



(51) International Patent Classification:

C07C 245/00 (2006.01)

(21) International Application Number:

PCT/US2012/028741

(22) International Filing Date:

12 March 2012 (12.03.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/454,127 18 March 2011 (18.03.2011)

US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: CONTINUOUS FLOW PROCESS FOR THE PRODUCTION OF DIAZO ESTERS

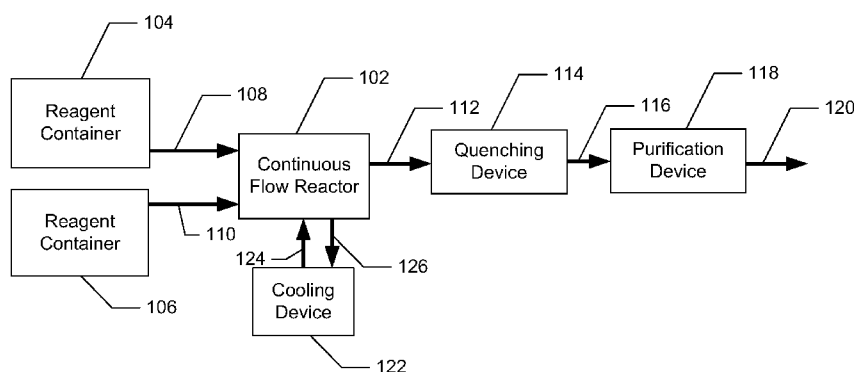


FIG. 1

(57) Abstract: Processes for producing diazo ester derivatives in a single phase system in a continuous flow reactor.

CONTINUOUS FLOW PROCESS FOR THE PRODUCTION OF DIAZO ESTERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Ser. No. 61/454,127 filed March 18, 2011, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention generally relates to the production of compounds in a single phase solution via a continuous flow process. In particular, the present invention relates to processes for producing compounds of formula (II) (e.g., diazo esters or derivatives thereof) in a single phase system by contacting a salt of a compound of formula (I) with a diazotizing agent in a continuous flow reactor.

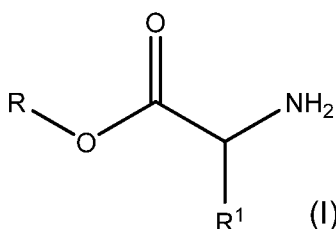
BACKGROUND OF THE INVENTION

[0003] Diazo esters are reagents that may be used in numerous ways in synthetic organic chemistry. Thermally or otherwise induced expulsion of the diazo group may be used to form carbenes, and used in a variety of carbenoid reactions. Further, diazo esters may be used synthetically with the retention of the diazo group to take part in 1,3-dipolar cycloaddition reactions with dipolarophiles.

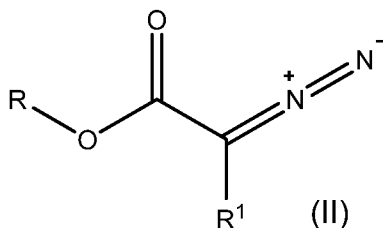
[0004] Despite their utility, the use of diazo esters is limited by their relatively low thermal stability and their high reactivity in the presence of acid. Existing methods of diazo ester production focus on small scale or *in situ* formation of the diazo ester. These methods generally include reacting the diazotizing agent and the amino ester in a water-organic biphasic system such that the resulting diazo ester is promptly isolated in the organic phase to prevent product degradation. This process, however, is not suitable for scale up reactions, thus, large scale use and commercial production of diazo esters has been limited. Therefore, there is a need for processes of producing diazo esters in a safe and efficient manner that is compatible with large scale production.

SUMMARY OF THE INVENTION

[0005] Processes for the production of a compound of formula (II) in a single phase system are provided. The process involves contacting a first solution including a salt of the compound of formula (I) with a second solution including a diazotizing agent in a continuous flow reactor to provide a solution including a compound of formula (II). The compound of formula (I) corresponds to the following structure:



and the compound of formula (II) corresponds to the following structure:



wherein R is chosen from hydrocarbyl or substituted hydrocarbyl; and

R¹ is chosen from hydrogen, hydrocarbyl, or substituted hydrocarbyl group.

[0006] Another embodiment described herein provides a process for the production of ethyl diazoacetate. The process involves contacting a first solution including glycine ethyl ester hydrochloride and an acid with a second solution including sodium nitrite in a continuous flow reactor to provide a solution including ethyl diazoacetate. The process further includes, optionally, contacting the solution including ethyl diazoacetate with an organic solvent to form an aqueous layer or ionic layer and an organic layer, wherein the organic layer includes substantially all of the ethyl diazoacetate.

DESCRIPTION OF THE FIGURES

[0007] **FIG. 1** illustrates a continuous flow reactor and associated equipment that may be used according to some embodiments of the invention.

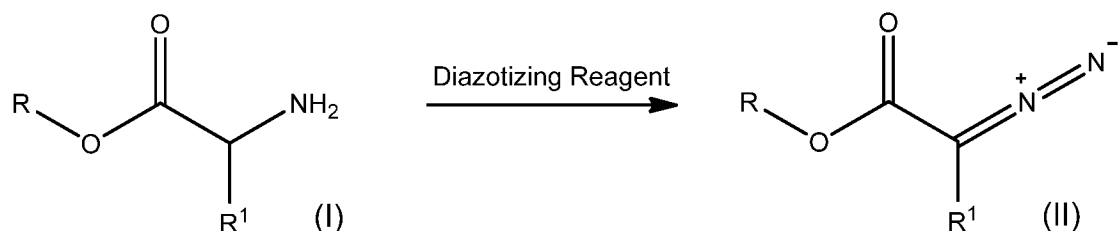
DETAILED DESCRIPTION OF THE INVENTION

[0008] In one aspect, the present invention provides a process for the production of compounds of formula (II) (e.g., diazo esters) in a continuous flow reactor. The processes employ a single phase for the diazotization reaction occurring as a result of contacting a solution comprising a salt of a compound of formula (I) (e.g., a solution comprising a salt of an amino ester) with a solution comprising a diazotizing agent to provide a solution comprising a compound of formula (II). The solution comprising the compound of formula (II) is a single and homogeneous liquid phase under the reaction conditions. The diazotization reaction may further include a quench step that may result in the separation of substantially all of the compound of formula (II) produced from the reaction into an organic layer (phase). The process may also include one or more purification steps where the compound of formula (II) may be recovered in a solution of organic solvent which has been dried and/or neutralized. Such a solution may optionally be concentrated to provide the compound of formula (II) in neat form, or substantially neat form.

[0009] Another embodiment described herein is the use of a continuous flow process for the formation of the compound of formula (II). By continuous flow process, it is meant a process in which the starting materials (including, for example, the salt of the compound of formula (I), the diazotizing agent, acids, co-reagents, buffers) may be continuously added to a reaction vessel and the product (e.g., the compound of formula (II)) may be continuously withdrawn from the reaction vessel. The device used for the continuous flow process is described below.

[0010] In one embodiment, a process for the production of a compound of formula (II) from a first solution comprising a salt of the compound of formula (I) and a second solution comprising a diazotizing agent is provided. While not wishing to be bound by any particular theory, it is believed that for some embodiments of the present

invention, that when the salt of the compound of formula (I) is in solution, the salt of the compound of formula (I) may be in equilibrium with its non-salt form. Stated another way, the salt of the compound of formula (I) may be in equilibrium with the compound of formula (I). The compound of formula (I), possessing a “free” amino group, may undergo reaction with a number of diazotizing agents to provide the compound of formula (II). Thus, in certain embodiments, the diazotizing agent may not directly react with the salt of the compound of formula (I). For purposes of illustration, the diazotization reaction of the compound of formula (I) thus described is depicted in the scheme below:



wherein:

R is chosen from hydrocarbyl or substituted hydrocarbyl, and

R¹ is chosen from hydrogen, hydrocarbyl, or substituted hydrocarbyl.

[0011] In one exemplary embodiment, the salt of the compound of formula (I) is a salt of a glycine alkyl ester, such as glycine ethyl ester hydrochloride, the diazotizing agent is sodium nitrite, and the compound of formula (II) is an alkyl diazoacetate, such as ethyl diazoacetate.

[0012] As illustrated in the reaction scheme, the diazotization reaction is performed by contacting a first solution comprising the salt of the compound of formula (I) with a second solution comprising a diazotizing agent in a manner such that compound (II) is formed. The reaction is carried out in a continuous flow reactor, as described in more detail below.

[0013] One substrate for preparation of the compound of formula (II) is a salt of a compound of formula (I). In one embodiment, R is hydrocarbyl or substituted hydrocarbyl. In some such embodiments, R is an unsubstituted straight chain or branched alkyl group, or is straight chain or branched alkyl group further substituted with one or more aryl groups. In another embodiment, R is a hydrocarbyl or substituted

hydrocarbyl having from one to twenty carbon atoms. In yet another embodiment, R is a hydrocarbyl or substituted hydrocarbyl having from one to ten carbon atoms. In yet another embodiment, R is a hydrocarbyl or substituted hydrocarbyl having from one to six carbon atoms. In yet another embodiment, R is an amino acid, and the compound of formula (I) is a poly(amino acid). In an exemplary embodiment, R is ethyl, and the compound of formula (I) is an ethyl glycine ester. In yet another exemplary embodiment, R is benzyl. In yet another exemplary embodiment, R is *tert*-butyl.

[0014] In various embodiments, R¹ may be hydrogen, hydrocarbyl or substituted hydrocarbyl. In another embodiment, R¹ may be a straight chain or branched alkyl group. In another embodiment, R¹ is a hydrocarbyl or substituted hydrocarbyl having from one to twenty carbon atoms. In yet another embodiment, R¹ is a hydrocarbyl or substituted hydrocarbyl having from one to ten carbon atoms. In yet another embodiment, R¹ is a hydrocarbyl or substituted hydrocarbyl having from one to six carbon atoms. In some embodiments, R¹ is methyl, ethyl, *n*-propyl, isopropyl, allyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, cyclopentyl, hexyl, and cyclohexyl. In an exemplary embodiment, R¹ is chosen from hydrogen or methyl. In other embodiments, R¹ may be a side chain found in an amino acid, such as that found in any of the natural α -amino acids, or may be protected derivative of such a side chain. For example, R¹ may be CH₃ (*i.e.*, an alanine side chain), CH₂OH (*i.e.*, a serine side chain), CH₂OP wherein P is a protecting group (*i.e.*, a protected serine side chain), CH₂CH₂CO₂H (*i.e.*, a glutamic acid side chain), CH₂CH₂CO₂P (*i.e.*, a protected glutamic acid side chain), CH₂CH₂CH₂CH₂NH₂ (*i.e.*, a lysine side chain), CH₂CH₂CH₂CH₂NHP (*i.e.*, a protected lysine side chain), and so forth. Examples of suitable protecting groups for amino acid side chains are well known in the art and include those generally described in T. H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York (1999).

[0015] Suitable salts of compounds of formula (I) include acid salts including but not limited to those prepared or otherwise derived from mineral acids and organic acids. Non-limiting examples of suitable salts of compounds of formula (I) include, but are not limited to, acetate salts, citrate salts, dibenzenesulfonate salts,

fumarate salts, hydroiodide salts, hydrobromide salts, hydrochloride salts, maleate salts, methanesulfonate salts, trifluoromethanesulfonate salts, phosphate salts (including mono- and dihydrogen phosphate salts), *p*-toluenesulfonate salts, sulfamate salts, sulfate salts, and combinations thereof. In an exemplary embodiment, the salt of the compound of formula (I) is a hydrochloride salt.

[0016] Numerous compounds of formula (I) and/or salt forms thereof are commercially available and may readily be used in any of the processes described herein. Examples of compounds of formula (I) and/or salt forms thereof which are applicable to the present technology include, but are not limited to: alanate esters (and salt forms thereof) such as L-alanine benzyl ester hydrochloride salt, L-alanine methyl ester hydrochloride salt, L-alanine ethyl ester hydrochloride salt, L-alanine benzyl ester *p*-toluenesulfonate salt, L-alanine *tert*-butyl ester hydrochloride salt, D-alanine methyl ester hydrochloride salt, L-alanine ethyl ester hydrochloride salt, D-alanine *tert*-butyl ester hydrochloride salt, D-alanine benzyl ester *p*-toluenesulfonate salt; aspartate esters (including side chain protected derivatives thereof and salt forms thereof) such as L-aspartic acid dimethyl ester hydrochloride salt, L-aspartic acid di-*tert*-butyl ester hydrochloride salt, L-aspartic acid 4-*tert*-butyl-1-methyl ester hydrochloride salt, L-aspartic acid bis-allyl ester *p*-toluenesulfonate salt, L-aspartic acid dibenzyl ester *p*-toluenesulfonate salt; glutamate esters (and side chain protected derivatives thereof and salt forms thereof) such as L-glutamic acid dimethyl ester hydrochloride salt, L-glutamic acid diethyl ester hydrochloride salt, L-glutamic acid di-*tert*-butyl ester hydrochloride salt, L-glutamic acid 5-*tert*-butyl 1-methyl ester hydrochloride salt; amino esters (and derivatives thereof and salt forms thereof) derived from glutamine such as L-glutamine *tert*-butyl ester hydrochloride salt; glycinate esters (and salt forms thereof) such as glycine methyl ester hydrochloride salt, glycine ethyl ester hydrochloride salt, glycine N-pentyl ester hydrochloride salt, glycine *tert*-butyl ester hydrochloride salt, glycine benzyl ester hydrochloride salt, glycine benzyl ester *p*-toluenesulfonate salt, glycine ethyl ester phosphate salt, glycine *tert*-butyl ester dibenzenesulfonimide salt, glycine-¹³C₂,¹⁵N ethyl ester hydrochloride salt, glycine N-butyl ester hydrochloride salt; histidinate esters (and side chain protected derivatives thereof, *e.g.*, protected at the

histidine nitrogen, as well as salt forms thereof) such as L-histidine methyl ester dihydrochloride salt; (iso)leucinate esters (and salt forms thereof) such as L-isoleucine methyl ester hydrochloride salt, L-isoleucine allyl ester *p*-toluenesulfonate salt, L-leucine methyl ester hydrochloride salt, L-leucine *tert*-butyl ester hydrochloride salt, L-leucine ethyl ester hydrochloride salt, L-leucine benzyl ester *p*-toluenesulfonate salt, L-lysine methyl ester dihydrochloride salt; lysinate esters (and side chain protected derivatives thereof and salt forms thereof) such as L-lysine ethyl ester dihydrochloride salt; cysteinate esters (and side chain protected derivatives thereof such as methioninate esters, and salt forms thereof) such as L-methionine methyl ester hydrochloride salt, L-methionine ethyl ester hydrochloride salt, D-methionine methyl ester, phenylalaninate esters (and salt forms thereof) such as L-phenylalanine methyl ester hydrochloride salt, L-phenylalanine benzyl ester hydrochloride salt, L-phenylalanine ethyl ester hydrochloride salt, L-phenylalanine *tert*-butyl ester hydrochloride salt, L-phenylalanine methyl-d3 ester hydrochloride salt, D-phenylalanine methyl ester hydrochloride salt; serinate esters (and side chain protected derivatives thereof and salt forms thereof) such as D-serine methyl ester hydrochloride salt, L-serine methyl ester hydrochloride salt, DL-serine methyl ester hydrochloride salt, L-serine benzyl ester hydrochloride salt, L-serine ethyl ester hydrochloride salt, D-serine benzyl ester benzenesulfonate salt, L-serine benzyl ester benzenesulfonate salt, *O-tert*-butyl-L-serine methyl ester hydrochloride salt, *O-tert*-butyl-L-serine *tert*-butyl ester hydrochloride salt; threoninate ester (and side chain protected derivatives thereof and salt forms thereof) such as L-threonine methyl ester hydrochloride salt, DL-threonine methyl ester hydrochloride salt, *O-tert*-butyl-L-threonine methyl ester hydrochloride salt, *O-tert*-butyl-L-threonine *tert*-butyl ester acetate salt, DL-threonine methyl ester hydrochloride salt; tryptophanate esters (and side chain protected derivatives thereof, *e.g.*, with protection at the indole nitrogen, and salt forms thereof) such as L-tryptophan methyl ester hydrochloride salt, D-tryptophan methyl ester hydrochloride salt, L-tryptophan ethyl ester hydrochloride salt, L-tryptophan benzyl ester, D-tryptophan benzyl ester, 5-hydroxy-DL-tryptophan ethyl ester hydrochloride salt, DL-tryptophan methyl ester, DL-tryptophan methyl ester hydrochloride salt, tryptophan ethyl ester hydrochloride salt, an alkyl ester of 1-methyl-

D-tryptophan; tyrosinate esters (and side chain protected derivatives thereof and salt forms thereof) such as L-tyrosine methyl ester, L-tyrosine methyl ester hydrochloride salt, L-tyrosine ethyl ester hydrochloride salt, L-tyrosine ethyl ester, L-tyrosine methyl ester (ring-13C6) hydrochloride salt, α -methyl-DL-tyrosine methyl ester hydrochloride salt, L-tyrosine *tert*-butyl ester, *O-tert*-butyl-L-tyrosine methyl ester hydrochloride salt, 3-nitro-L-tyrosine ethyl ester hydrochloride salt, α -methyl-DL-m-tyrosine methyl ester hydrochloride salt monohydrate, *O-tert*-butyl-L-tyrosine *tert*-butyl ester hydrochloride salt, L-tyrosine benzyl ester *p*-toluenesulfonate salt, L-tyrosine allyl ester *p*-toluenesulfonate salt, DL-tyrosine methyl ester hydrochloride salt, D-tyrosine benzyl ester *p*-toluenesulfonate salt; valinate esters (and salt forms thereof) such as DL-valine ethyl ester hydrochloride salt, L-valine methyl ester hydrochloride salt, D-valine methyl ester hydrochloride salt, L-valine ethyl ester hydrochloride salt, L-valine benzyl ester hydrochloride salt, L-valine *tert*-butyl ester hydrochloride salt, and DL-valine methyl ester hydrochloride salt.

[0017] The salt of the compound of formula (I) may be dissolved directly in a solvent to provide the first solution. Alternatively, the first solution may be prepared by adding the compound of formula (I), along with salt forming reagent to the solvent. Examples of such salt forming reagents include acids such as mineral acids and organic acids. Specific examples of such acids include, but are not limited to acetic acid, citric acid, sulfonic acids (*e.g.*, benzenesulfonic acid, dibenzenesulfonic acid, methanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, and the like), fumaric acid, maleic acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, phosphoric acid, sulfamic acids, sulfuric acid, and combinations thereof.

[0018] Examples of acceptable solvents for the first solution are aqueous solvents (*e.g.*, water) or ionic solvents. Non-limiting examples of ionic solvents include, but are not limited to ionic liquids such as ammonium nitrates, imidazolium comprising compounds, pyridinium comprising compounds, pyrrolidinium comprising compounds, and mixtures thereof. In some embodiments, the solvent is water. In an exemplary embodiment, the ionic solvent is 1-butyl-3-methylimidazolium (BMIM) or 1-butyl-3,5-dimethylpyridinium bromide.

[0019] The solvents for the first solution and second solution are selected to provide a single phase solution when mixed. Stated another way, the solvents for the first solution and the second solution are selected to be miscible with one another. The term “single phase”, as used herein, describes a homogeneous liquid mixture.

[0020] The concentration of the salt of the compound of formula (I) in the first solution can and will vary. The concentration of the salt of the compound of formula (I) in the first solution may be about 10% by weight, about 15% by weight, about 20% by weight, about 25% by weight, about 30% by weight, about 35% by weight, about 40% by weight, about 45% by weight, about 50% by weight, about 55% by weight, about 60% by weight, about 65% by weight, about 70% by weight, about 75% by weight, about 80% by weight, about 85% by weight, about 90% by weight, or may be a range between and including any two of these values. Thus, in some embodiments, the concentration of the salt of the compound of formula (I) in the first solution ranges from about 10% by weight to about 90% by weight, from about 30% by weight to about 60% by weight, from about 20% to about 30% by weight, from about 25% to about 35% by weight, from about 30% to about 35% by weight, from about 30% to about 40% by weight, from about 35% to about 45% by weight, from about 40% to about 50% by weight, from about 45% to about 50% by weight, from about 50% to about 60% by weight, from about 55% to about 65% by weight, or from about 60% to about 70% by weight. In an exemplary embodiment, the concentration of the salt of the compound of formula (I) in the first solution is about 40% by weight.

[0021] The first solution comprising the salt of the compound of formula (I) is contacted, mixed, or otherwise combined with a second solution comprising a diazotizing reagent. The solvent for the diazotizing agent in the second solution may be an aqueous solvent or an ionic solvent, as described above.

[0022] As used herein, the term “diazotizing agent” refers to a nitrogen-containing agent that is capable of transforming an amino group of the compound of formula (I) to a diazo group, either by itself, or in the presence of one or more co-reagents. For example, treatment of the diazotizing agent sodium nitrite (NaNO_2) with an acid co-reagent such as hydrochloric acid generates nitrous acid (a source of

nitrosonium ion, NO^+ , a reactive diazotization species) which may transform an amino group to a diazo group. Thus, as used herein, the term “diazotizing agent” specifically includes precursor reagents, from which reactive diazotization species such as nitrosonium ion may be prepared. Non-limiting examples of diazotizing agents include dinitrogen tetroxide, dinitrogen trioxide, hydrazones, compounds comprising nitrosyl, nitrous acid, nitrites, and combinations thereof. As used herein, the term “nitrite” refers to a compound comprising at least one nitrite group, whether in ionic form (e.g., NaNO_2) or covalent form (e.g., ethyl nitrite, $\text{CH}_3\text{CH}_2\text{ONO}$). Non-limiting examples of nitrites include, but are not limited to alkali metal nitrites, alkaline earth metal nitrites, alkyl nitrites, ammonium nitrites, or mixtures thereof. Specific examples of such nitrites include, but are not limited to barium nitrite, butyl nitrite, calcium nitrite, dicyclohexylammonium nitrite, ethyl nitrite, isoamyl nitrite, isobutyl nitrite, potassium nitrite, *tert*-butyl nitrite, and sodium nitrite. In an exemplary embodiment, the diazotizing agent is a nitrite and the nitrite is sodium nitrite.

[0023] As indicated above, treatment of a nitrite with acid generates nitrous acid (e.g., via protonation of a nitrite ion), a source of nitrosonium ion which thought to be the reactive species in diazotization of amines such as the compound of formula (I). Acids such as mineral or organic acids, may be used as co-reagent with a nitrite to generate reactive diazotization species. Acids may also be resin-based. The acid may further be monoprotic, diprotic, or triprotic. Non-limiting examples of suitable acids include acetic acid, AMBERLYST™ resins, citric acid, dibenzenesulfonic acid, fluorosulfonic acid, fumaric acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, maleic acid, methanesulfonic acid, phosphoric acid, *p*-toluenesulfonic acid, trifluoromethanesulfonic acid, organic sulfonic acids, sulfamic, sulfuric acid, and combinations thereof. In an exemplary embodiment, the acid is hydrochloric acid.

[0024] Where nitrite is employed as the diazotizing agent, the acid co-reagent necessary to generate the reactive diazotization species may be present in the second solution comprising the diazotizing agent. Alternatively, the acid co-reagent may be present in the first solution comprising the salt of the compound of formula (I). In the latter instance, the reactive diazotization species will be formed upon contacting

the first and the second solutions. In general, where nitrite is used as the diazotizing agent, it is preferred to have the acid co-reagent in the first solution comprising the salt of the compound of formula (I). In this regard, it is possible to generate the reactive diazotization species in a controlled manner. Finally, and as will be appreciated by those of skill the art, the acid co-reagent may also be used generate the salt of the compound of formula (I) from the compound of formula (I). For example, acid may be added in sufficient quantity to a solution of the compound (I) to both form the salt of the compound of formula (I) and to provide sufficient acid necessary to generate the reactive diazotization species upon contact of the first solution with the second solution comprising a nitrite. Thus, in some embodiments, the first solution of the salt of the compound of formula (I) also comprises acid.

[0025] The molar ratio of nitrite to the acid can and will vary within the ranges defined herein. Typically, only catalytic quantity of acid is needed. In general, the molar ratio of the nitrite to a monoprotic acid may range from about 100:1 to about 5:1. For example, the ratio of nitrite to monoprotic acid may be about 5:1, about 10:1, about 13:1, about 15:1, about 18:1, about 20:1, about 25:1, about 30:1, about 35:1, about 40:1, about 45:1, about 50:1, about 55:1, about 60:1, about 65:1, about 70:1, about 75:1, about 80:1, about 85:1, about 90:1, about 95:1, about 100:1, or may be a range between and including any two of these values. In some embodiments, the molar ratio of the nitrite to the monoprotic acid is from about 60:1 to about 15:1, from about 70:1 to about 5:1, from about 50:1 to about 10:1, from about 40:1 to about 20:1, from about 75:1 to about 13:1, or from about 50:1 to about 18:1. The molar ratio of the nitrite to a diprotic acid may range from about 200:1 to about 10:1. For example, the ratio of nitrite to diprotic acid may be about 10:1, about 20:1, about 26:1, about 30:1, about 36:1, about 40:1, about 50:1, about 60:1, about 70:1, about 80:1, about 90:1, about 100:1, about 110:1, about 120:1, about 130:1, about 140:1, about 150:1, about 160:1, about 170:1, about 180:1, about 190:1, about 200:1, or may be a range between and including any two of these values. In some embodiments, the molar ratio of the nitrite to the diprotic acid is from about 120:1 to about 30:1, from about 140:1 to about 10:1, from about 100:1 to about 20:1, from about 80:1 to about 40:1, from about 150:1 to about

26:1, or from about 100:1 to about 36:1. The molar ratio of the nitrite to a triprotic acid may range from about 300:1 to about 15:1. For example, the ratio of nitrite to triprotic acid may be about 15:1, about 30:1, about 39:1, about 45:1, about 54:1, about 60:1, about 75:1, about 90:1, about 105:1, about 120:1, about 135:1, about 150:1, about 165:1, about 180:1, about 195:1, about 210:1, about 225:1, about 240:1, about 255:1, about 270:1, about 285:1, about 300:1, or may be a range between and including any two of these values. In some embodiments, the molar ratio of the nitrite to the triprotic acid is from about 180:1 to about 45:1, from about 210:1 to about 15:1, from about 150:1 to about 30:1, from about 120:1 to about 60:1, from about 225:1 to about 39:1, or from about 150:1 to about 54:1.

[0026] The molar ratio of the compound of formula (I) to the diazotizing agent may vary from about 1:0.1 to about 1:5. For example, the molar ratio of the compound of formula (I) to the diazotizing agent may be about 1:0.1, about 1:0.5, about 1:0.6, about 1:0.7, about 1:0.8, about 1:0.9, about 1:1, about 1:1.1, about 1:1.2, about 1:1.3, about 1:1.4, about 1:1.5, about 1:1.6, about 1:1.7, about 1:1.8, about 1:1.9, about 1:2, about 1:3, about 1:4, about 1:5, or a range between and including any two of these values. Thus, in some embodiments, the molar ratio of the compound of formula (I) to the diazotizing agent may range from about 1:0.8 to about 1:2, from about 1:1 to about 1:2, from about 1:0.8 to about 1:1, from about 1:0.9 to about 1:1.1, from about 1:0.9 to about 1:1.2, from about 1:1 to about 1:1.2, from about 1:1.2 to about 1:1.3, from about 1:1.3 to about 1.5, or from about 1:1.4 to about 1:1.5. In an exemplary embodiment, the molar ratio of the compound of formula (I) to the diazotizing agent is about 1:1.2 or is 1:1.3. In some such embodiments, the diazotizing agent is a nitrite. In further embodiments, the nitrite is sodium nitrite.

[0027] In general, the diazotization reaction between the first solution comprising the salt of compound of formula (I) and the second solution comprising the diazotizing agent may be performed at a temperature ranging from about 0 °C and about 90 °C. For example, the reaction may be performed at a temperature of about 0 °C, about 5 °C, about 10 °C, about 15 °C, about 20 °C, about 25 °C, about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, about 60 °C, about 65 °C,

about 70 °C, about 75 °C, about 80 °C, about 85 °C, about 90 °C, or at a temperature range between and including any two of these values. Thus, in some embodiments, the reaction is performed at a temperature range from about 0 °C to about 50 °C, from about 40 °C to about 90 °C, from about 5 °C to about 20 °C, from about 15 °C to about 30 °C, from about 25 °C to about 40 °C, from about 35 °C to about 50 °C, from about 45 °C to about 60 °C, from about 55 °C to about 70 °C, or from about 65 °C to about 80 °C. In an exemplary embodiment, the reaction is performed at a temperature of about 35 °C.

[0028] In some embodiments, the first solution comprising the salt of the compound of formula (I) and/or the second solution comprising the diazotizing agent further includes a buffer, *i.e.*, the diazotization reaction may be performed in the presence of a buffer. Non-limiting examples of suitable examples of buffers include dipotassium phosphate, disodium phosphate, lithium acetate, lithium borate, monopotassium phosphate, monosodium phosphate, potassium acetate, potassium borate, sodium acetate, sodium borate, and combinations thereof. The pH of the diazotization reaction can and will vary. In some embodiments thus described, the reaction mixture will be acidic and have a pH of less than about 7, less than about 6, less than about 5, less than about 4, less than about 3, less than about 2, or less than about 1. Acidic reaction mixtures will generally be observed where the diazotizing agent is nitrite and acid is used to generate reactive diazotization species from the nitrite.

[0029] In one embodiment, the solution comprising the compound of formula (II) provided from contacting the first solution comprising the salt compound of formula (I) with the second solution comprising the diazotizing agent may be cooled or otherwise temperature controlled by a proximity heat transfer device that may further include a working fluid. In this regard, the rate of the reaction may be controlled and/or the reaction may be performed under adiabatic conditions. For proximity heat transfer devices including a working fluid, the temperature of the working fluid may range from about 0 °C to about 50 °C. Thus, the temperature of the working fluid may be about 0 °C, about 5 °C, about 10 °C, about 17 °C, about 20 °C, about 25 °C, about 30 °C, about 35 °C, about 40 °C, about 45 °C, about 0 °C, or a range between and including any two of these values. Thus, in some embodiments, the temperature of the working fluid may

range from about 0 °C to about 10 °C, from about 5 °C to about 15 °C, from about 10 °C to about 20 °C, and from about 15 °C to about 20 °C. In exemplary embodiments, the temperature of the working fluid of the heat transfer device is about 17 °C, about 10 °C, about 5 °C, or about 0 °C. In some such embodiments, any of the aforementioned temperatures is a starting temperature of the working fluid, *i.e.*, the temperature of the working fluid prior to removing thermal energy from, or adding thermal energy to, the reaction. The working fluid may be any known working fluid, including but not limited to water, poly(ethylene glycol), or combinations thereof.

[0030] The diazotization reaction between the first solution comprising the salt of compound of formula (I) and the second solution comprising the diazotizing agent provides a single phase solution which includes the compound of formula (II) along with reaction byproducts and/or unreacted starting materials. The solution comprising the compound of formula (II) and associated byproducts, hereinafter “the continuous flow reactor effluent” may optionally be quenched and further purified to provide the compound of formula (II) in a desired form (*e.g.*, neat or as a solution in a solvent).

[0031] In one embodiment, the output from the continuous flow reactor is connected by additional tubing which delivers the continuous flow reactor effluent to an organic solvent, such that quenching occurs continuously as the compound of formula (II) is formed. In another embodiment, the continuous flow reactor effluent is collected and, in a separate step, manually added to the organic solvent to quench the diazotization reaction (*i.e.*, the diazotization reaction is quenched in bulk, rather than continuously).

[0032] A variety of organic solvents are suitable for quenching the reaction. Preferably, such organic solvents are immiscible (or minimally miscible) with the aqueous solvent or ionic solvent of the continuous flow reactor effluent. Due to the instability of the compound of formula (II) in acid, non-acidic solvents may be preferred for quenching. While not wishing to be bound by any particular theory, solvents which can protonate the ester carbonyl group of the compound of formula (II) may cause degradation of the compound of formula (II), such as by loss of nitrogen (N₂), thereby reducing its yield.

[0033] Non-limiting examples of organic solvents suitable for quenching the diazotization reaction include polar aprotic solvents, non-polar aprotic solvents, and protic solvents. Non-limiting examples of organic solvents include alkane and substituted alkane solvents (including cycloalkanes), halogenated solvents, aromatic hydrocarbons, esters, ethers, ketones, and combinations thereof. Non-limiting examples of specific organic solvents that may be used for quenching include, acetonitrile, acetone, benzene, butyl acetate, chlorobenzene, chloroform, chloromethane, cyclohexane, cyclopentane, dichloromethane (*i.e.*, methylene chloride), dichloroethane, diethyl ether, dioxane, ethyl acetate, ethylene dichloride, ethylene bromide, fluorobenzene, heptane, hexane, isobutyl methylketone, isopropyl acetate, methylene bromide, methyl ethyl ketone, methyltetrahydrofuran (including 2-methyltetrahydrofuran), pentyl acetate, *n*-propyl acetate, tetrahydrofuran, tetrachloroethane, toluene, trichloroethane, xylene, and combinations thereof. Protic solvents may include higher alkanols including, but not limited to, butanol, pentanol, hexanol, heptanol, octanol, nonanol, decanol, and the like. Preferably, the organic solvent is insoluble, or minimally soluble, in water. As used herein, the term “minimally soluble” means that the organic solvent is capable of forming a biphasic mixture with water. In an exemplary embodiment, the organic solvent is dichloromethane or toluene.

[0034] In another embodiment, quenching is accomplished at or below a temperature of about 25 °C, such as at a temperature of about 25 °C, about 20 °C, about 15 °C, about 10 °C, or about 0 °C. The organic solvent may be cooled prior to introduction of the continuous flow reactor effluent and/or may be continuously throughout the process. The organic solvent may be cooled by any number of known methods in the art, including, but not limited to, a jacketed vessel or by contacting the vessel containing the organic solvent with the working solution of the heat transfer device.

[0035] The quenching may be performed by introducing the continuous flow reactor effluent into a quench vessel containing the organic solvent. In an exemplary embodiment, the quench vessel may further provide agitation of the vessel's

contents using known methods including, but not limited to, suitable stirring devices such as a magnetic stirrer and stirring bar or an overhead stirrer.

[0036] The quench step typically comprises the formation of two layers (*i.e.*, two liquid phases): (i) an organic layer, arising from the organic solvent used in quenching and (ii) an aqueous layer or an ionic layer, arising from the solvent(s) selected for the first and second solutions. The presence of an aqueous layer or an ionic layer will depend if the first solution comprising the salt of formula (I) and the second solution comprising the diazotizing agent were prepared from an aqueous solvent or an ionic solvent. In either case, due to the differential solubilities of the starting materials, byproducts, and product of the diazotization reaction, the compound of formula (II) will preferentially partition into the organic layer, while any unreacted starting materials (*e.g.*, the salt of the compound of formula (I), the diazotizing agent, acid, etc.) and byproducts will preferentially partition into the aqueous or ionic layer. Stated another way, the compound of formula (II) is preferentially extracted into the organic layer.

[0037] In some embodiments, the organic layer comprises substantially all of the compound of formula (II). As defined herein, "substantially all of the compound of formula (II)" means that at least about 80% of the total amount of the compound of formula (II) produced from the diazotization reaction is present in the organic solvent. In some embodiments, at least about 85%, at least about 90%, at least about 95%, or at least about 99%, or about 100% of the compound of formula (II) produced from the diazotization reaction is present in the organic layer.

[0038] The organic layer may be separated from the aqueous or ionic layer using any number of techniques well known in the art (*e.g.*, by equipping the quenching vessel with a valve to remove the lower layer, by transferring the biphasic mixture to a separate container such as a separatory funnel followed by separation, using a pipette to selectively remove either the upper or lower layer, etc.). The layers may further be transferred into separate containers in discrete batches or in continuous process. In an exemplary embodiment, the organic layer is denser than the aqueous or ionic layer and is manually drained into a separate container by opening a valve

positioned at a lower part of the quenching vessel (*i.e.*, the aqueous or ionic layer remains in the quenching vessel after separation).

[0039] The organic layer may be neutralized with base. Due to the propensity of the compound of formula (II) to degrade in the presence of acid, it is preferred to neutralize residual acid in the organic layer prior to concentrating the organic layer or otherwise attempting to isolate the compound of formula (II). In this regard, the yield of the compound of formula (II) will be increased. Suitable bases for neutralization include, but are not limited to, ammonium hydroxide, calcium carbonate, potassium bicarbonate, potassium borate, potassium carbonate, potassium hydroxide, sodium acetate, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide, and sodium phosphate. In an exemplary embodiment, the base is sodium carbonate. In some embodiments, the base is in the form of a solution, such as an aqueous solution. In some such embodiments, the organic layer is neutralized by washing the organic layer with an aqueous solution of base. In other embodiments, the base is insoluble in the organic layer. In such embodiments, the insoluble base may be removed by filtration after the organic layer is neutralized.

[0040] In yet another embodiment described herein, the organic layer may also be dried with a drying agent to reduce residual water, such as water arising from contact of the organic layer with the aqueous or ionic layer. In one embodiment of the invention, the drying agent is insoluble in the organic layer such that it can be removed by filtration. Suitable drying agents include, but are not limited to alumina, calcium carbonate, calcium chloride, calcium sulfate, magnesium oxide, magnesium sulfate, molecular sieves, potassium carbonate, potassium hydroxide, sodium carbonate, and sodium sulfate. In yet another embodiment, the drying agent and the base are the same. In an exemplary embodiment, the drying agent and the base are anhydrous sodium carbonate. In such an embodiment, the neutralized and dried organic layer is separated from the spent sodium carbonate by filtration.

[0041] As will be appreciated, the neutralized and dried organic layer provides the compound of formula (II) in a convenient format, *i.e.*, the compound of formula (II) as a solution in an organic solvent. In particular, the concentration of the

compound of formula (II) in the organic solvent may be predetermined by using predefined quantities of organic solvent in quenching. As will be further appreciated, the handling of compounds of formula (II) in solution is often preferred for safety reasons, since many such compounds may be kinetically and/or thermally unstable, particularly in neat form. Low molecular weight compounds such as methyl or ethyl diazoacetate are understood to be particularly labile.

[0042] The process described herein may optionally comprise a concentration step where the concentration of the compound of formula (II) in the organic layer is increased by removing the organic solvent from the organic layer. Typically, such a concentration step will be performed after the organic layer has been neutralized and dried. The organic solvent may be removed using equipment commonly known in the art, such as a stripper, a rotary evaporator, a vacuum distiller, and any combination thereof. Typically, the organic solvent will be removed at reduced pressure. The organic solvent may be removed completely to provide the compound of formula (II) in neat form, or may be partially removed to provide the compound of formula (II) as a more concentrated solution (in comparison to the concentration of the compound of formula (II) in solution prior to removal of the organic solvent). In some embodiments, about 10% by weight, about 20% by weight, about 30% by weight, about 40% by weight, about 50% by weight, about 60% by weight, about 70% by weight, about 80% by weight, about 90% by weight, about 95% by weight, about 99% by weight of the solvent is removed. In other embodiments, about 100% by weight of the organic solvent is removed, and the compound of formula (II) is provided in neat form. In yet other embodiments, after concentration, the compound of formula (II) is obtained which is less than about 30% by weight, less than about 25% by weight, less than about 20% by weight, less than about 15% by weight, less than about 10% by weight, less than about 5% by weight, or less than about 1% by weight organic solvent. In one such embodiment, the compound of formula (II) is 0% by weight organic solvent, *i.e.*, the compound of formula (II) is in neat form.

[0043] The yield of the compound of formula (II) can and will vary. Typically, the yield of the compound of formula (II) may be at least about 65%, at least

about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 99%, or a range which is between and including any two of these values. Thus, in one embodiment, the yield of the compound of formula (II) may range from about 65% to about 75%, from about 75% to about 85%, or from about 85% to about 95%. In another embodiment, the yield of the compound of formula (II) may be greater than about 95%.

[0044] In one embodiment, the process of producing the compound of formula (II) takes place within a continuous flow reactor. As defined herein, a continuous flow reactor refers to a vessel to which one or more starting materials may be continuously added and from which one or more products may be continuously withdrawn. Such starting materials include any of those described herein for the process of producing the compound of formula (II), such as the compound of formula (I) or a salt thereof, a diazotizing agent, additives and/or co-reagents (*e.g.*, buffers, acids, etc.), and solvent(s). The rate at which the one or more starting materials are added to the continuous flow reactor is equal to the rate at which the one or more products are withdrawn.

[0045] An embodiment of a continuous flow reactor and associated equipment is illustrated schematically in **FIG. 1**. A first solution of the salt of the compound of formula (I) within a first reagent container 104 may be transferred into the continuous flow reactor 102 through a first conduit 108. A second solution comprising the diazotizing agent within a second reagent container 106 may be transferred into the continuous flow reactor 102 through a second conduit 110. The diazotization reaction described herein takes place within the continuous flow reactor, and a solution comprising the compound of formula (II) as well as any byproducts and unused reagents (*e.g.*, unreacted salt of the compound of formula (I), unreacted diazotizing agent, acid, etc.) is transferred out of the continuous flow reactor through a reactor outlet 112. The temperature of the reagents within the continuous flow reactor 102 may be regulated by a cooling device 122 that is connected to the reactor 102 by a coolant delivery conduit 124 and a coolant removal conduit 126. The resulting solution may be transferred from the reactor outlet 112 to a quenching device 114, and an organic layer

(phase) containing the compound of formula (II) may be transferred through the quenching outlet 116 into a purification device 118. The compound of formula (II) may be delivered through a purification outlet 120.

[0046] The continuous flow reactor 102 may be made of a variety of materials. Suitable examples of materials for the continuous flow reactor 102 include but are not limited to glass, fluorinated poly(ethylene) (FPE), fluorinated ethylene poly(propylene) (FEP), high density poly(ethylene) (HDPE), poly(chlorotrifluoroethylene) (PCT), poly(ether ether ketone) (PEEK), poly(tetrafluoroethylene) (PTFE), poly(vinyl fluoride) (PVF), perfluoroalkoxy (PFA) polymers, and combinations or copolymers thereof. The continuous flow reactor 102 receives reagents continuously through the conduits 108 and 110 and delivers the resulting solution containing the compound of formula (II) continuously through the reactor outlet 112. Within the continuous flow reactor 102, the reagents are contacted in order to implement certain embodiments of the diazotization reaction scheme described herein. Because the reaction product (*i.e.*, compound of formula (II)) may display limited stability, the continuous flow reactor 102 may continuously supply these products to subsequent processes, such as processes where the compound of formula (II) is used as a reagent or starting material. Further, the continuous flow reactor may be sized and configured to produce the compound of formula (II) at a wide range of rates and scales. In some embodiments, the compound of formula (II) may be produced in an amount greater than or equal to 1 kilogram, greater than or equal to 5 kilograms, greater than or equal to 10 kilograms, greater than or equal to 50 kilograms, or greater than or equal to 100 kilograms.

[0047] Non-limiting examples of devices suitable for use as a continuous flow reactor 102 include a tubular reactor, a stirred tube reactor, an extruder, a static mixer, a continuously-stirred tank reactor, or any combination thereof. The continuous flow reactor 102 may comprise a single device, or may comprise two or more devices connected in series or in parallel.

[0048] In one embodiment, the continuous flow reactor is a tubular reactor comprising a length of pipe. The pipe may have a length ranging from about 1 meter to about 20 meters. Thus, the pipe may have a length of about 1 meter, about 2 meters,

about 3 meters, about 4 meters, about 5 meters, about 6 meters, about 7 meters, about 8 meters, about 10 meters, about 12 meters, about 14 meters, about 16 meters, about 18 meters, about 20 meters, or a range between and including any two of these values. Thus, in some embodiments, the pipe has a length from about 2 meters to about 10 meters, from about 3 meters to about 4 meters, from about 4 meters to about 5 meters, from about 5 meters to about 6 meters, or from about 6 meters to about 7 meters. In general, the pipe may have a diameter that ranges from about 0.1 centimeters to about 2 centimeters, for example, about 0.1 centimeters, about 0.3 centimeters, about 0.5 centimeters, about 1 centimeter, about 1.5 centimeters, about 2 centimeters, or may be range between and including any two of these values. In some embodiments, the pipe has a diameter from about 0.3 centimeters to about 1 centimeter. In a preferred embodiment, the pipe length is about 5 meters and the diameter of the pipe is about 0.5 centimeters.

[0049] The length of pipe may be straight, curved, coiled, or any combination thereof along its length. The pipe may comprise two or more pipes connected in parallel. The pipe may have a cross-sectional area that is essentially constant along the length of the pipe, or the cross-sectional area of the pipe may increase or decrease one or more times along the length of the pipe. In an exemplary embodiment, the continuous flow reactor comprises flexible tubing configured in a helical shape.

[0050] The one or more reagents may be introduced continuously into the continuous flow reactor 102 using any known methods. Each reagent may enter the reactor 102 through a single conduit, or through multiple conduits in a continuous supply. A continuous supply of reagents may be provided by reagent containers 104 and 106 containing the reagents, as illustrated in **FIG. 1**. Alternatively, the reagent may be continuously produced and introduced into the reactor 102. Each reagent may be stored in a separate reagent container, or as mixtures of two or more reagents in the same reagent container, or any combination thereof. The reagent containers may be refillable such that the reactor may receive an uninterrupted continuous supply of reagents.

[0051] Reagents may be introduced into the continuous flow reactor 102 in varying concentrations by diluting the reagents to the desired concentration before introducing the reagents to the reactor. Depending on the reaction parameters, the reagents may be introduced at the same or at different concentrations. In addition to controlling the molar ratio of reagents through the concentration of the reagents introduced into the reactor 102, the transfer rate of the reagents into the reactor 102 may be varied to achieve a desired molar ratio of reagents. The transfer rate may be modulated by valves installed within conduits 108 and 110, controllable transfer pumps that pump reagents across the conduits into the reactor, controllable pressure pumps that pressurize the reagents stored within the reagent containers to predetermined pressures selected to move the reagents out of the containers at desired transfer rates, and any combination thereof. Non-limiting examples of pumps suitable for use as transfer pumps include gear pumps, diaphragm pumps, centrifugal pumps, piston pumps, and peristaltic pumps.

[0052] Mixing of the one or more reagents within the continuous flow reactor 102 to produce the compound of formula (II) may occur by any known mechanism including but not limited to diffusion, convection, or any combination thereof. Diffusion, as used herein, refers to the transportation of a reagent from one location to another within a fluid containing the reagent due to differences or spatial gradients in the concentration of the reagent at different locations in the flow. Convection, as used herein, refers to the movement of a reagent from one location to another in a flow due to the physical movement of a relatively small sub-volume of fluid flow within which the reagent is dissolved; for example, stirring is one method by which convective mixing may occur.

[0053] The extent of the mixing may be influenced by one or more factors including but not limited to the dimensions of the reactor 102 such as the volume or cross-sectional area, the inclusion of mixing elements such as mixing paddles or stirrers, and combinations thereof. For example, if the continuous flow reactor is a tubular reactor with a relatively narrow cross-sectional diameter, mixing may occur primarily through diffusion due to the relatively short diffusion pathways. In another

example, convective mixing may be provided by in-line mixers or continuous stirrers included within the reactor 102. In yet another example, convective mixing may be induced by fixed vanes or screens situated within the reactor 102 such that turbulent flow induced downstream of the fixed vanes or screens mixes the reagents. In an embodiment, the continuous flow reactor 102 may further comprise stirring elements including but not limited to stirring paddles, propellers, and combinations thereof.

[0054] The reactor 102 may impel the reaction mixture comprising the reagents from the input to the output of the reactor using any known method. For example, the reactor 102 may include stirring elements that may additionally induce the movement of the reaction mixture through the reactor 102. Other non-limiting examples of methods by which the reaction mixture may be impelled through the reactor 102 include applying a pressure differential between the inlet and outlet of the reactor 102 using one or more pumps including but not limited to at least one suction pump operatively connected at the outlet of the reactor 102, at least one pressurization pump at the inlet of the reactor 102, and any combination thereof. The reaction mixture may move in a laminar flow pattern through the reactor, in a turbulent flow pattern, or any combination thereof.

[0055] The reagents may be impelled through the reactor 102 at a flow rate corresponding to a desired production rate, such that the reaction is substantially complete at when the reaction mixture reaches the outlet of the reactor 102. The dwell time of the reagents within the reactor 102 may be specified based on the rate of the reaction such that the reaction is substantially complete when the reaction mixture reaches the output of the reactor 102. For example, longer dwell times within a tubular reactor comprising a tube may be accomplished by varying one or more factors including but not limited to lengthening the tube, reducing the flow rate through the reactor, increasing the cross-sectional area of the tube, or any combination thereof. Typically, the flow rate ranges from about 0.1 milliliters per minute (mL/min) to about 1000 mL/min. For example, the flow rate may be about 0.1 mL/min, about 0.5 mL/min, about 1 mL/min, about 5 mL/min, about 10 mL/min, about 15 mL/min, about 20 mL/min, about 30 mL/min, about 40 mL/min, about 50 mL/min, about 60 mL/min, about 70

mL/min, about 80 mL/min, about 90 mL/min, about 100 mL/min, about 110 mL/min, about 125 mL/min, about 150 mL/min, about 175 mL/min, about 200 mL/min, about 225 mL/min, about 250 mL/min, about 275 mL/min, about 300 mL/min, about 325 mL/min, about 350 mL/min about 400 mL/min about 500 mL/min, about 600 mL/min, about 700 mL/min, about 800 mL/min, about 900 mL/min, about 1000 mL/min, or the flow rate may be a range between and including any two of these values. Thus, in some embodiments, the flow rate ranges from about 10 mL/min to 50 mL/min, from about 40 mL/min to about 80 mL/min, from about 70 mL/min to about 110 mL/min, from about 100 mL/min to about 175 mL/min, from about 150 mL/min to about 200 mL/min, from about 175 mL/min to about 225 mL/min, from about 200 mL/min to about 250 mL/min, from about 275 mL/min to about 325 mL/min, from about 300 mL/min to about 350 mL/min. In an exemplary embodiment, the flow rate is about 15 mL/min.

[0056] The temperature of the reaction mixture within the reactor 102 may be controlled using any known methods including but not limited to heat sinks, heat dissipating vanes, jacketing devices, chillers, or any other existing devices that transfer heat from the reaction mixture to a working fluid circulating near the reaction pathway. The cooling device may be sized and configured to maintain the temperature of the reaction mixture reagents within any of the temperatures and temperature ranges described herein, or to otherwise maintain adiabatic reaction conditions. The working fluid of a heat transfer device may be any known working fluid, including but not limited to water, poly(ethylene glycol), and combinations thereof.

[0057] The continuous flow reactor 102 may further include release valves installed along any of the conduits supplying reagents and conduits withdrawing the product from the reactor to alleviate pressure build-ups within the reactor and associated conduits due to one or more factors including but not limited to gases released by the reaction mixture within the reactor, pressures applied to impel the reaction mixture through the reactor, increased temperature within the reactor, and combinations thereof.

[0058] The resulting continuous flow reactor effluent comprising the compound of formula (II) exiting the reactor outlet 112 may be introduced into a

quenching device 114. The quenching device may halt the reaction within the aqueous or ionic solvent and transfer the compound of formula (II) from the aqueous or ionic solvent to a second phase comprising an organic solvent as previously described. The quenching device 114 may be attached to the reactor outlet of the continuous flow reactor 112 using any known method including a sealed connection such as a threaded and gasketed connector, submerging the reactor outlet beneath the organic solvent contained in the quenching device 114, and any other suitable connection method. The continuous flow reactor effluent exiting the reactor outlet may be introduced continuously, or in discrete batches to the quenching device 114.

[0059] To further protect against the thermal instability of the reaction, the quenching device 114 may further comprise temperature regulation through any known method including but not limited to jacketing the quenching vessel, contacting the quench vessel walls with a heat sink or heat dissipation vanes, circulation of a working fluid to absorb and remove heat from the contents of the quenching device or any combination thereof.

[0060] In an embodiment, the continuous flow reactor effluent exiting the reactor outlet may be cooled prior to introducing the continuous flow reactor effluent into the quenching device. In this embodiment, any known method of cooling may be used to reduce the continuous flow reactor effluent. Non-limiting examples of devices suitable for cooling the continuous flow reactor effluent prior to entering the quenching device include chillers, condensers, jacketing devices, and combinations thereof.

[0061] The quenching device 114 may mix the liquid within the quenching device 114 to enhance the contact between the organic solvent the continuous flow reactor effluent to facilitate the partitioning or exaction of the compound of formula (II) to the organic solvent. Mixing may be provided by any known methods including, but not limited to, a magnetic stirrer, stir paddles, a stir bar, and an overhead stirrer.

[0062] An inert atmosphere may be provided over the contents within the quenching device 114. The inert atmosphere may be provided by any known method, including, but not limited to, vacuum suction of the quenching device followed by addition of an inert gas, and introduction of an inert gas having a higher density than air

into the quenching device. Non-limiting examples of inert gases suitable for use in providing an inert atmosphere include helium, nitrogen, argon, and mixtures thereof.

[0063] In an embodiment, purification of the organic layer (*i.e.*, the organic layer comprising the compound of formula (II)) may be performed using a purification device 118 for drying, neutralizing, and/or reducing the organic solvent in the organic layer separated from the quenching device. Purification may be accomplished in any vessel suitable for contacting drying and neutralizing reagents with the organic layer. Non-limiting examples of devices suitable for use as purification devices include a stirred tank reaction vessel or a packed column. The purification device 118 may additionally provide for the removal of any drying and neutralizing reagents. The removal of the drying and neutralizing reagents may be accomplished by any known method including, but not limited to, filtration, distillation, extraction, or combinations thereof. In an exemplary embodiment, solid drying and neutralizing agents are removed by filtration.

[0064] The purification device 118 may further provide for the reduction of the organic solvent in the organic layer, *i.e.*, the organic layer comprising the compound of formula (II) may be concentrated. Reduction of the organic solvent may be provided by any known means for removing the solvent. Non-limiting examples include evaporating devices suitable for use in a purification device such as a stripper, a rotary evaporator, a vacuum distiller, and any combination thereof. In an exemplary embodiment, the organic solvent from the organic layer is reduced using a rotary evaporator with a bath temperature of about 25 °C and at a pressure ranging from about 300 bar to about 200 bar.

DEFINITIONS

[0065] To facilitate understanding of the process described herein, several terms are defined below:

[0066] The term “alkenyl” as used herein describes groups which are preferably lower alkenyl containing from two to eight carbon atoms in the principal chain

and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

[0067] The term “amino ester” as used herein describes a compound having an amino group and an ester group. An “amino ester salt” refers to any salt form of the amino ester.

[0068] The term “aromatic” as used herein alone or as part of another group denotes optionally substituted homo- or heterocyclic aromatic groups. These aromatic groups are preferably monocyclic, bicyclic, or tricyclic groups containing from 6 to 14 atoms in the ring portion. The term “aromatic” encompasses the “aryl” and “heteroaryl” groups defined below.

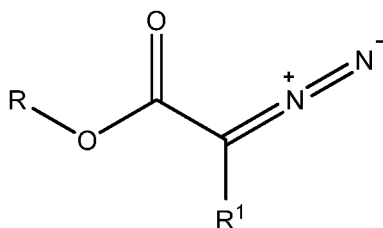
[0069] The term “aryl” or “Ar” as used herein alone or as part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl.

[0070] The term “carbonyl” as used herein alone or as part of another group denotes a group comprising a carbon oxygen double bond.

[0071] The term “diazo” as used herein alone or as part of another group denotes a group of the general formula:



attached to carbon atom, such as is found in diazo esters of the general formula:



wherein R is a hydrocarbyl or substituted hydrocarbyl; and R¹ is a hydrogen, hydrocarbyl or substituted hydrocarbyl. Non-limiting examples of diazo esters include, but are not limited to, methyl diazoacetate, ethyl diazoacetate, *tert*-butyl diazoacetate, benzyl diazoacetate, phenyl diazoacetate, and the like.

[0072] The terms "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine.

[0073] The term "heteroatom" shall mean atoms other than carbon and hydrogen.

[0074] The terms "heterocyclo" or "heterocyclic" as used herein alone or as part of another group denote optionally substituted, fully saturated or unsaturated, monocyclic or bicyclic, aromatic or non-aromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heterocyclo group preferably has 1 or 2 oxygen atoms and/or 1 to 4 nitrogen atoms in the ring, and is bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heterocyclo groups include heteroaromatics as described below. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, cyano, ketals, acetals, esters and ethers.

[0075] The term "heteroaryl" as used herein alone or as part of another group denote optionally substituted aromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heteroaryl group preferably has 1 or 2 oxygen atoms and/or 1 to 4 nitrogen atoms in the ring, and is bonded to the remainder of the molecule through a carbon.

[0076] The terms "hydrocarbon" and "hydrocarbyl" as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

[0077] The "substituted hydrocarbyl" moieties described herein are hydrocarbyl moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a hetero atom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These substituents include halogen, heterocyclo, alkoxy, alkenoxy, aryloxy, hydroxy, protected

hydroxy, acyl, acyloxy, nitro, amino, amido, nitro, cyano, ketals, acetals, esters and ethers. In some embodiments, substituted hydrocarbyl moieties may be amino acids.

[0078] When introducing elements of the embodiments described herein, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[0079] Having described the invention in detail, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims.

EXAMPLES

[0080] The following examples detail various embodiments of the process described herein. Starting materials, reagents, and solvents were obtained from commercial sources (Sigma-Aldrich, St. Louis, MO) and used without further purification unless otherwise noted. In general, the continuous flow reactor used in the Examples below included: 2 peristaltic pumps (HPLC, gear) capable of achieving flow rates from about 1 to about 50 mL/min, a custom reactor system, and a quenching vessel (typically a 1–25 L jacketed flask, depending on the scale of the reaction). The custom reactor system included a glass housing, a T-mixer (PEEK construction, 1–250 μ L), and PFA tubing (1/16" to 1/8"), and a residency time unit (0.5–50 mL). Adiabatic conditions were maintained with a Tango heater-chiller (10–40 $^{\circ}$ C). Each flow process was performed using two reactant solutions of approximately equal volume.

Example 1. General Procedure for the Synthesis of Diazo Esters

[0081] An amino ester salt (20 moles) is dissolved in a solution of deionized water (6 L) and concentrated hydrochloric acid (~12M, ~50–100 mL, ~0.6–1.2 moles). Equivalent molar amounts of other acids may be used in place of concentrated hydrochloric acid. Separately, a solution of sodium nitrite (~22–30 moles, 1.1–1.5 equivalents) in deionized water (6 to 7 L) is prepared. The amino ester salt solution and

the sodium nitrite solution are pumped into the reactor system at a flow rate of ~20 mL/min each. The effluent from the reactor system which includes the diazo ester product is collected in a quenching vessel containing a minimally water miscible solvent such as dichloromethane or toluene (~2–10L).

[0082] The effect of flow rate(s) on reactant conversion may be monitored by suitable analytical techniques, such as NMR or HPLC. The flow rates may be further optimized accordingly. When optimized, the continuous flow reactor will operate for about 1–5 hours and the analysis of the reactor system effluent by ^1H NMR indicates about 98-99% conversion of the starting materials.

[0083] The organic layer is removed from the aqueous layer, neutralized (and dried) with anhydrous sodium carbonate, and filtered to provide an organic solution of the diazo ester. The concentration of the diazo ester solution may be determined using a suitable analytical technique, such as NMR or HPLC. The diazo ester solution thus formed may be used directly in a subsequent reaction (or stored), or may be further concentrated (e.g., by rotary evaporation) to provide the diazo ester as a neat material. For shipping and transportation, it is preferable to use solutions of diazo esters rather than the corresponding neat materials.

[0084] An amino ester may be used in place of an amino ester salt in the above procedure by increasing the volume of acid by the appropriate amount.

Example 2a. Synthesis of Ethyl Diazoacetate (Neat)

[0085] Glycine ethyl ester hydrochloride (2.00 kg, 14.3 mol) was dissolved in deionized water (2.8 L) to make a ~40 wt. % solution. Concentrated hydrochloric acid (~12M, 20 mL, ~0.24 moles) was added to the glycine ethyl ester hydrochloride solution. In a separate container, sodium nitrite (1.2 kg, 17.4 moles, 1.2 equivalents) was dissolved in deionized water (3.4 L) to make a ~26 wt. % solution. The reactant solutions were fed into a continuous flow reactor at a rate of about 15 mL/min. The continuous flow reactor included an in-line static mixer with 5 m of tubing. The flow reactor effluent was continuously drained into a quenching vessel containing dichloromethane (2.5 L) at 10 °C. After the reagent solutions were pumped through the

flow reactor, the effluent and dichloromethane mixture was stirred for an additional 15 min. The biphasic mixture was allowed to settle. The organic layer was removed and neutralized (and dried) with anhydrous sodium carbonate. After filtration, the solution was concentrated at reduced pressure by rotary evaporation to provide ethyl diazoacetate (13.4 mol, 94%) containing minimal amounts of residual dichloromethane (typically less than 15 wt. % (e.g., ~5 wt. %) when sufficiently concentrated).

[0086] In comparison to the batch process at similar scale, the continuous flow process provided a ~25% increase in yield (94% vs. 76%), a ~40% reduction in total waste, a ~57% reduction in organic solvents, and a ~40% reduction in labor (*i.e.*, time). Further, the continuous flow process was readily scalable without limitation, more controllable, and provided ethyl diazoacetate with less impurities.

Example 2b. Synthesis of Ethyl Diazoacetate (~15 wt. % in toluene)

[0087] A 15 wt. % solution of ethyl diazoacetate was prepared by minor modification of Example 2a. At the same scale, the flow reactor effluent was continuously drained into a quenching vessel containing toluene (10.5 L, 9.10 kg). The organic layer was removed, neutralized (and dried) with anhydrous sodium carbonate, and filtered to provide ethyl diazoacetate (1.60 kg, 14.0 moles, 92%) in toluene (10.5 L, 9.10 kg). The total volume of the ethyl diazoacetate solution was ~13 L.

Example 3a. Synthesis of *tert*-Butyl Diazoacetate (Neat)

[0088] Glycine *tert*-butyl ester hydrochloride (250 g, 1.49 mol) was dissolved in deionized water (300 mL) to make a ~45 wt. % solution. Concentrated hydrochloric acid (~12M, 8 mL, ~0.096 moles) was added to the glycine *tert*-butyl ester hydrochloride solution. In a separate container, sodium nitrite (125 g, 1.81 moles, 1.2 equivalents) was dissolved in deionized water (400 mL) to make a ~24 wt. % solution. The reactant solutions were fed into a continuous flow reactor at a rate of about 15 mL/min. The continuous flow reactor included an in-line static mixer with 5 m of tubing. The flow reactor effluent was continuously drained into a quenching vessel containing dichloromethane (300 mL) at 10 °C. After the reagent solutions were pumped through

the flow reactor, the effluent and dichloromethane mixture was stirred for an additional 15 min. The biphasic mixture was allowed to settle. The organic layer was removed and neutralized (and dried) with anhydrous sodium carbonate. After filtration, the solution was concentrated at reduced pressure by rotary evaporation to provide *tert*-butyl diazoacetate (1.37 mol, 92%) containing minimal amounts of residual dichloromethane (typically less than 15 wt. % (e.g., ~5-8 wt. %) when sufficiently concentrated).

[0089] In comparison to the batch process at similar scale, the continuous flow process provided a ~30% increase in yield (92% vs. 71%), a ~40% reduction in total waste, and an ~80% reduction in labor (i.e., time). Further, the continuous flow process was readily scalable without limitation, more controllable, and provided *tert*-butyl diazoacetate with less impurities.

Example 3b. Synthesis of *tert*-Butyl Diazoacetate (~15 wt. % in toluene)

[0090] A 15 wt. % solution of *tert*-butyl diazoacetate was prepared by minor modification of Example 3a. At the same scale, the flow reactor effluent was continuously drained into a quenching vessel containing toluene (1.20 L, 1.04 kg). The organic layer was removed, neutralized (and dried) with anhydrous sodium carbonate, and filtered to provide *tert*-butyl diazoacetate (210 g, 1.48 moles, 99%) in toluene (1.20 L, 1.04 kg). The total volume of the *tert*-butyl diazoacetate solution was ~1.5 L.

Example 4a. Synthesis of Benzyl Diazoacetate (Neat)

[0091] Glycine benzyl ester hydrochloride (200 g, 0.992 mol) was dissolved in deionized water (300 mL) to make a ~40 wt. % solution. Concentrated hydrochloric acid (~12M, 8 mL, ~0.096 moles) was added to the glycine benzyl ester hydrochloride solution. In a separate container, sodium nitrite (90 g, 1.3 moles, 1.3 equivalents) was dissolved in deionized water (410 mL) to make a ~18 wt. % solution. The reactant solutions were fed into a continuous flow reactor at a rate of about 15 mL/min. The continuous flow reactor included an in-line static mixer with 5 m of tubing. The flow reactor effluent was continuously drained into a quenching vessel containing

dichloromethane (300 mL) at 10 °C. After the reagent solutions were pumped through the flow reactor, the effluent and dichloromethane mixture was stirred for an additional 15 min. The biphasic mixture was allowed to settle. The organic layer was removed and neutralized (and dried) with anhydrous sodium carbonate. After filtration, the solution was concentrated at reduced pressure by rotary evaporation to provide benzyl diazoacetate (0.912 mol, 92%) containing minimal amounts of residual dichloromethane (typically less than 15 wt. % when sufficiently concentrated).

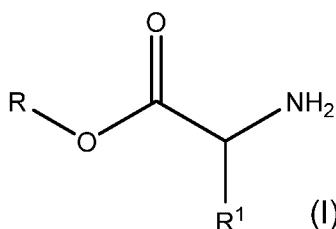
Example 4b. Synthesis of Benzyl Diazoacetate (~15 wt. % in toluene)

[0092] A 15 wt. % solution of benzyl diazoacetate was prepared by minor modification of Example 4a. At the same scale, the flow reactor effluent was continuously drained into a quenching vessel containing toluene (1.20 L, 1.04 kg). The organic layer was removed, neutralized (and dried) with anhydrous sodium carbonate, and filtered to provide benzyl diazoacetate (170 g, 0.965 moles, 96%) in toluene (1.20 L, 1.04 kg).

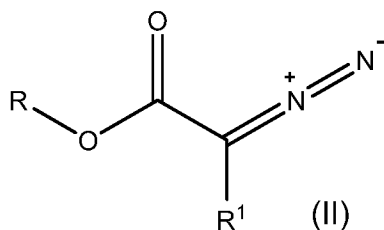
CLAIMS

What is claimed is:

1. A process for the production of a compound of formula (II) in a single phase, the process comprising contacting a first solution comprising a salt of a compound of formula (I) with a second solution comprising a diazotizing agent in a continuous flow reactor to provide a solution comprising the compound of formula (II); wherein the compound of formula (I) corresponds to the following structure:



and the compound of formula (II) corresponds to the following structure:



wherein R is a hydrocarbyl or substituted hydrocarbyl group, and R¹ is a hydrogen, hydrocarbyl or substituted hydrocarbyl.

2. The process of claim 1, wherein the molar ratio of the salt of the compound of formula (I) to the diazotizing agent is from about 1:1 to about 1:2.
3. The process of claim 1, wherein the concentration of the salt of the compound of formula (I) in the first solution is between about 30% and about 60% by weight.
4. The process of claim 1, wherein the concentration of the diazotizing agent in the second solution is between about 5% and about 45% by weight.

5. The process of claim 1, wherein the salt of the compound of formula (I) is chosen from an acetate salt, a dibenzenesulfonate salt, a hydrobromide salt, a hydrochloride salt, a methanesulfonate salt, a trifluoromethanesulfonate salt, a phosphate salt, a propionate salt, a *p*-toluenesulfonate salt, a sulfamate salt, and a sulfate salt.
6. The process of claim 1, wherein the first solution and the second solution are each aqueous solutions.
7. The process of claim 1, wherein the first solution and the second solution are each ionic solutions.
8. The process of claim 1, wherein the diazotizing agent is a nitrite.
9. The process of claim 8, wherein the nitrite is chosen from an alkali metal nitrite, an alkaline earth metal nitrite, an alkyl nitrite, an ammonium nitrite, and mixtures thereof.
10. The process of claim 1, wherein the first solution or the second solution further comprise acid.
11. The process of claim 1, wherein R is an alkyl group having from one to ten carbon atoms, optionally substituted with one or more aryl groups.
12. The process of claim 1, wherein R¹ is chosen from hydrogen and alkyl groups.
13. The process of claim 12, wherein the alkyl group is chosen from methyl, ethyl, *n*-propyl, isopropyl, allyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, cyclopentyl, hexyl, and cyclohexyl.

14. The process of claim 1, wherein the yield of the compound of formula (II) is at least about 80%.
15. The process of claim 1, wherein first solution and the second solution are contacted at a temperature of about 10° C to about 80° C.
16. The process of claim 1, wherein the diazotizing agent is a nitrite; R is an alkyl group having from one to ten carbon atoms; and the salt of the compound of formula (I) is chosen from an acetate salt, a dibenzenesulfonate salt, a hydrobromide salt, a hydrochloride salt, a methanesulfonate salt, a trifluoromethanesulfonate salt, a phosphate salt, a propionate salt, a *p*-toluenesulfonate salt, a sulfamate salt, and a sulfate salt.
17. The process of claim 1, wherein R is chosen from *tert*-butyl, benzyl, and ethyl; and R¹ is hydrogen.
18. The process of claim 1, wherein the salt of the compound of formula (I) is a hydrochloride salt of ethyl glycinate; the diazotizing agent is sodium nitrate; and the compound of formula (II) is ethyl diazoacetate.
19. The process of claim 1, wherein the first solution and the second solution are contacted in a tubular reactor of a length from about 2 meters to about 10 meters and a diameter of about 0.5 centimeters.
20. The process of claim 1, further comprising contacting the solution comprising the compound of formula (II) with an organic solvent to form an aqueous or ionic layer and an organic layer, wherein the organic layer comprises substantially all of the compound of formula (II).

21. The process of claim 20, wherein the organic solvent is chosen from carbon tetrachloride, benzene, cyclopentane, cyclohexane, 2,2-difluoro-1,1-dichloroethane, ethyl acetate, ethylene dichloride, hexane, methylene bromide, dichloromethane, pentane, tetrachloroethylene, toluene, trichloroethylene, and mixtures thereof.
22. The process of claim 20, wherein the organic solvent is at a temperature of less than or equal to about 25 °C.
23. The process of claim 20, further comprising separating the organic layer from the aqueous or ionic layer.
24. The process of claim 23, further comprising neutralizing the organic layer with a base.
25. The process of claim 24, further comprising drying and optionally filtering the organic layer.
26. The process of claim 25, further comprising concentrating the organic layer to provide the compound of formula (II) which is less than about 30% by weight organic solvent.
27. The process of claim 26, wherein the compound of formula (II) is less than about 15% by weight organic solvent.
28. The process of claim 1, wherein the compound of formula (II) is produced in an amount greater than or equal to one kilogram.
29. A process for the production of ethyl diazoacetate, the process comprising:

- (a) contacting a first solution comprising glycine ethyl ester hydrochloride and an acid with a second solution comprising sodium nitrite in a continuous flow reactor to provide a solution comprising ethyl diazoacetate; and
- (b) optionally contacting the solution comprising ethyl diazoacetate with an organic solvent to form an aqueous or ionic layer and an organic layer, wherein the organic layer comprises substantially all of the ethyl diazoacetate.
30. The process of claim 29, wherein the organic solvent is dichloromethane or toluene.
31. The process of claim 29, wherein the first solution and the second solution are each an aqueous solution.
32. The process of claim 29, wherein the first solution and the second solution are each an ionic solutions.
33. The process of claim 29, further comprising separating the organic layer from the aqueous or ionic layer.
34. The process of claim 33, further comprising neutralizing the organic layer with a base.
35. The process of claim 35, further comprising drying and optionally filtering the organic layer.
36. The process of claim 35, further comprising concentrating the organic layer to provide ethyl diazoacetate which is less than about 30% by weight organic solvent.

37. The process of claim 36, wherein the ethyl diazoacetate is less than about 15% by weight organic solvent.

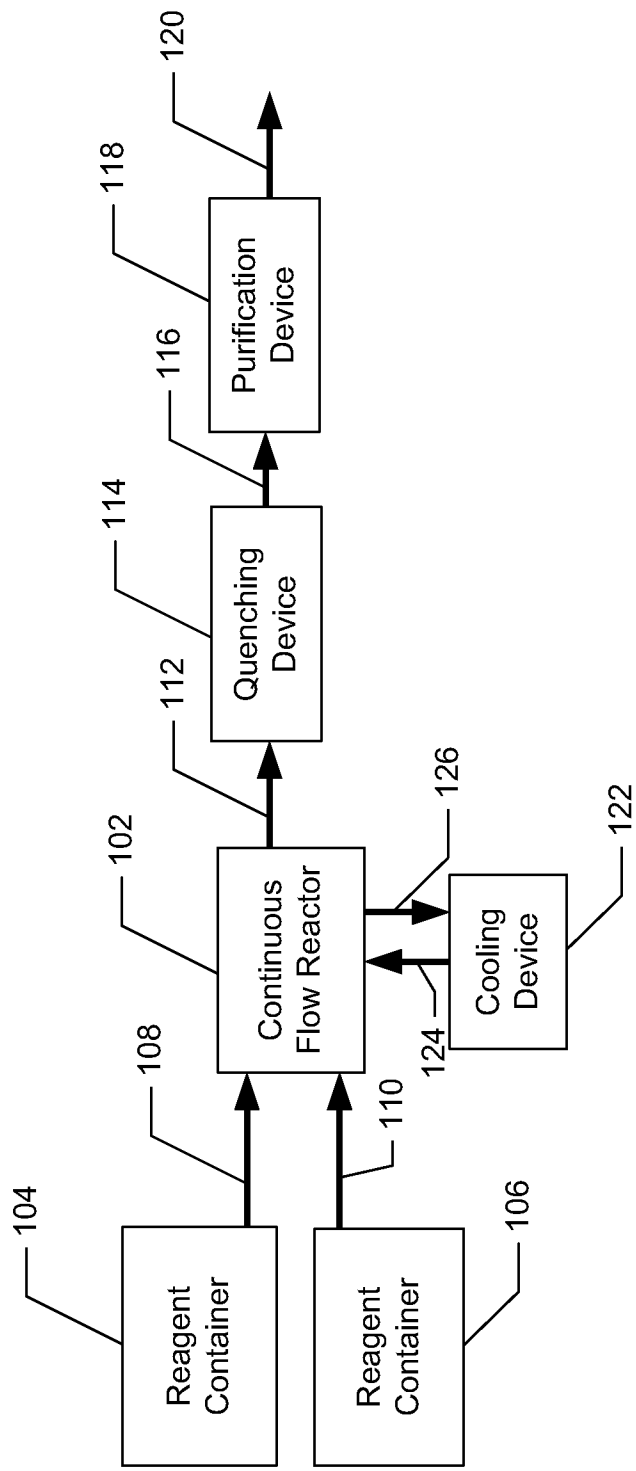


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/28741

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07C 245/00 (2012.01)

USPC - 534/558

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)

USPC - 534/558 (see search terms below)

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

USPC - 514/564; 514/664; 534/579 (see search terms below)

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

USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: process, preparation, alkyl diazoacetate, alkyl ester, glycine, acid salt, hydrogen chloride salt, acid catalyst, alkali metal nitrite, sodium nitrite, organic solvent, methylene chloride, ethyl diazoacetate, continuous process, reactor, aqueous solution, diazotization, glycine ester, hydrochloride. I

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,897,478 A (SHIM et al.) 29 July 1975 (29.07.1975), col 2, ln 1-50; col 3, ln 4-67; col 4, ln 1-6; col 5, ln 22-38.	1-37
A	US 2,490,714 A (SEARLE) 13 May 1947 (13.05.1947), col 1, ln 1 - col 4, ln 14.	1-37

☐ Further documents are listed in the continuation of Box C.

* 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

05 June 2012 (05.06.2012)

Date of mailing of the international search report

19 JUN 2012

Name and mailing address of the ISA/US

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