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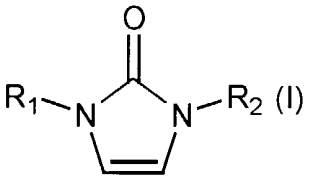
(54) Title: A TRACELESS SOLID-PHASE SYNTHESIS OF 2-IMIDAZOLONES



(57) Abstract: (Formula I) A traceless solid-phase synthesis of 2-imidazolones is described. A polymer-bound haloacetaldehyde acetal, which is prepared from an acetal exchange of haloacetaldehyde diethyl acetal with polymer-bound 1,2-ethylenediol, is reacted with a primary amine of the formula R_1NH_2 to afford a polymer-bound aminoacetaldehyde acetal. The latter is reacted with an isocyanate of the formula R_2NCO to afford the corresponding polymer-bound urea acetal intermediate, which upon treatment with an acid provides the 2-imidazolone compounds.

SPECIFICATION

A TRACELESS SOLID-PHASE SYNTHESIS OF 2-IMIDAZOLONES

FIELD OF THE INVENTION

This invention relates to a novel process for preparing 2-imidazolones compounds. This invention also relates to novel polymer-bound halo- and amino-acetaldehyde acetal compounds. This invention also relates to a novel process for preparing polymer-bound halo- and amino-acetaldehyde acetal compounds.

BACKGROUND

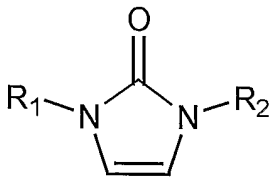
2-Imidazolone derivatives have long been known to possess interesting biological activities. Examples include herbicial agents (R. W. Luckenbaugh, US 3,216,816), antifungal agents (Itoh, K. et al., EP 884,311), anti-coagulants (Mohan, R. et al., WO 96/38421) and PDE IV inhibitors (Freyne, E. J. E. et al., WO 96/31485).

Several synthetic procedures for preparing 2-imidazolones have been described in the literature (Lehmstedt et al., *J. Liebigs, Ann. Chem.* 456, 269 (1927); R. Duschinsky, E. Fell, US 2,707,186; W. B. Wright Jr. et al., US 3,355,457; R. W. Luckenbaugh, US 3,216,816). The most convenient of these is an intramolecular *N*-acyliminium ion cyclization of a urea acetaldehyde acetal precursor. Under acidic conditions, the acetal protecting group of the urea acetaldehyde acetal is removed and the resulting urea acetaldehyde intermediate formed. Subsequently, urea acetaldehyde cyclizes to afford a five-membered *N*-acyliminium ion which spontaneously deprotonates to afford the 2-imidazolone in the absence of any nucleophiles. However, this reaction takes place in the solution phase. It does not appear that such a reaction can be adapted for use in a traceless solid-phase synthesis of 2-imidazolones.

SUMMARY OF THE INVENTION

I have found that a urea acetaldehyde acetal mounted on a solid support under acidic conditions releases a urea acetaldehyde intermediate from the solid support and simultaneously undergoes cyclization and deprotonation to afford the 2-imidazolone. Thus, 2-imidazolones prepared by this solid-phase method leave no trace of the linker used for tethering the starting material to the solid support.

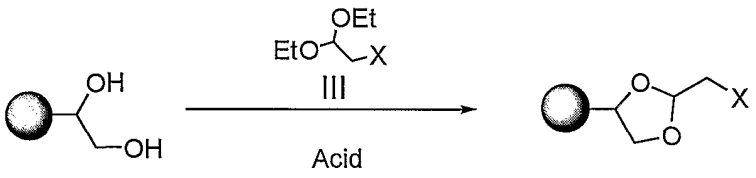
In one aspect, this invention provides a process for preparing a 2-imidazolone compound of the formula (I)



(I)

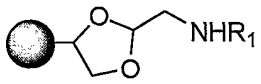
comprising the steps of

1) Reacting a haloacetaldehyde diethyl acetal (III) with a polymer-bound 1,2-ethylenediol (II) under acidic conditions to form a polymer-bound haloacetaldehyde acetal (IV),



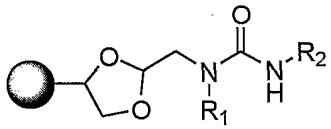
II IV

2) Reacting said polymer-bound haloacetaldehyde acetal (IV) with a primary amine of the formula R_1NH_2 to form a polymer-bound aminoacetaldehyde acetal (V),



(V)

3) Reacting said polymer-bound aminoacetaldehyde acetal (V) with an isocyanate of the formula R_2NCO to form a polymer-bound urea acetaldehyde acetal (VI), and,



(VI)

4) Reacting said polymer-bound urea acetaldehyde acetal (VI) with an acid to provide the 2-imidazolone (I), wherein R_1 and R_2 independently represent hydrogen, alkyl, heterocyclyl, aryl, or heteroaryl groups.

Preferably, said acid in the step 4) is trifluoroacetic acid or hydrochloric acid.

In another aspect, this invention also provides a polymer-bound haloacetaldehyde acetal compound of formula (IV), wherein x is chloro, bromo or iodo.

In still another aspect, this invention also provides a process for preparing a polymer-bound haloacetaldehyde acetal compound of formula (IV) by reacting a haloacetaldehyde diethyl acetal (III) with a polymer-bound 1,2-ethylenediol under acidic conditions, wherein x is chloro, bromo or iodo.

In still another aspect, this invention also provides a polymer-bound aminoacetaldehyde acetal compound of formula (V), wherein R_1 represents hydrogen, alkyl, heterocyclyl, aryl, or heteroaryl groups.

In still another aspect, this invention also provides a process for preparing a polymer-bound aminoacetaldehyde acetal compound of formula (V) by reacting a polymer-bound haloacetaldehyde acetal (IV) with a primary amine of the formula R_1NH_2, wherein R_1 represents hydrogen, alkyl, heterocyclyl, aryl, or heteroaryl groups.

DETAILED DESCRIPTION OF THE INVENTION

The detailed description of the invention which follows is not intended to be exhaustive or to limit the invention to the precise details or examples disclosed. Details and examples have been chosen to explain the invention to others skilled in the art.

The processes of this invention described herein and in the claims, may be performed in several ways. Preferred methodologies are described as follows.

Under acidic conditions, reaction of a haloacetaldehyde diethyl acetal with a polymer-bound 1,2-ethylenediol affords the polymer-bound haloacetaldehyde acetal (IV). The acids that make acidic conditions in this reaction include but not limited to *p*-toluenesulfonic acid, camphor sulfonic acid, hydrochloric acid and Lewis acids. The preferred acid is camphor sulfonic acid.

The polymer-bound 1,2-ethylenediol is purchased from commercial sources (e.g. polymer-bound glycerol) or may be prepared from a polymer through derivatization. For instance, a polymer-bound glycerol can be prepared from a polymer and a glycerol derivative (Lenzoff, C.C. et al., *Can. J. Chem.* 51, 3756(1973)).

Reaction of a polymer-bound haloacetaldehyde acetal (IV) with a primary amine of the formula R_1NH_2 in a solvent forms a polymer-bound aminoacetaldehyde acetal (V). There is no restriction on the solvent used for this reaction step, except that the amine R_1NH_2 be at least somewhat soluble therein. For example, most organic solvents such as DMSO, DMF or toluene can be utilized successfully for the reaction. However, DMSO is the preferred solvent. Preferably, the reaction is conducted at the elevated temperature, for example, at 80°C.

Reaction of a polymer-bound aminoacetaldehyde acetal (V) with isocyanates of the formula R_2NCO gives a urea acetaldehyde acetal intermediate (VI) under a variety of conditions. The reaction goes smoothly in solvents such as THF, CH_2Cl_2 or toluene. The reaction can be conducted in the presence or absence of bases. In order to ensure the completion of the reaction with relatively unreactive isocyanates or sterically hindered substituents on the polymer-bound aminoacetaldehyde acetal, the reaction was preferably conducted at 60°C in toluene in the presence of DMAP or DIPEA.

Treatment of a urea acetaldehyde acetal intermediate (VI) with an acid gives the desired 2-imidazolone (I) in good yields and purity. The preferred acid is trifluoroacetic acid (TFA). Purification of the final product can be done with conventional purification procedure.

These steps provide a traceless solid-phase synthesis of 2-imidazolones. The process described in the invention could be useful for making a large number of compounds for, but not limited to, high-throughput screening. One of the potential advantages of this reaction is that it yields a reusable polymer along with the product.

This invention also provides a polymer-bound haloacetaldehyde acetal compound of formula (IV), wherein x is chloro, bromo or iodo, which may be prepared by the process described throughout this specification. This polymer-bound haloacetaldehyde is a useful intermediate in preparing compounds with aldehyde functionalities or the like.

The process for making a polymer-bound haloacetaldehyde acetal compound of formula (IV) by reacting a haloacetaldehyde diethyl acetal (III) with a

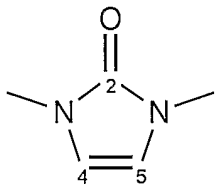
polymer-bound 1,2-ethylenediol under acidic conditions is performed according to descriptions throughout this specification.

This invention also provides a polymer-bound aminoacetaldehyde acetal compound of formula (V), wherein R_1 represents hydrogen, alkyl, heterocyclyl, aryl, or heteroaryl groups, which is a useful intermediate in preparing compounds with aldehyde and/or amino functionalities.

The process for preparing the polymer-bound aminoacetaldehyde acetal compound of formula (V) by reacting a polymer-bound haloacetaldehyde acetal (IV) with a primary amine of the formula R_1NH_2, wherein R_1 represents hydrogen, alkyl, heterocyclyl, aryl, or heteroaryl groups, is conducted according to descriptions throughout this specification.

DEFINITIONS

Generally and for illustration purposes, the parent 2-imidazolone ring structure is IUPAC numbered as follows:



As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Acid", as used herein, means an acid that facilitates acetal hydrolysis. It includes organic acids such as trifluoroacetic acid, *p*-toluenesulfonic acid, acetic acid, formic acid or inorganic acids such as hydrohalic acids. The preferred acid in the invention for the cleavage (hydrolysis) of acetal functionality from the solid support is trifluoroacetic acid or hydrochloric acid.

"Acid labile linkage", as used herein, means the link between an organic molecule and a solid support (or polymer, resin) can be removed or cleaved by treatment with an acid while remaining stable to other reagents. Examples of acid labile linkage include ether or ester bond on Wang resin (Wang, S.-S. *J. Am. Chem. Soc.* 95, 1328 (1973)), amide bond on Rink resin (Rink, H., *Tetrahedron Lett.* 28, 3787 (1987)), or acetal on the polymer as described in the invention. Preferred

acids to cleave the product from these polymers (resins) are trifluoroacetic acid (TFA) or HF.

"Alkyl", as used herein, means a cyclic, branched, or straight chain chemical group containing only carbon and hydrogen, such as methyl, pentyl, and adamantyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents, e.g., halogen, alkoxy, acyloxy, amino, cyano, nitro, hydroxyl, mercapto, carboxy, benzyloxy, aryl, heteroaryl, or other functionality that may be suitably blocked, if necessary for purposes of the invention, with a protecting group. Alkyl groups can be saturated or unsaturated (e.g., containing -C=C- or -C≡C- subunits), at one or several positions. Typically, alkyl groups will comprise 1 to 12 carbon atoms, preferably 1 to 10, and more preferably 1 to 8 carbon atoms.

"Aryl", as used herein, means a monovalent unsaturated aromatic carbocyclic group having a single-ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl), which can be optionally unsubstituted or substituted with amino, cyano, hydroxyl, lower alkyl, haloalkyl, alkoxy, nitro, halo, mercapto, and other substituents.

"Halo", as used herein, means chloro, bromo or iodo atoms in the invention. The fluorine atom is excluded in the invention.

"Heteroaryl", as used herein, means a monovalent unsaturated aromatic carbocyclic group having a single ring (e.g., pyrridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl) and having at least one hetero atom, such as N, O, or S, within the ring, which can optionally be unsubstituted or substituted with amino, cyano, nitro, hydroxyl, alkyl, haloalkyl, alkoxy, aryl, halo, mercapto, and other substituents.

"Heterocyclyl", as used herein, means radical heterocycles which are saturated, or unsaturated and non-aromatic. These may be substituted or unsubstituted, and are attached to the core structure via any available valence, preferably any available carbon. More preferred heterocycles are of 5 or 6 members. In six membered non-aromatic monocyclic heterocycles, the heteroatom(s) are from one to three Ns, and wherein when the heterocycle is five membered and non-aromatic, preferably it has one or two heteroatoms selected from O, N, or S.

"Polymer-bound 1,2-ethylenediol", as used herein, means that 1,2-dihydroxyl ethane unit is linked through an ethylene carbon to a polymer via any stable linkage. For example, polymer-bound glycerol that linked glycerol to the polymer through a stable ether bond is regarded as a polymer-bound 1,2-ethylenediol.

"Protecting group", as used herein, means a chemical group that exhibits the following characteristics: (I) reacts selectively with the desired functionality in good yield to give a protected substrate that is stable to the projected reactions for which protection is desired; 2) is selectively removable from the protected substrate to yield the desired functionality; and 3) is removable in good yield by reagents compatible with the other functional group(s) generated in such protected reactions. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Synthesis,* 2nd Ed. John Wiley & Sons, (1991).

"Solid-phase synthesis", as used herein, means a heterogeneous reaction in which one of reactants is covalently connected to a solid support (polymer or resin, etc.). Other reactants are dissolved in an organic solvent or solvents and the product is obtained through a cleavage step from the solid support.

"Solid support", as used herein, means a substrate which is inert to the reagents and reaction conditions described herein, as well as being substantially insoluble in the media used. Representative solid supports include inorganic substrates such as kieselguhr, silica gel, and controlled pore glass; organic polymers including polystyrene, polypropylene, polyethylene glycol, polyacrylamide, cellulose, and the like; and composite inorganic/polymeric compositions such as polyacrylamide supported within a matrix of kieselguhr particles. *See* J.M. Stewart and J.D. Young, *Solid Phase Peptide Synthesis,* 2nd. Ed., Pierce Chemical Co. (Chicago, IL, 1984). A polymer is preferably used in this invention. In addition, "solid support" includes polymeric supports such as the polyethylene glycol supports described by Janda et al., *Proc. Natl. Acad. Sci. USA,* 92, 6419-6423 (1995) and S. Brenner, WO 95/16918, which are soluble in many solvents but can be precipitated by the addition of a precipitating solvent. The solid support is designated as  in this specification.

"Solvent", as herein used, means a liquid that can dissolve another compound and has no adverse effect on the reaction or on the reagents involved.

Examples of suitable solvents include alcohols (methanol, 1-butanol, phenol, trifluoroethanol, hexafluoro-2-propanol, etc.), hydrocarbons (benzene, toluene, etc.), amides (dimethyl acetamide, dimethylformamide, etc.), halides (dichloromethane, dichloroethane, etc.), and ethers (tetrahydrofuran, dioxane, etc.). Other solvents include water, 1-methyl-2-pyrrolidine, diethyl phosphite, tetramethaylsulphone, dimethyl sulphoxide, acetonitrile and pyridine.

"Traceless solid-phase synthesis", as used herein, means that a solid-phase synthesis that leaves no trace of the linker used for tethering the starting building blocks to the solid support.

"Under acidic conditions", as used herein, means the acetal formation reaction is conducted in the presence of an acid which itself is not part of the reactant. The acid can be either inorganic acids such as hydrochloric acid, sulfuric acid or Lewis acids or organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, camphor sulfonic acid. Preferred acids are camphor sulfonic acid or any Lewis acids.

The following abbreviations have the indicated meanings:

Bn = benzyl

$CDCl_3$= deutered chloroform

CD_3OD= deutered methanol

CH_2Cl_2 = dichloromethane

CSA = camphor sulfonic acid

DIPEA = diisopropylethyl amine

DMAP= 4-(dimethylamino)-pyridine

DMF= N,N-dimethylformamide

DMSO = dimethylsulfoxide

ESIMS = electron spray mass spectrometry

EtOAc = ethyl acetate

HCl = hydrochloric acid

HF = hydrofluoric acid

MeOH = methanol

$MgSO_4$ = magnesium sulfate

PDE = phosphordiesterase

Ph = phenyl

TFA = trifluoroacetic acid

THF= tetrahydrofuran

TLC = thin layer chromatography

The following alkyl group abbreviations are used.

Me = methyl

Et = ethyl

n-Bu = normal butyl

EXAMPLES

To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

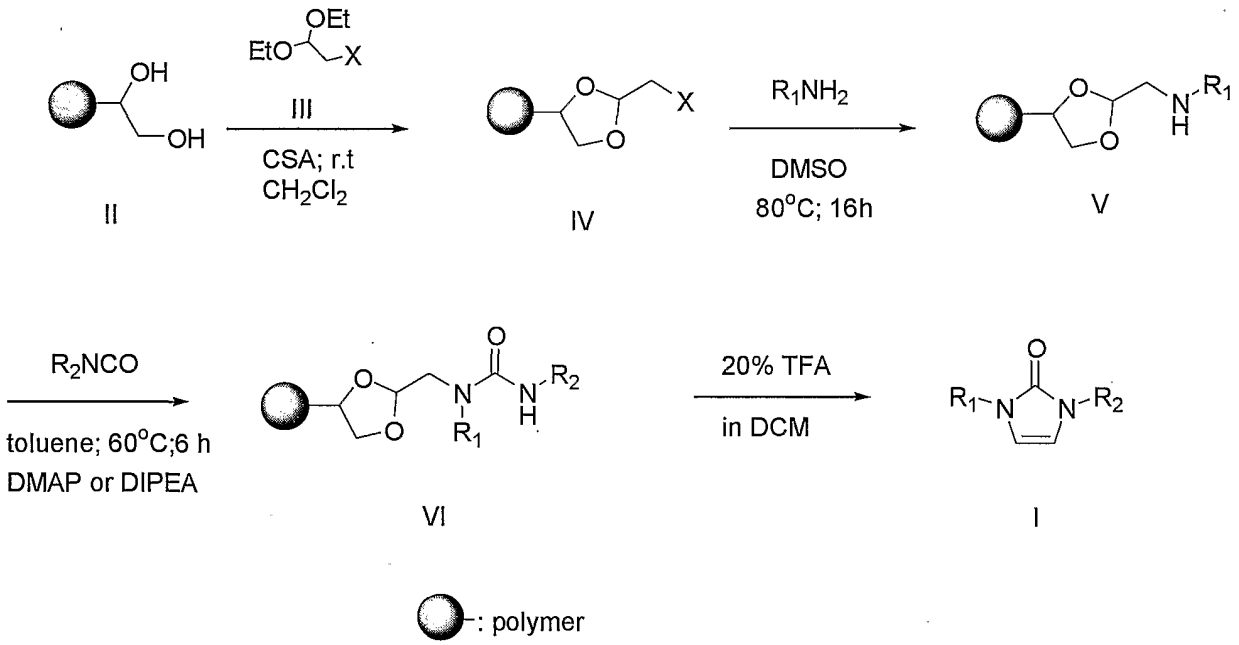
Trademarks used herein are examples only and reflect illustrative materials used at the time of the invention. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the invention.

^1H nuclear magnetic resonance spectra (NMR) is measured in $CDCl_3$ or other solvents as indicated by a Varian NMR spectrometer (Unity Plus 400, 400 MHz for ^1H) unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows, s, singlet; d, doublet; t, triplet; m, multiplet.

Example 1

The 2-imidazolone compounds of the invention are prepared according to the following scheme (Example Scheme 1).

Example Scheme 1



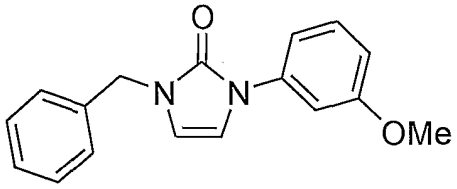
The polymer that used in the reaction is a commercially available polymer-bound glycerol (II). Acetal exchange of a haloacetaldehyde diethyl acetal such as bromoacetaldehyde diethyl acetal with the polymer-bound glycerol affords the polymer-bound haloacetaldehyde acetal (IV) in the presence of camphor sulfonic acid in CH_2Cl_2 at room temperature. The formation of the halide on the solid support is confirmed by infrared spectrometric analysis and weight change of the resin.

Amination of the intermediate bromoacetaldehyde acetal (IV) with a primary amine of the formula R_1NH_2 in DMSO afforded the desired aminoacetaldehyde acetal (V) on the solid support. The reaction is conducted at 80°C.

Reaction of the polymer-bound aminoacetaldehyde acetal (V) with isocyanates of the formula R_2NCO gave the corresponding urea acetaldehyde acetal (VI) in the presence of DIPEA or DMAP in toluene at 60°C. Finally, treatment of the urea acetaldehyde acetal (VI) with trifluoroacetic acid (TFA) released the corresponding urea acetaldehyde, which spontaneously cyclized to give the desired 2-imidazolone (I) in good yield and purity.

Example 2

Preparation of N-benzyl-N'-(m-methoxyphenyl)-imidazol-2-one (VII)



VII

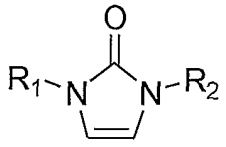
CSA (1eq.) was added followed by 2-bromoacetaldehyde diethyl acetal (10 eq) to the suspension of polymer-bound glycerol (250 mg, 1.38 mmol/g, Aldrich) in CH_2Cl_2 (3 mL) in a 10 mL tube with frit and screw cap. The suspension was shaken in a shaker at room temperature for 12 h. The solvent was drained, and the polymer was washed with DMF (3 x 6 mL), MeOH (3 x 6 mL) and CH_2Cl_2 (3 x 6 mL) and dried under vacuum at room temperature.

To the suspension of the dried polymer-bound bromoacetaldehyde in DMSO (3 mL) was added benzylamine (6 mmol) at room temperature. The reaction suspension was then heated in an oven shaker at 80°C for 16 h. The solvent was drained and the polymer was washed and dried as described above to give the resin-bound aminoacetaldehyde acetal.

To the polymer-bound aminoacetaldehyde acetal suspended in toluene (3 mL) was added *m*-methoxyphenylisocyanate (10 eq) and DMAP (1 eq). The suspension was heated to 60°C in the oven shaker for 6 h. After washing and drying, the polymer was cleaved with 20% TFA in CH_2Cl_2 followed by 50% TFA in H_2O to afford the crude product. Further purification by preparative TLC (30% ethyl acetate in hexanes) gave the *N*-benzyl-*N'*-(m-methoxylphenyl)-2-imidazolone in 61% yield. ^1H NMR δ7.5 (d, 1H), 7.3 (m, 6H), 7.0 (m, 2H), 6.4 (d, 1H), 6.2 (d, 2H), 4.8 (s, 2H), 3.8 (s, 3H). ESIMS: *m/z* 281 (M+H), $C_{17}H_{16}N_2O_2$.

Example 3

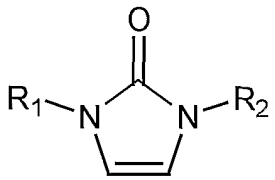
The following compounds were prepared according to method described in the above examples.



Compound	R_1	R_2
VIII	$PhCH_2CH_2$	Ph
IX	$PhCH_2CH_2$	m-CF_3Ph
X	$PhCH_2CH_2$	m-MeOPh
XI	$PhCH_2CH_2$	Et
XII	n-Bu	Ph
XIII	n-Bu	m-CF_3Ph
XIV	n-Bu	m-MeOPh
XV	Bn	Ph
XVI	Bn	Et

We claim:

1. A process for preparing a 2-imidazolone compound of the formula



comprising the steps of

1) Reacting a haloacetaldehyde diethyl acetal with a polymer-bound 1,2-ethylenediol under acidic conditions to form a polymer-bound haloacetaldehyde acetal,

2) Reacting said polymer-bound haloacetaldehyde acetal with a primary amine of the formula R_1NH_2 to form a polymer-bound aminoacetaldehyde acetal,

3) Reacting said polymer-bound aminoacetaldehyde acetal with an isocyanate of the formula R_2NCO to form a polymer-bound urea acetaldehyde acetal, and,

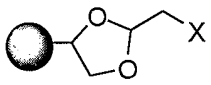
4) Reacting said polymer-bound urea acetaldehyde acetal with an acid to provide the 2-imidazolone,

wherein

R_1 and R_2 independently represent hydrogen, alkyl, heterocyclyl, aryl, or heteroaryl groups.

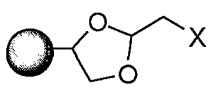
2. The process of claim 1, wherein said acid in step 4) is trifluoroacetic acid or hydrochloric acid.

3. A polymer-bound haloacetaldehyde acetal compound of formula



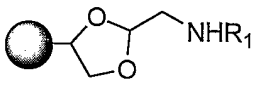
wherein x is chloro, bromo or iodo.

4. A process for preparing a polymer-bound haloacetaldehyde acetal compound of the formula



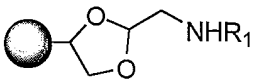
by reacting the haloacetaldehyde diethyl acetal with a polymer-bound 1,2-ethylenediol under acidic conditions, wherein x is chloro, bromo or iodo.

5. A polymer-bound aminoacetaldehyde acetal compound of the formula



wherein R_1 represents hydrogen, alkyl, heterocyclyl, aryl, or heteroaryl groups.

6. A process for preparing a polymer-bound aminoacetaldehyde acetal compound of the formula



by reacting a polymer-bound haloacetaldehyde acetal with a primary amine of the formula R_1NH_2, wherein R_1 represents hydrogen, alkyl, heterocyclyl, aryl, or heteroaryl groups.