halogenate, alcohol, ketone, ester, aromatic or aliphatic hydrocarbon, amide, carbonate, DMSO, and water.

9. The method according to any one of Claims 5 to 8, wherein the second reagent comprises as active principle one or more linear, branched, cyclic, aromatic, heterocyclic tertiary amines, and/or a quaternary salt thereof, in a concentration ranging between 0.1 and 1.0 M.

10. The method according to any one of Claims 5 to 9, wherein the second reagent comprises a buffer, chosen in the group of: HEPES, MOPS, TRIS, tri-Na-citrate, Tris-Cl, and TAPS.

11. The method according to any one of Claims 5 to 10, wherein the solvent of Reagent 2 is chosen in the group of: aliphatic ether, halogenate, alcohol, ketone, ester, aromatic or aliphatic hydrocarbon, amide, carbonate, DMSO, and water.

12. The method according to any one of Claims 5 to 11, wherein the second reagent may further comprise an additive for the buffer.

13. The method according to Claim12, wherein the additive for the buffer of the second reagent is chosen in the group of: NaCl, Na_2HPO_4, NaOAc, KCl, SDS, glycine, boric acid, EDTA, and NaN_3.

14. The method according to any one of Claims 5 to 13, wherein the solvent of Reagents 1 and 2 is water and is applied to waste products of the foodstuffs industry and used for tanning of leather.

15. The method according to Claim 14, comprising the steps of:

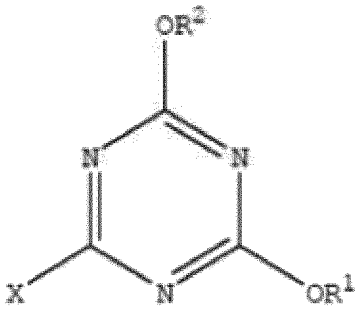
a) suspension in water of pelt in a reactor;
b) addition of the two tanning reagents in water in a concentration ranging between 3 and 22 wt% with respect to the weight of pelt set to react;
c) removal of the spent bath from the reactor and flushing of the reactor with water.

16. The method according to Claims 14 and 15, wherein the two reagents are added, simultaneously or in succession, first Reagent 1 and then Reagent 2, to the bath containing pelts in suspension.

17. The method according to Claims 14 to 16, wherein the two reagents are added simultaneously to the bath containing pelts in suspension pre-stirred, at a temperature between 10°C and 45°C.

Patentansprüche

1. Verwendung der Verbindung der Formel III (2-Halo-4,6-dialkoxy-1,3,5-triazin)



(III)

wobei:
R^1 und R^2 sind unabhängig voneinander ausgewählt aus: $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, und X ist Cl^- oder Br^-, als aktives Prinzip eines Reagenzes, das an einem Verfahren zur Stabilisierung von Kollagenmatrices und zur Kondensation von natürlichen und synthetischen Polymeren beteiligt ist.

2. Verwendung nach Anspruch 1, worin das Verfahren zur Stabilisierung von Kollagenmatrices und zur Kondensation von Polymeren durch Reaktionen von Kondensation, Vernetzung, Pfropfen und Aushärten implementiert wird.

3. Verwendung nach Anspruch 2, worin die Polymere Polyacrylsäure, Polyethylen, Cellulose, modifizierte Cellulose, Polysaccharide, Stärke und Lignin sind.

4. Verwendung nach den Ansprüchen 1 bis 3 in einem Verfahren der Stabilisierung von Kollagen, das aus Abfällen der Lebensmittelindustrie stammt.

5. Verfahren zur Stabilisierung. von Kollagenmatrices und zur Kondensation von natürlichen und synthetischen Polymeren, umfassend die einstufige Reaktion mit einem Paar von Reagenzien, worin ein erstes Reagenz eine Zusammensetzung ist, die umfasst:

a) mindestens eine Verbindung der Formel III (2-Halo-4,6-dialkoxy-1,3,5-triazin), worin R^1 und R^2 unabhängig voneinander ausgewählt sind aus: $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$,;
und X ist Cl^- oder Br^-;
b) einen Puffer;
c) ein anorganisches Salz;
d) ein Lösungsmittel, und ein zweites Reagenz ist eine Zusammensetzung, die umfasst:

a) ein tertiäres Amin und/oder ein quartäres Salz davon;
b) einen Puffer; und
c) ein Lösungsmittel.

6. Verfahren nach Anspruch 5, worin das erste Reagenz als Wirkstoff ein oder mehrere 2-Halo-4,6-dialkoxy-1,3,5-triazine der Formel III in einer Konzentration im Bereich zwischen 0,1 und 1,0 M umfasst.

7. Verfahren nach den Ansprüchen 5 und 6, worin das erste Reagenz einen Puffer umfasst, ausgewählt in der Gruppe von: MES, ACES, BES, BIS-Tris, MOPS, TEA, TAPSO, POPSO, TAPS, Formiat, Phosphat und Succinat; und eine Base oder ein Salz der Formel X^+Y^-, worin X^+ ausgewählt ist aus Na^+, K^+, Ag^+, und Y^- ausgewählt ist aus: ClO_4, BF_4^-, PF_6, CO_3^-, Cl^- und HCO_3^-.

8. Verfahren nach einem der Ansprüche 5 bis 7, wobei das Lösungsmittel von Reagenz 1 ausgewählt ist in der Gruppe: aliphatischer Ether, Halogenat, Alkohol, Keton, Ester, aromatischer oder aliphatischer Kohlenwasserstoff, Amid, Carbonat, DMSO und Wasser.

9. Verfahren nach einem der Ansprüche 5 bis 8, worin das zweite Reagenz als aktives Prinzip ein oder mehrere lineare, verzweigte, cyclische, aromatische, heterocyclische tertiäre Amine und/oder ein quartäres Salz davon in einer Konzentration im Bereich zwischen 0,1 und 1,0 M umfasst.

10. Verfahren nach einem der Ansprüche 5 bis 9, worin das zweite Reagenz einen Puffer umfasst, ausgewählt in der Gruppe von: HEPES, MOPS, TRIS, Tri-Na-Citrat, Tris-Cl und TAPS.

11. Verfahren nach einem der Ansprüche 5 bis 10, wobei das Lösungsmittel von Reagenz 2 ausgewählt ist in der Gruppe: aliphatischer Ether, Halogenat, Alkohol, Keton, Ester, aromatischer oder aliphatischer Kohlenwasserstoff, Amid, Carbonat, DMSO und Wasser.

12. Verfahren nach einem der Ansprüche 5 bis 11, worin das zweite Reagens ferner ein Additiv für den Puffer umfassen kann.

13. Verfahren nach Anspruch 12, worin das Additiv für den Puffer des zweiten Reagenzes ausgewählt ist in der Gruppe von: NaCl, Na_2HPO_4, NaOAc, KCl, SDS, Glycin, Borsäure, EDTA und NaN_3.

14. Verfahren nach einem der Ansprüche 5 bis 13, worin das Lösungsmittel der Reagenzien 1 und 2 Wasser ist und bei Abfallprodukten der Lebensmittelindustrie angewandt wird und zum Gerben von Leder verwendet wird.

15. Verfahren nach Anspruch 14, umfassend die Schritte von:

a) Suspendieren von Fell in Wasser in einem Reaktor;
b) Zugabe der beiden Gerbereagenzien zu Wasser in einer Konzentration im Bereich von 3 bis 22 Gew.-%, bezogen auf das Gewicht des umzusetzenden Fells;
c) Entfernen des verbrauchten Bades aus dem Reaktor und Spülen des Reaktors mit Wasser.

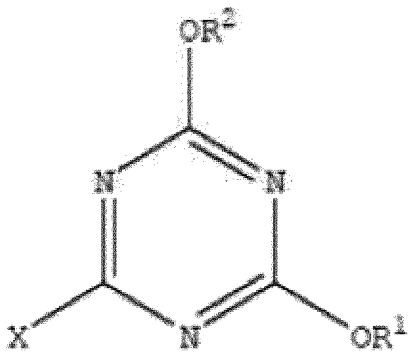
16. Verfahren nach den Ansprüchen 14 und 15, worin die beiden Reagenzien gleichzeitig oder nacheinander, zuerst

Reagenz 1 und dann Reagenz 2, zu dem Bad zugegeben werden, das Pelze in Suspension enthält.

17. Verfahren nach den Ansprüchen 14 bis 16, worin die beiden Reagenzien gleichzeitig dem Bad zugegeben werden, das Pelze in Suspension vorgerührt enthält, bei einer Temperatur zwischen 10°C und 45°C.

Revendications

1. Utilisation du composé de formule III (2-halo-4,6-dialcoxy-1,3,5-triazine)



(III)

où :
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^-,
comme principe actif d'un réactif impliqué dans un procédé pour la stabilisation de matrices de collagène et pour la condensation de polymères naturels et synthétiques.

2. Utilisation selon la revendication 1, dans lequel le procédé de stabilisation de matrices de collagène et de condensation de polymères est mis en oeuvre par l'intermédiaire de réactions de condensation, de réticulation, de greffage, et de durcissement.

3. Utilisation selon la revendication 2, dans lequel les polymères sont un polyacide acrylique, un polyéthylène, une cellulose, une cellulose modifiée, des polysaccharides, un amidon, et une lignine.

4. Utilisation selon les revendications 1 à 3 dans un procédé de stabilisation de collagène dérivant de déchets de l'industrie alimentaire.

5. Procédé pour la stabilisation de matrices de collagène et pour la condensation de polymères naturels et synthétiques, comprenant la réaction en une étape avec une paire de réactifs, dans lequel un premier réactif est une composition comprenant :

a) au moins un composé de formule III (2-halo-4,6-dialcoxy-1,3,5-triazine)
où R^1 et R^2 sont choisis indépendamment parmi : $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$;
X est Cl^- ou Br^- ;
b) un tampon ;
c) un sel inorganique ;
d) un solvant, et

un second réactif est une composition comprenant :

a) une amine tertiaire, et/ou un sel quaternaire de celle-ci ;
b) un tampon ; et
c) un solvant.

6. Procédé selon la revendication 5, dans lequel le premier réactif comprend comme principe actif une ou plusieurs 2-halo-4,6-dialcoxy-1,3,5-triazines de formule III à une concentration située entre 0,1 et 1,0 M.

7. Procédé selon les revendications 5 et 6, dans lequel le premier réactif comprend un tampon, choisi dans le groupe comprenant : MES, ACES, BES, BIS-Tris, MOPS, TEA, TAPSO, POPSO, TAPS, formiate, phosphate, et succinate ; et une base ou un sel de formule X^+Y^-, où X^+ est choisi parmi Na^+, K^+, Ag^+, et Y^- est choisi parmi : ClO_4^-, BF_4^-, PF_6, CO_3^-, Cl^-, et HCO_3^-.

8. Procédé selon l'une quelconque des revendications 5 à 7, dans lequel le solvant du réactif 1 est choisi dans le groupe comprenant : un éther aliphatique, un halogénate, un alcool, une cétone, un ester, un hydrocarbure aromatique ou aliphatique, un amide, un carbonate, le DMSO, et l'eau.

9. Procédé selon l'une quelconque des revendications 5 à 8, dans lequel le second réactif comprend comme principe actif une ou plusieurs amines tertiaires linéaires, ramifiées, cycliques, aromatiques, hétérocycliques, et/ou un sel quaternaire de celles-ci, à une concentration située entre 0,1 et 1,0 M.

10. Procédé selon l'une quelconque des revendications 5 à 9, dans lequel le second réactif comprend un tampon, choisi dans le groupe comprenant : HEPES, MOPS, TRIS, tri-Na-citrate, Tris-Cl, et TAPS.

11. Procédé selon l'une quelconque des revendications 5 à 10, dans lequel le solvant du réactif 2 est choisi dans le groupe comprenant : un éther aliphatique, un halogénate, un alcool, une cétone, un ester, un hydrocarbure aromatique ou aliphatique, un amide, un carbonate, le DMSO, et l'eau.

12. Procédé selon l'une quelconque des revendications 5 à 11, dans lequel le second réactif peut comprendre en outre un additif pour le tampon.

13. Procédé selon la revendication 12, dans lequel l'additif pour le tampon du second réactif est choisi dans le groupe comprenant : NaCl, Na_2HPO_4, NaOAc, KCl, SDS, glycine, acide borique, EDTA, et NaN_3.

14. Procédé selon l'une quelconque des revendications 5 à 13, dans lequel le solvant des réactifs 1 et 2 est l'eau et est appliqué à des déchets de l'industrie alimentaire et utilisé pour le tannage du cuir.

15. Procédé selon la revendication 14, comprenant les étapes suivantes :

    a) la mise en suspension dans de l'eau d'une peau dans un réacteur ;
    b) l'ajout des deux réactifs de tannage à l'eau à une concentration située entre 3 et 22 % en poids par rapport au poids de la peau prête à réagir ;
    c) le retrait du bain usé à partir du réacteur et le rinçage du réacteur avec de l'eau.

16. Procédé selon les revendications 14 et 15, dans lequel les deux réactifs sont ajoutés, simultanément ou successivement, le premier réactif 1 et ensuite le réactif 2, au bain contenant des peaux en suspension.

17. Procédé selon les revendications 14 à 16, dans lequel les deux réactifs sont ajoutés simultanément au bain contenant des peaux en suspension préalablement agité, à une température située entre 10 °C et 45 °C.

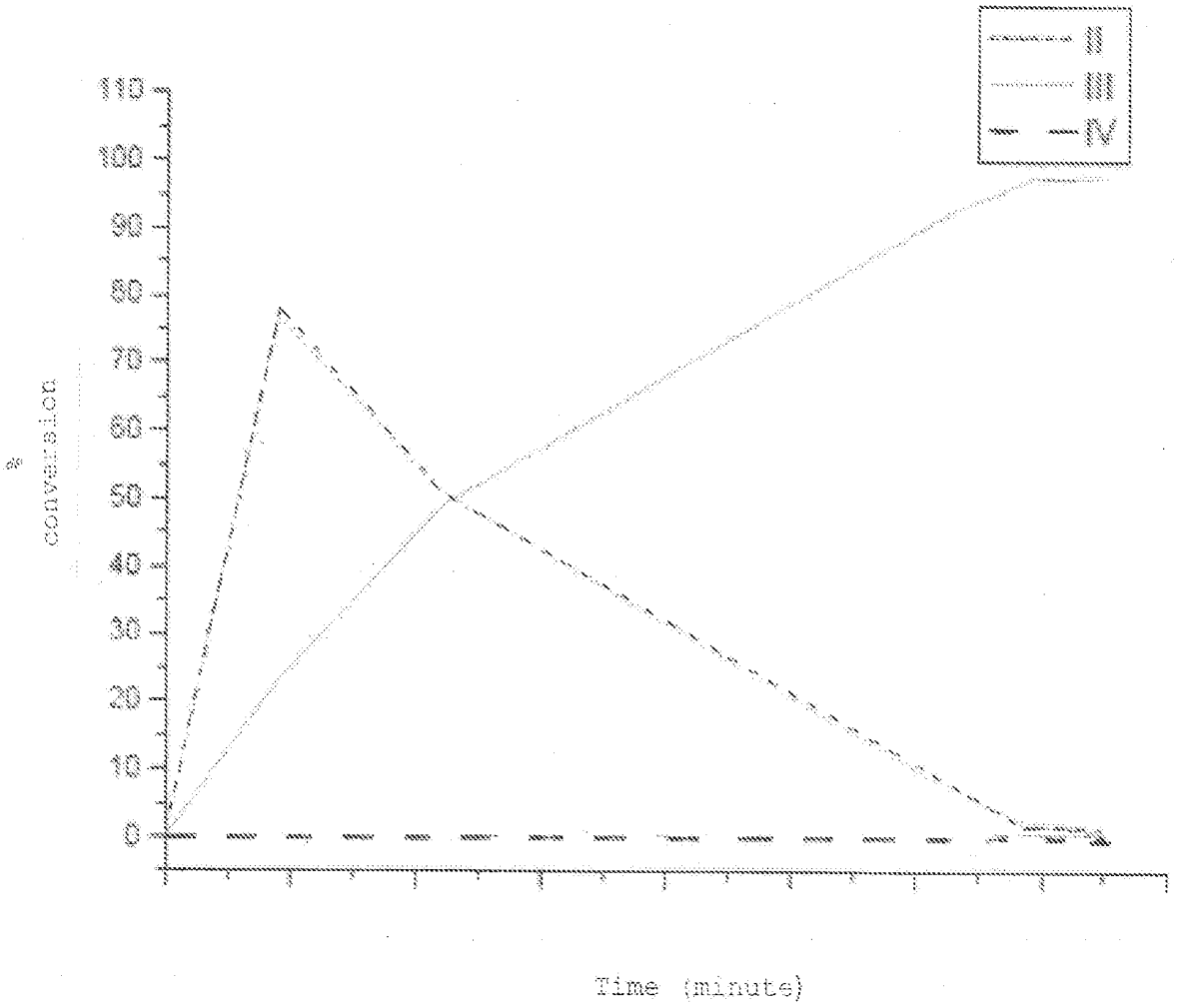

II
III
IV
110
100
90
80
70
60
50
40
30
20
10
0
% conversion
Time (minute)

Figure 1

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 8691279 B **[0004]**
- US 20120009223 A1 **[0004]**
- US 6458948 B1 **[0007] [0008]**
- EP 1748985 B1 **[0007]**
- US 20080234254 A1 **[0007]**
- US 2011118265 A1 **[0007]**
- US 8119592 B **[0007]**
- WO 2010056778 A **[0007]**
- WO 2014063102 A **[0008]**
- US 20030153785 A1 **[0008] [0010]**
- WO 174962B12006 A **[0008]**
- WO 2007051496 A1 **[0008]**
- US 20130123508 A1 **[0010]**
- EP 1992364 A1 **[0010]**
- US 20020123628 A **[0012]**

Non-patent literature cited in the description

- **A. EL-FAHAM.** *Chem. Rev.,* 2011, vol. 111, 6557-6602 **[0004]**
- **E. KHOR.** *Biomaterials,* 1997, vol. 18, 95-105 **[0006]**
- **X. DUAN.** *Biomaterials,* 2006, vol. 27, 4608-4615 **[0006]**
- **Z.J. KAMINSKI.** *J. Am. Chem. Soc.,* 2005, vol. 127, 16912-16920 **[0007]**
- **S. S.A. RAW.** *Tetrah. Lett.,* 2009, vol. 50, 946-948 **[0008]**
- *Chem. Eur. J.,* 2012, vol. 18, 15856-15867 **[0009]**
- **DUDLEY.** *J. Am. Chem. Soc.,* 1951, vol. 73, 2986-2990 **[0013]**
- **J. CRONIN.** *Synth. Commun.,* 1996, vol. 26, 3491-3494 **[0013]**
- **C. DEMITRI.** *International J. Polymer Science,* 2013, 1-6 **[0034]**