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(54) Title: PROCESS FOR PREPARING ELECTRON DEFICIENT OLEFINS

(57) Abstract: This invention relates to a process for preparing electron deficient olefins, such as 2-cyanoacrylates, using an acid catalyzed two-step process including an esterification reaction followed by a Knoevenagel condensation reaction.

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PROCESS FOR PREPARING ELECTRON DEFICIENT OLEFINS**BACKGROUND****Field**

[0001] This invention relates to a process for preparing electron deficient olefins, such as 2-cyanoacrylates, using an acid catalyzed two-step process including an esterification reaction followed by a Knoevenagel condensation reaction.

Brief Description of Related Technology

[0002] Cyanoacrylate adhesives are known for their fast adhesion and ability to bond a wide variety of substrates. They are marketed as "super glue" type adhesives. They are useful as an all-purpose adhesive since they are a single component adhesive, very economical as only a small amount will do, and generally do not require any equipment to effectuate curing.

[0003] Traditionally, cyanoacrylate monomers have been produced by way of a Knoevenagel condensation reaction between a formaldehyde precursor, such as paraformaldehyde, and an alkyl cyanoacetate under base catalysed conditions. During the reaction, cyanoacrylate monomer forms and, due to the basic reaction conditions, polymerises *in situ* to a prepolymer. The prepolymer is subsequently thermally cracked or depolymerised, yielding cyanoacrylate monomer. This approach has remained essentially the same over time, though improvements and variants have been introduced. See e.g. U.S. Patent Nos. 6,245,933, 5,624,699, 4,364,876, 2,721,858, 2,763,677 and 2,756,251.

[0004] U.S. Patent No. 5,455,369 defines an improvement in a process for preparing methyl cyanoacrylate, in which methyl cyanoacetate is reacted with formaldehyde to form a polymer that is then depolymerized to the monomeric product, and in which the purity of yield is 96% or better. The improvement of the '369 patent is reported to be conducting the process in a poly(ethylene glycol) diacetate, dipropionate, or dibutyrate, having a number average molecular weight of 200-400, as the solvent.

[0005] U.S. Patent No. 6,096,848 defines a process for the production of a biscyanoacrylate, which comprises the steps of esterifying a 2-cyanoacrylic acid or transesterifying an alkyl ester thereof to obtain a reaction mixture; and fractionally crystallizing the reaction mixture to obtain the biscyanoacrylate.

[0006] Vijayalakshmi et al., J. Ad. Sci. Technol., 4, 9, 733 (1990) describes some approaches to the synthesis of cyanoacetates and corresponding cyanoacrylates, including preparation from chloroacetic acid and its esters by subsequent reaction with sodium cyanide.

[0007] Guseva et al., Russian Chem. Bull., 42, 3, 478 (1993) describes functionalized cyanoacetates, many of which were used in the subsequent synthesis of corresponding cyanoacrylates. [See also Guseva et al., Russian Chem. Bull., 43, 4, 595 (1994), and Golobolov and Gruber, Russian Chem. Rev., 66, 11, 953 (1997).]

[0008] One of the functionalized cyanoacetates noted in the preceding paragraph is glycidyl cyanoacetate. While the synthesis and characterisation of glycidyl cyanoacetate has been reported, the synthesis, characterisation and provision of performance characteristics of the corresponding glycidyl cyanoacrylate monomer have not to

date been published. One explanation for this is that glycidyl cyanoacetate would not survive the conditions of a Knoevenagel reaction to make a cyanoacrylate monomer (initial base catalysis then subsequent exposure to high temperature in presence of strong acids) since epoxides are ring opened under such conditions. And while alternative routes to the glycidyl cyanoacrylate monomer may be conceivable, they would not employ glycidyl cyanoacetate at the outset.

[0009] Certain novel compounds having activated methylene groups, including cyanoacetate hybrid molecules, are described and claimed in U.S. Patent No. 8,481,755.

[0010] Other cyanoacetates have been described, such as those with siliconised functionalities. See e.g. Senchenya et al., Russian Chem. Bull., 42, 5, 909 (1993) and European Patent Document No. EP 0 459 617.

[0011] The preparation of mono-, di-, tri- and tetra-functional cyanoacetates, albeit as curatives for epoxy resins for adhesive applications, has been described. Renner et al., "Cure of Epoxy Resins with Esters of Cyanoacrylic Acid", J. Polym. Sci., Polym. Chem. Ed., 23, 2341 (1985) and U.S. Patent Nos. 4,202,920 and 4,512,357.

[0012] And of course methods for the manufacture of cyanoacrylates are legion.

[0013] In U.S. Patent No. 3,142,698, the synthesis of difunctional cyanoacrylates using a Knoevenagel condensation reaction is described. However, the ability to thermally depolymerise the resulting, now crosslinked, prepolymer in a reliable and reproducible manner to produce pure difunctional monomers in high yields is questionable [see J. Buck, J. Polym. Sci., Polym. Chem. Ed., 16, 2475-2507 (1978), and U.S. Patent Nos. 3,975,422, 3,903,055,

4,003,942, 4,012,402, and 4,013,703]. A variety of other processes for producing cyanoacrylate monomers are known, and some of which are described below.

[0014] U.S. Patent No. 5,703,267 defines a process for producing a 2-cyanoacrylic acid which comprises subjecting a 2-cyanoacrylate and an organic acid to a transesterification reaction.

[0015] U.S. Patent No. 3,654,340 (Banitt) describes and claims an added step in the condensation of formaldehyde and esters of 2-cyanoacetic acid to produce 2-cyanoacrylate esters which consists essentially of catalyzing the reaction by means of a mixture of an acid and the salt of a primary or secondary amine with the same or stronger acid. The acid/amine combination is reported to reduce the extent of polymerization; however, polymerization still occurs and a thermal cracking step is required. The catalytic mixture should have a pH value of 5 or less when exact amounts of its components are dissolved in 25 ml. of water. The '340 patent describes the process to be effective with fluorinated 2-cyanoacrylate esters.

[0016] U.S. Patent No. 3,728,375 is directed to and claims monomeric α -cyanoacrylate esters having esters of an alkyl group of 1-16 carbon atoms, a cyclohexyl group, a phenyl group, an alkoxyalkyl group of 2-16 carbon atoms, a haloalkyl group of 1-10 carbon atoms, an alkenyl group of 2-16 carbon atoms, an arylalkyl group of 7-16 carbon atoms, or an acetoethyl group, and methods of forming the monomeric α -cyanoacrylate esters. Compositions made with these monomeric α -cyanoacrylate esters are prepared containing less than 200 ppm of water.

[0017] Recently, a series of U.S. patents have been granted that describe and claim the use of ionic liquids

and/or iminium salts in an alternative synthesis of electron deficient olefins. See e.g. U.S. Patent Nos. 7,659,423; 7,718,821; 7,569,719; 8,022,251; 8,053,589; and 8,686,105.

[0018] In addition, International Patent Publication No. WO2015/150882 A1 describes a process for preparing 1,1-disubstituted ethylene monomers using a catalytic amount of an ammonium or iminium salt in homogeneous phase or supported on a solid substrate. The process is reported to be a direct synthesis of such monomers, which does not require a cracking or thermal depolymerization step.

[0019] Nonetheless, commercial production of cyanoacrylate monomers ordinarily relies on the depolymerisation of a prepolymer formed under base-catalyzed Knoevenagel condensation reaction conditions, as noted above. Still today the Knoevenagel condensation reaction is believed to remain the most efficient and prevalent commercial method for producing high yields of monofunctional cyanoacrylates.

[0020] It would be desirable to not have to resort to thermally induced depolymerisation of a prepolymer produced by the Knoevenagel condensation reaction. This prospect may also enable facile access to highly useful difunctional monomers, such as so-called biscyanoacrylates or hybrid materials of cyanoacrylate and other polymerizable or reactive functionality.

[0021] The types of ester side chains that can be introduced to the cyanoacrylic acid ester both in terms of functionality and size is ordinarily limited when a basic catalyst is used in the synthetic steps, largely due to the thermal cracking step that follows in an attempt to liberate a cyanoacrylate monomer. Therefore a synthetic

route which avoids the use of a basic catalyst and thermal cracking step is desirable and from a process perspective would be more cost-effective.

[0022] U.S. Patent No. 4,587,059 defines a process for the preparation of monomeric 2-cyanoacrylates comprising the steps of (a) reacting (i) a 2,4-dicyanoglutarate with (ii) formaldehyde, cyclic or linear polymers of formaldehyde, or a mixture thereof, in the presence of between about 0.5 and about 5 mols of water per mol of 2,4-dicyanoglutarate, at an acid pH of about 3 to slightly less than 7, and at a temperature of about 70 to about 140, to form an oligomeric intermediate product, and (b) removing water that is present from step (a) and thermolyzing the oligomeric intermediate product for a period of time sufficient to effect its conversion to monomeric 2-cyanoacrylates.

[0023] Nonetheless, commercial production of cyanoacrylate monomers ordinarily relies on the depolymerisation of a prepolymer formed under base-catalyzed Knoevenagel condensation reaction conditions, as noted above. Still today the Knoevenagel condensation reaction is believed to remain the most efficient and prevalent commercial method for producing high yields of monofunctional cyanoacrylates.

[0024] It would be desirable to not have to resort to thermally induced depolymerisation of a prepolymer produced by the Knoevenagel condensation reaction, for many of the reasons stated above. This prospect may also enable facile access to highly useful difunctional monomers, such as so-called biscyanoacrylates or hybrid materials of cyanoacrylate and other polymerizable or reactive functionality. The technical literature is replete with

references to acid-catalyzed Knoevenagel condensation reactions, some of which even using lanthanide series elements, such as ytterbium. For instance, reference may be made to J. Molec. Cat. A: Chemical, 240, 99-102 (2005); J. Org. Chem., 80, 3101-10 (2015); and J. Kor. Chem. Soc., Vol. 55, No. 6, 1000-1006 (2011).

[0025] Absent from the published literature is a one-pot method to produce electron deficient olefins *in situ* from a two-step process using an acid catalyst in an esterification reaction to produce an electron deficient olefin precursor, which together with aldehyde using an acid catalyst reacts in a Knoevenagel condensation to produce an electron deficient olefin. Until now.

SUMMARY

[0026] By employing an acid catalyst in the esterification reaction and one in the Knoevenagel condensation reaction that follows, electron deficient olefins may be realized in a one-pot, two-step synthetic process. And not having to employ a thermal depolymerization step to yield the electron deficient olefin opens the possibility of facile access to highly useful difunctional monomers, such as so-called biscyanoacrylates or hybrid materials of cyanoacrylate and other polymerizable or reactive functionality.

[0027] The process for the preparation of a reactive electron deficient olefin is provided herein, where in one, more focused, aspect, the invention includes the steps of:

(a) reacting a cyanoacetic acid and an alcohol in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate

conditions and for a time sufficient to yield a cyanoacetate;

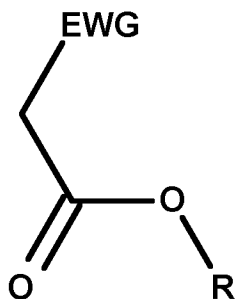
(b) optionally, separating the so formed cyanoacetate substantially free from the cyanoacetic acid, the alcohol, and/or the catalyst, and any by-products;

(c) reacting the so formed cyanoacetate and an aldehyde (or source of an aldehyde), in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield a cyanoacrylate; and

(d) optionally, separating the so formed cyanoacrylate substantially free from the cyanoacetate, the aldehyde, and/or the catalyst, and any by-products.

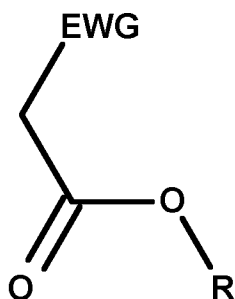
[0028] In another, more broad, aspect, the invention provides a process for the preparation of a reactive electron deficient olefin precursor that includes the steps of:

(a) reacting a 2-electron withdrawing group-substituted carboxylic acid embraced by:



where EWG represents an electron withdrawing group, such as cyano or nitrile, alkoxy or aryloxy (which may itself be substituted by an EWG in the ortho and/or para position on the aromatic ring), carboxyl (e.g., carboxylic acids or carboxylic esters), sulphonic acids, carbonyls, halogens (e.g., F, Cl, Br, and I), nitro, isocyanate, sulfoxide and

phosphine oxide; and R here represents hydrogen; and an alcohol, in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield an electron deficient olefin precursor embraced by:



where EWG represents an electron withdrawing group, such as cyano or nitrile, alkoxy or aryloxy (which may itself be substituted by an EWG in the ortho and/or para position on the aromatic ring), carboxyl (e.g., carboxylic acids or carboxylic esters), sulphonic acids, carbonyls, halogens (e.g., F, Cl, Br, and I), nitro, isocyanate, sulfoxide and phosphine oxide; and R here represents straight chain, branched, cyclic or fused C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, and C₆₋₂₀ aryl or C₇₋₂₀ alkaryl, with or without substitution or interruption by one or more heteroatoms;

(b) optionally, separating the so formed electron deficient olefin precursor substantially free from the 2-electron withdrawing group-substituted carboxylic acid, the alcohol and/or the catalyst, and any by-products;

(c) reacting the electron deficient olefin precursor and an aldehyde (or a source of aldehyde) in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield an electron deficient olefin; and

(d) optionally, separating the so formed electron deficient olefin substantially free from the electron deficient olefin precursor, the aldehyde (or source of aldehyde) and/or the catalyst, and any by-products.

BRIEF DESCRIPTION OF THE FIGURE

[0029] FIG. 1 depicts a synthetic scheme according to the present invention. More specifically, FIG. 1 shows the esterification reaction of a cyanoacetic acid with an alcohol at ambient temperature in the presence of ytterbium trifluoromethane sulfonate [Yb(OTf)₃], followed by the condensation reaction with formaldehyde in the presence of ytterbium trifluoromethane sulfonate [Yb(OTf)₃] to generate the target 2-cyanoacrylate.

DETAILED DESCRIPTION

[0030] As noted above, the present invention provides a process for the preparation of a reactive electron deficient olefin precursor. In one, more focused, aspect, the invention includes the steps of:

(a) reacting a cyanoacetic acid and an alcohol, in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield a cyanoacetate;

(b) optionally, separating the so formed cyanoacetate substantially free from the cyanoacetic acid, the alcohol, and/or the catalyst, and any by-products;

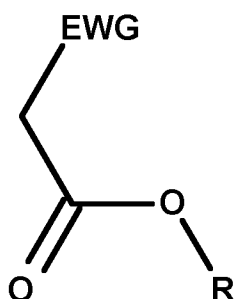
(c) reacting the so formed cyanoacetate and an aldehyde (or source of an aldehyde), in the presence of a catalyst comprising a lanthanide element or a transition

element, under appropriate conditions and for a time sufficient to yield a cyanoacrylate; and

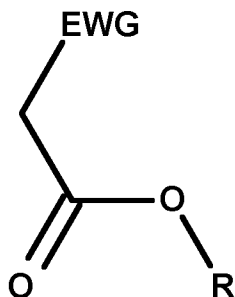
(d) optionally, separating the so formed cyanoacrylate substantially free from the cyanoacetate, the aldehyde, and/or the catalyst, and any by-products.

[0031] In another, more broad, aspect, the invention provides a process for the preparation of a reactive electron deficient olefin precursor that includes the steps of:

(a) reacting a 2-electron withdrawing group-substituted carboxylic acid embraced by:



where EWG represents an electron withdrawing group, such as cyano or nitrile, alkoxy or aryloxy (which may itself be substituted by an EWG in the ortho and/or para position on the aromatic ring), carboxyl (e.g., carboxylic acids or carboxylic esters), sulphonic acids, carbonyls, halogens (e.g., F, Cl, Br, and I), nitro, isocyanate, sulfoxide and phosphine oxide; and R here represents hydrogen; and an alcohol, in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield an electron deficient olefin precursor embraced by:



where EWG represents an electron withdrawing group, such as cyano or nitrile, alkoxy or aryloxy (which may itself be substituted by an EWG in the ortho and/or para position on the aromatic ring), carboxyl (e.g., carboxylic acids or carboxylic esters), sulphonic acids, carbonyls, halogens (e.g., F, Cl, Br, and I), nitro, isocyanate, sulfoxide and phosphine oxide; and R here represents straight chain, branched, cyclic or fused C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, and C₆₋₂₀ aryl or C₇₋₂₀ alkaryl, with or without substitution or interruption by one or more heteroatoms;

(b) optionally, separating the so formed electron deficient olefin precursor substantially free from the 2-electron withdrawing group-substituted carboxylic acid, the alcohol and/or the catalyst, and any by-products;

(c) reacting the electron deficient olefin precursor and an aldehyde (or a source of aldehyde), in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield an electron deficient olefin; and

(d) optionally, separating the so formed electron deficient olefin substantially free from the electron deficient olefin precursor, the aldehyde (or source of aldehyde) and/or the catalyst, and any by-products.

[0032] Reference to FIG. 1 may be useful to appreciate further the present invention, which is described in more detail below and in the Examples section that follows.

[0033] As an initial reactant in the inventive processes is the so-described 2-electron withdrawing group-substituted carboxylic acid. Representative examples of the 2-electron withdrawing group-substituted carboxylic acid used as a reactant include malonic acid, glycolic acid, alkyl (e.g., ethyl) nitroacetic acid, alkyl (e.g., ethyl) haloacetic (like bromoacetic, chloroacetic, and iodoacetic), and cyanoacetic acid, some of which are commercially available for instance from Aldrich Chemical Co. A particularly desirable example of 2-electron withdrawing group-substituted carboxylic acid is cyanoacetic acid.

[0034] The amount of 2-electron withdrawing group-substituted carboxylic acid that should be used in the inventive process is in the range of about 0.5 to about 2 equivalents, such as about 0.8 equivalents.

[0035] Together with the 2-electron withdrawing group-substituted carboxylic acid as an initial reactant in the inventive processes is an alcohol.

[0036] The alcohol may be any mono-, di- or multi-functional hydroxyl compound. Mono-, di- or multi-functional C₁₋₂₀ alkanols, C₂₋₂₀ alkenols, and C₂₋₂₀ alkynols, whether straight chain, branched, cyclic or fused, may be used. Aromatic alcohols, such as phenol, benzyl alcohol and derivatives thereof, may be used.

[0037] The alcohol should be used in an amount of about 0.5 to about 2 equivalents, such as about 0.8 equivalents.

[0038] The alcohol and the compound should be used in a molar ratio of about 0.5 to about 2 equivalents, such as about 0.8 equivalents.

[0039] As noted, the catalyst is one that comprises lanthanide element or a transition element. The catalyst is acidic in nature, as measured or determined by its ability to donate a hydrogen (proton or hydrogen ion, H⁺), or, alternatively, its ability to form a covalent bond with an electron pair.

[0040] To the lanthanide element or the transition element is bonded, coordinated or complexed, as appropriate, one or more ligands. The ligands may be selected for instance from conventional leaving groups used in organic synthetic schemes. Halogens, tosylates, mesylates, nitrates, and triflates are chief among ligands that are suitable for use herein.

[0041] A prime example of a lanthanide element suitable for use in this connection is ytterbium, though others may also be useful, such as lanthanum, cerium, samarium, europium, and dysprosium. Prime examples of a transition element suitable for use in this connection is niobium, zirconium or scandium, with niobium being particularly desirable in this regard.

[0042] Desirable catalysts for use in the inventive process include ytterbium trifluoromethane sulfonate [Yb(OTf)₃] and niobium halides, such as niobium chloride.

[0043] The catalyst should be used in an amount of up to about 20 mol%, such as about 10 mol%.

[0044] The electron deficient olefin precursor so formed by the inventive processes may be a variety of olefins having an electron withdrawing group attached to a carbon atom that is alpha to the carbonyl of a carboxylic acid.

[0045] This electron deficient olefin precursor contains a methylene linkage having at least one electron withdrawing substituent attached thereto, where the electron withdrawing substituent is selected from cyano or nitrile, alkoxy or aryloxy, carboxyl (such as carboxylic acids and carboxylic esters), sulphonic acids, carbonyls, halogens (e.g., F, Cl, Br, and I), nitro, isocyanate, sulfoxide and phosphine oxide.

[0046] Representative examples of these electron deficient olefin precursors include malonic acid esters, ethyl nitroacetate, cyanoacetic acid esters (i.e., cyanoacetate), and glycolic acid esters, some of which are commercially available for instance from Aldrich Chemical Co. A particularly desirable example is cyanoacetate.

[0047] In a desirable embodiment, the reactive electron deficient olefin precursor so formed will be a 2-cyanoacetate.

[0048] Representative examples of 2-cyanoacetates so formed by the inventive processes include those having ester groups of methyl, ethyl, propyl, isoamyl, propargyl, butyl, pentyl, hexyl, octyl, nonyl, oxononyl, decyl, dodecyl, allyl, ethynyl, butenyl, cyclohexyl, phenyl, phenethyl, tetrahydrofurfuryl, chloroethyl, 2,2,2-trifluoroethyl, hexafluoroisopropyl, methoxymethyl, thiomethoxymethyl, methoxyethyl, thiomethoxyethyl, methoxybutyl, thiomethoxybutyl, ethoxyethyl, thioethoxyethyl, propoxyethyl, thiopropoxyethyl, butoxymethyl, thiobutoxymethyl, butoxyethyl, thiobutoxyethyl and dimethyl siloxane esters of 2-cyanoacrylic acid. This recitation is by no means however exhaustive.

[0049] While no solvent is ordinarily needed, the reaction of the inventive processes may proceed in solvent either forming a solution or a suspension. Solvents that may be used include acetonitrile, benzonitrile, chlorobenzene, nitromethane, tetrachloroethene, toluene, THF, 1,4-dioxane, and (poly)ethylene glycol dialkyl ethers or esters, and of course combinations thereof. Ionic liquids may also be used as the solvent. The reaction of the inventive processes may proceed with or without heating or cooling, depending of course on the specific reactants and the scale of the reaction.

[0050] While the reaction ordinarily occurs at ambient temperature, gentle heating up to a temperature of 70°C may be applied. The temperature may be reached through an external heating element or internally by means of the exotherm that may be generated depending on the identity of the reactants. The temperature of the reaction should be controlled however to accommodate any such exothermic processes.

[0051] The time of reaction may be monitored by reference to the formation of the desired electron deficient olefin precursor product. ¹H NMR spectrometer is a particularly useful tool in this regard. The time of reaction may be as little as 30 minutes, for instance, or longer or shorter for that matter depending again on the identity of the specific reactants, the scale of the reaction and whether heat is added to the reaction conditions.

[0052] The so-formed electron deficient olefin precursor is then used in the Knoevenagel condensation reaction of the second step. The other reactant in the second step is an aldehyde (or source of aldehyde). The aldehyde source

may be aldehyde compounds having the structure $R-CH=O$, where R is hydrogen or vinyl. The aldehyde compound may be an aldehyde itself or a source of an aldehyde, such as one that yields an aldehyde like formaldehyde under reaction conditions. The aldehyde compound in a desirable embodiment includes formaldehyde (or a source thereof, such as paraformaldehyde), formalin, 1,3,5-trioxane, methylene diacetate, dimethoxymethane, or vinyl aldehydes, such as acrolein.

[0053] The source of aldehyde should be used in an amount of 1.0-2.0 equivalents, such as 2.0 equivalents.

[0054] Once again, in the Knoevenagel condensation reaction of the second step, a catalyst is acidic in nature, as measured or determined by its ability to donate a hydrogen (proton or hydrogen ion H^+), or, alternatively, its ability to form a covalent bond with an electron pair. To the lanthanide element or the transition element is bonded, coordinated or complexed, as appropriate, one or more ligands. The ligands may be selected for instance from conventional leaving groups used in organic synthetic schemes. Halogens, tosylates, mesylates, nitrates and triflates are chief among ligands that are suitable for use herein.

[0055] A prime example of a lanthanide element suitable for use in this connection is ytterbium, though others may also be useful, such as scandium, lanthanum, and samarium. A prime example of a transition element suitable for use in this connection is niobium.

[0056] Desirable catalysts for use in the Knoevenagel condensation reaction of the second step of the inventive processes include ytterbium trifluoromethane sulfonate $[Yb(OTf)_3]$ and niobium chloride.

[0057] Here, the catalyst should be used in an amount of 0-20mol%, such as 0.5 to 10 mol%, desirably 1 to 5 mol%, based on the electron deficient olefin precursor.

[0058] The electron deficient olefin so formed by the inventive processes may be a variety of olefins having at least one electron withdrawing group attached thereto. In a desirable embodiment, the electron deficient olefin so formed will have two or more electron withdrawing groups attached thereto, which may be the same or different. In a desirable embodiment, the electron deficient olefin so formed will have two or more electron withdrawing groups attached thereto, which may be the same or different. For instance, the electron deficient olefin may be a compound having one end terminating with a cyanoacrylate, cyanopentadienoate, cyanohexadienoate, or alkylene derived from dimalonate and another end terminating with a group selected from branched and unbranched alkyl esters, esters containing aromatics and heterocyclic nuclei, (meth)acrylates, cyanoacrylates, siloxanes, blocked and unblocked isocyanates, anhydrides, silanes, vinyls, acetylenes, and epoxies.

[0059] Particularly desirable products have two electron withdrawing groups attached thereto which are different, such as 2-cyanoacrylate esters.

[0060] Representative examples of 2-cyanoacrylate esters so formed by the inventive processes include those having ester groups of methyl, ethyl, propyl, isoamyl, propargyl, butyl, pentyl, hexyl, octyl, nonyl, oxononyl, decyl, dodecyl, allyl, ethynyl, butenyl, cyclohexyl, phenyl, phenethyl, tetrahydrofurfuryl, chloroethyl, 2,2,2-trifluoroethyl, hexafluoroisopropyl, methoxymethyl, thiomethoxymethyl, methoxyethyl, thiomethoxyethyl,

methoxybutyl, thiomethoxybutyl, ethoxyethyl, thioethoxyethyl, propoxyethyl, thiopropoxyethyl, butoxymethyl, thiobutoxymethyl, butoxyethyl, thiobutoxyethyl and dimethyl siloxane esters of 2-cyanoacrylic acid. This recitation is by no means however exhaustive.

[0061] While no solvent is ordinarily needed, the esterification reaction of the first step of the inventive processes may proceed in solvent either forming a solution or a suspension. Solvents that may be used include acetonitrile, benzonitrile, chlorobenzene, nitromethane, tetrachloroethene, toluene, THF, 1,4-dioxane, and (poly)ethylene glycol dialkyl ethers or esters. Ionic liquids may also be used as the solvent. The Knoevenagel condensation reaction of the second step of the inventive processes ordinarily is performed with solvent, any of those noted above being a suitable choice. The reaction of the inventive processes may proceed with or without heating or cooling, depending of course on the specific reactants and the scale of the reaction.

[0062] While the esterification reaction of the first step ordinarily occurs at ambient temperature, gentle heating up to a temperature of 70°C may be applied. The temperature may be reached through an external heating element or internally by means of the exotherm that may be generated depending on the identity of the reactants. The temperature of the reaction should be controlled however to accommodate any such exothermic processes. Likewise, the temperature conditions of the Knoevenagel condensation reaction of the second step may be moderated in similar fashion.

[0063] The time of reaction of the esterification reaction of the first step may be monitored by reference to the formation of the desired electron deficient olefin precursor product. ^1H NMR spectrometer is a particularly useful tool in this regard. The time of reaction may be as little as 30 minutes, for instance, or longer or shorter for that matter depending again on the identity of the specific reactants, the scale of the reaction and whether heat is added to the reaction conditions. Likewise, the reaction time and monitoring of the progress of the Knoevenagel condensation reaction of the second step may be similar.

[0064] The following example is intended to illustrate but in no way limit the present invention.

EXAMPLES

Example 1

[0065] To a 50ml round bottomed flask was added 4.78g (0.056mol) of cyanoacetic acid, 5.00g (0.0675mol) of *n*-butanol and 3.47g (6.75mmol, 10mol%) of ytterbium triflate. The flask was fitted with a magnetic stirrer and rigorously stirred at room temperature for a period of time of about 39.5 hours. A crude ^1H NMR taken at this point indicated a conversion to butyl cyanoacetate of about 68.50%. The flask was then charged with 1.80g (0.060mol) of paraformaldehyde, 10mL of nitromethane and 5 mL of acetonitrile, fitted with a reflux condenser and the reaction temperature was raised to about 90°C. The reaction was stopped after a period of time of 6 hours, at which the relative conversion of cyanoacetate to cyanoacrylate as monitored by 500MHz ^1H NMR was determined to be 14.00%. The relative conversion after a period of time was observed to be about 8.70% and after a

period of time of about 4 hours was observed to be about 12.50%.

Example 2

[0066] To a 50ml round bottomed flask is added 5.716g (0.062mol) of cyanoacetic acid, 4.936g (0.056mol) of 2-pentanol and 3.47g (6.75mmol, 10mol%) of ytterbium triflate. The flask is fitted with a magnetic stirrer and rigorously stirred at room temperature for a period of time of about 24 hours. Conversion is monitored by crude ^1H NMR taken to indicate the conversion to 2-pentyl cyanoacetate. At the required conversion the flask is then charged with 3.00g (0.10mol) of paraformaldehyde, 15mL of nitromethane and 5 mL of acetonitrile, fitted with a reflux condenser and the reaction temperature is raised to about 105°C. The reaction is stopped after a period of time of 6 hours, with the relative conversion of cyanoacetate to cyanoacrylate monitored by 500MHz ^1H NMR.

Example 3

[0067] To a 50ml round bottomed flask is added 7.15g (0.084mol) of cyanoacetic acid, 6.84g (0.056mol) of Phenyl ethanol and 3.47g (6.75mmol, 10mol%) of ytterbium triflate. The flask is fitted with a magnetic stirrer and rigorously stirred at room temperature for a period of time of about 21 hours. Conversion is monitored by crude ^1H NMR taken to indicate the conversion to 2-phenyl ethyl cyanoacetate. At the required conversion the flask is then charged with 3.00g (0.10mol) of paraformaldehyde, 15mL of nitromethane and 5 mL of acetonitrile, fitted with a reflux condenser and the reaction temperature is raised to about 105°C. The reaction is stopped after a period of time of 6 hours, with

the relative conversion of cyanoacetate to cyanoacrylate
monitored by 500MHz ¹H NMR.

WHAT IS CLAIMED IS:

1. A process for the preparation of a cyanoacrylate, steps of which comprise:

(a) reacting cyanoacetic acid and an alcohol in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield a cyanoacetate;

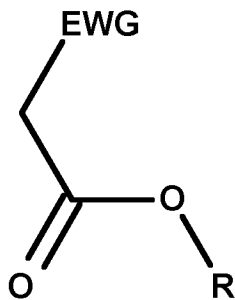
(b) reacting the so formed cyanoacetate from step (a) with a source of aldehyde, in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield a cyanoacrylate; and

(c) optionally, separating from the mixture the so formed cyanoacrylate substantially free from the cyanoacetic acid, the alcohol and/or the catalyst and by-products.

2. A process for the preparation of an electron deficient olefin, steps of which comprise:

(a) providing as reactants:

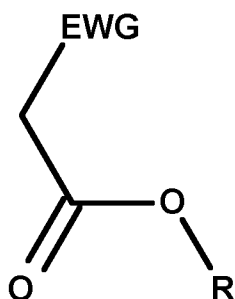
(i) a 2-electron withdrawing group-substituted methylene compound embraced by:



wherein EWG represents an electron withdrawing group; and R here represents hydrogen; and

(ii) an alcohol;

(b) reacting the 2-electron withdrawing group-substituted methylene compound and the alcohol in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield an electron deficient olefin precursor embraced by:



wherein EWG represents an electron withdrawing group; and R here represents straight chain, branched, cyclic or fused C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, and C₆₋₂₀ aryl or C₇₋₂₀ alkaryl, with or without substitution or interruption by one or more heteroatoms;

(c) reacting the electron deficient olefin precursor and a source of aldehyde, in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield an electron deficient olefin; and

(d) optionally, separating from the mixture the so formed electron deficient olefin substantially free from the reactants and by-products.

3. The process of any one of Claims 1-2, wherein the catalyst comprising a lanthanide element or a transition element has one or more ligands bound to the element(s).

4. The process of any one of Claims 1-2, wherein the catalyst comprises a lanthanide element.

5. The process of any one of Claims 1-2, wherein the catalyst comprises a transition element.

6. The process of any one of Claims 1-2, wherein the catalyst comprises ytterbium.

7. The process of any one of Claims 1-2, wherein the catalyst comprises niobium.

8. The process of Claim 3, wherein the one or more ligands is selected from halogens, triflates, nitrates, mesylates or tosylates.

9. The process of any one of Claims 1-2, wherein the alcohol is any mono-, di- or multi-functional hydroxyl compound.

10. The process of any one of Claims 1-2, wherein the alcohol is any mono-, di- or multi-functional C₁₋₂₀ alkanol, C₂₋₂₀ alkenol, C₂₋₂₀ alkynol.

11. The process of any one of Claims 1-2, wherein the alcohol is an aromatic alcohol.

12. The process of any one of Claims 1-2, wherein the alcohol is phenol, benzyl alcohol and derivatives thereof.

13. The process of Claim 2, wherein the so-formed electron deficient olefin precursor is a cyanoacetate.

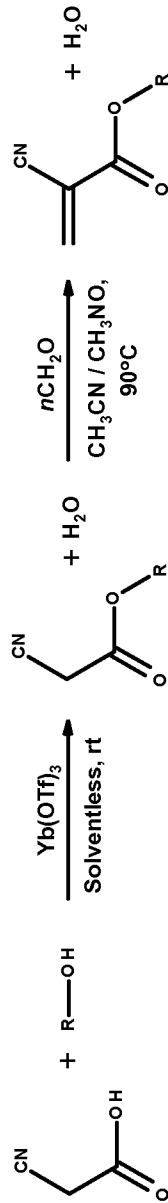
14. The process of any one of Claims 1-2, wherein EWG represents cyano, halogens, nitro, isocyanate, sulfoxide and phosphine oxide.

15. A process for the preparation of a cyanoacrylate, steps of which comprise:

- (a) providing as reactants a cyanoacetic acid and an alcohol;
- (b) reacting the cyanoacetic acid and the alcohol in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield a cyanoacetate;
- (c) reacting the so formed cyanoacetate with a source of aldehyde, in the presence of a catalyst comprising a lanthanide element or a transition element, under appropriate conditions and for a time sufficient to yield a cyanoacrylate; and
- (d) optionally, separating from the mixture the so formed cyanoacrylate substantially free from the reactants and by-products.

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FIG. 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/082353

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C253/30 C07C67/08
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07C
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WEN-BIN YI, YA-QING YIN, CHUN CAI: "Ytterbium Perfluorooctanesulfonate-Catalyzed Knoevenagel Condensation in a Fluorous Biphasic System", ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL, vol. 39, no. 1, 18 February 2009 (2009-02-18), pages 71-75, XP002778436, DOI: 10.1080/00304940709458582 the entire document, in particular page 71, reaction equation; page 72, reaction equation; page 73, Table 1, entries 1 to 11; page 74, "Typical Procedure for Knoevenagel Condensation in FBS" ----- -/--</p>	1-15

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search 22 February 2018	Date of mailing of the international search report 05/03/2018
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sen, Alina

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/082353

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>A. ILANGO VAN, S. MURALIDHARAN, S. MARUTHAMUTHU: "A Systematic Study on Knoevenagel Reaction and Nazarov Cyclization of Less Reactive Carbonyl Compounds Using Rare Earth Triflates and Its Applications", JOURNAL OF THE KOREAN CHEMICAL SOCIETY, vol. 55, no. 6, 2011, pages 1000-1006, XP002778437, DOI: 10.5012/jkcs.2011.55.6.1000 page 1001, Table 1, entries 1 to 5, and Table 2, entries 1 to 12; page 1002, Scheme 1, 1h->3m, "Reaction of 3,4,5-trimethoxybenzaldehyde (1h) and ethyl cyanoacetate (2b) gave the adduct 3m in quantitative yields"; pages 1003-1004, "General Experimental Procedure for the Synthesis of Substituted Alkenes"</p> <p>-----</p>	1-15
Y	<p>US 6 436 866 B1 (NISHIKIDO JOJI [JP] ET AL) 20 August 2002 (2002-08-20) column 1, lines 5-19; column 13, lines 49-52; examples, e.g. Example 8</p> <p>-----</p>	1-15
Y	<p>G. BARTOLI ET AL: "Highly Efficient Solvent-Free Condensation of Carboxylic Acids with Alcohols Catalysed by Zinc Perchlorate Hexahydrate, Zn(ClO₄)₂ · 6 H₂O", ADVANCED SYNTHESIS & CATALYSIS, vol. 347, no. 1, 2005, pages 33-38, XP055031893, ISSN: 1615-4150, DOI: 10.1002/adsc.200404171 page 33, right-hand column, lines 6-9; page 34, Table 1; pages 35-37, Table 2; page 37, "Typical Experimental Procedure"</p> <p>-----</p>	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/082353

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6436866	B1	20-08-2002	NONE