(54) Title: ALCOHOL-MEDIATED ESTERIFICATION OF CARBOXYLIC ACIDS WITH CARBONATES

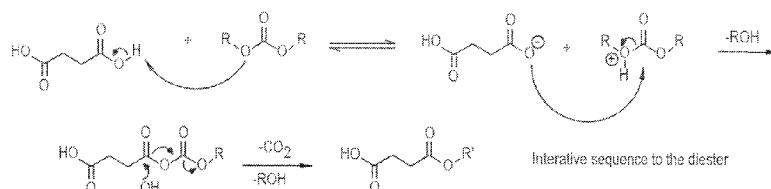

Fig. 1

(57) Abstract: A process for making esters from organic acids by means of reacting a carboxylic acid with dialkylcarbonate in an alcohol-containing solvent without any extrinsic acid or base catalyst is described. A benefit of the preparation process is that it can make the separation and extraction of ester products simpler and more facile vis-a-vis conventional isolation techniques.

ALCOHOL-MEDIATED ESTERIFICATION OF CARBOXYLIC ACIDS WITH CARBONATES

CLAIM OF PRIORITY

The present Applications claims benefit of priority from U.S. Provisional Application No.
61/719,537, filed on 29 October 2012, the contents of which are herein incorporated.

FIELD OF INVENTION

The present invention relates to a chemical process for preparing esters from organic acids.
In particular, the invention pertains to reactions of carboxylic acids with carbonates in a solvent to
produce esters.

BACKGROUND

Esters are an important class of compounds that are encountered in various roles in all areas
of synthetic organic chemistry. General methods of preparing esters start from carboxylic acids which
are directly condensed with alcohol using acid catalysis (Fischer esterification). These prior
esterification methods, in spite of their utility, suffer from several environmental drawbacks. Fischer
esterification is an equilibrium process typically catalyzed by strong, corrosive, mineral acids (e.g.,
pKa <0). The water generated in the reaction has to be continuously removed by azeotroping or by
use of a dehydrative agent or its role countered by use of a large excess of alcohol. Commonly used
alcohols, such as methanol and ethanol, can generate genotoxic alkyl sulphates. Acylation and
alkylation are inherently polluting because of salt generation, the use of toxic catalysts and reagents
and use of chlorinated solvents.

In recent years chemists have looked to other ester preparation approaches that can be less
polluting and more environmentally friendly. Dimethylcarbonate (DMC) has gained prominence as a
"green" reagent in either acid- or base-catalyzed methylation or methoxycarbonylation of anilines,
phenols, active methylene compounds and carboxylic acids. The attraction of DMC lies in the fact
that it is non-toxic and gives rise only to CO_2 and methanol (recoverable) as the byproducts.

Several groups have proposed different approaches of using DMC in base-catalyzed
methylation or methoxycarbonylation of anilines, phenols, active methylene compounds and
carboxylic acids. Others have proposed a chemoselective process for the esterification of carboxylic
acids under mild (~80-90°C) and solvent-free conditions using DMC and diethylcarbonate (DEC)
under acid catalysis. (See, Vamsi V. Rekha et al., "A Simple, Efficient, Green, Cost Effective and
Chemoselective Process for the Esterification of Carboxylic Acids," ORGANIC PROCESS RESEARCH &
DEVELOPMENT, Vol. 13, No.4, 769-773 (2009).) The process requires the use of strong acids (i.e.,
pKa <0) such as H_2SO_4, or p-toluenesulfonic acid (PTSA), or mild acids such as m-toluic acid (MTA),
which requires a downstream neutralization step prior to purification.

Another issue with current esterification reactions of organic acids with DMC is that they are often performed in dimethylformamide (DMF), which can be troublesome in post-synthesis downstream processing and purification, because of DMF's high boiling point (e.g., ~153°C) and propensity to decompose over time, which can lead to formation of highly toxic and reactive

5   dimethylamine. This contamination of the desired ester products can be costly and harmful.

In view of the foregoing disadvantages a new process of esterification is needed, that can eliminate or minimize the issues associated with esterification reactions that depend on an extrinsic catalyst.

10   SUMMARY OF THE INVENTION

The present invention provides a method of preparing esters. The method involves the reaction of an organic acid with a dialkylcarbonate in the presence of an alcohol-containing solvent and without either an extrinsic acidic or basic catalyst species. The method further comprises isolating the corresponding esters. The organic acid is a mono-, di-, tri-carboxylic acid or

15   combination of such organic acids. The solvent is composed of an alcohol, a mixture of different alcohols, or a combination of an alcohol and a non-alcoholic species. The alcohol functions as a mediating agent in the reaction between the dialkylcarbonate and organic acid. Absent are an extrinsic acid or a base catalyst, as the inherent nucleophilicity of the alcohol drives the ester synthesis. Depending on the reaction species, one can produce monoesters, diesters, or triesters

20   separately, or mixtures thereof in various combinations.

In another aspect the present invention relates to an ester compound formed from a reaction of a carboxylic acid with a carbonate in an alcohol-containing solvent without the presence of either an acid or base catalyst.

Additional features and advantages of the present methods will be disclosed in the following

25   detailed description. It is understood that both the foregoing summary and the following detailed description and examples are merely representative of the invention, and are intended to provide an overview for understanding the invention as claimed.

                                      BRIEF DESCRIPTION OF FIGURES

30   FIG. 1 is an illustration of an esterification reaction according to an iteration of the present process.

FIG. 2 is an illustration of a rate-limiting step for *in-situ* carbonate metathesis.

FIG. 3 shows a set of esterification reactions in which various carboxylic acids are reacted with methylcarbonate in methanol, according to an embodiment of the present invention.

35   FIG. 4 shows a set of esterification reactions in which various carboxylic acids are reacted with diethylcarbonate in ethanol, according to an embodiment of the present invention.

FIG. 5 shows a comparative set of esterification reactions in which levulinic acid is reacted in neat carbonates without an alcoholic solvent.

DETAILED DESCRIPTION OF THE INVENTION

Section I – Description

In the present disclosure, we describe a facile, effective method of preparing esters from organic acids using environmentally friendly or so-called "green," non-toxic dialkylcarbonates (e.g., dimethyl or diethylcarbonates) in an alcoholic solvent (e.g., methanol or ethanol). The process of ester synthesis involves an alcohol-mediated reaction between an organic acid and a carbonate without the presence of either an extrinsic acid or base catalyst, conducted over relatively short reaction times. This approach is unprecedented in that no additional extrinsic acid or base catalysts are necessary to effect the esterification. Esterification of an organic acid with a dialkylcarbonate according to the present process results in high conversion rates (e.g., $\geq$ 50%) of the organic acid into its corresponding organic acid alkyl esters in relatively high yield (e.g., $\geq$ 35%). The alkyl esters can be easily isolated from the reaction mixture without need for neutralization, such as by means of at least fractional distillation, chromatography, or both. This process is achieved with a minimal amount of side products.

Although not bound by theory, Figure 1 presents an illustration of a proposed, non-limiting mechanism for the present esterification reaction. In the proposed mechanism, the organic acid serves a dual role in the reaction. The organic acid itself serves, first, to activates the carbonate, and second, as a chemical reactant. Self-catalysis by the organic acid circumvents the need for an external catalyst. Additionally, the mechanism shows that an alcohol solvent/co-solvent serves as a reagent in the irreversible step of decomposition of the putative anhydride structure resulting in the formation of the product and CO_2.

In general, the present esterification reactions take advantage of solvolysis, in which the solvent serves as a reagent, driving the reaction forward by virtue of its great excess. For the esterification to proceed according to the present process, the solvent in the reaction is an alcohol. Solvolytic reactions entail nucleophilic substitutions (i.e., reactions in which an atom or a group of atoms in a molecule is replaced by another atom or group of atoms), where the electron rich solvents act as nucleophiles that add to then force the elimination of small molecules or group from the substrate.

Unlike conventional esterification reactions, in the present method the alcohol-containing solvent does not function according to traditional nucleophile substitution mechanisms, in which the R-substituent of the alcohol directly displaces a leaving group. Not to be bound by theory, Figure 2 illustrates a putative rate-limiting step of the present esterification reaction, which involves an *in-situ* generation of alkyl carbonates from dialkylcarbonates via a metathesis process, in which an anhydride ester is formed. This transient intermediate species in an intermolecular conversion rapidly

decomposes in the presence of alcohol to a corresponding alkyl ester with the release of CO_2 and a molar equivalent of alcohol. The solvent-metathesized carbonate is the statistically favored product.

This result suggests that the alcohol species drives the ester formation through the decomposition of the anhydride intermediate, not the carbonate itself, as whatever carbonate one may start with will be altered depending on which kind of alcohol is used. In general, when carboxylic acids are reacted with a dialkylcarbonate in a corresponding alkyl alcohol, the alkyl-group of the alcohol appears to control which ester species is generated. For instance, when the alkyl-group of the dialkylcarbonate is different from that of the alcohol (e.g., DMC with ethanol) the resulting ester will predominately have alkyl groups similar to that of the alcohol (i.e, diethyl-ester). Hence, the presence of an alcohol-containing solvent is important for this process. The esterification reaction can be driven by an alcohol solvent alone or a mixed solvent containing an alcohol and a non-alcoholic species, and requires no extrinsic acid or base catalysts.

It appears that a greater amount of alcohol in excess of the amount of carbonate in a reaction will help drive the esterification to completion. Hence, in certain embodiments the amount of alcohol present is about 1.5- to 3-fold excess of the stoichiometric amount of carbonate. In other embodiments the amount of alcohol used is about 2- to 4-fold, or desirably about 5- to 7- or 10-fold excess of the stoichiometric amount of carbonate.

The stoichiometric amount of carbonate used in the reaction should be in excess equivalents of the number of carboxyl groups of the organic acid. At minimum the carbonate should be about 1.5 or 2 equivalents per carboxyl group. Typically, the amount of carbonate is about 2.5 equivalents or more, more typically about 3 to about 5 or 7 equivalents per carboxyl group.

The present esterification reaction of carboxylic acid with dialkylcarbonate is performed typically in the liquid phase, in an alcohol-containing solvent. The particular amount of alcohol and species of alcohol may vary. The solvent may be composed entirely (i.e., 100%) of an alcohol or a mixture of different alcohols, or may comprise a mixture of an alcohol and a non-alcoholic species (e.g., an alcohol and CO_2 or carbonate mixture, which can generate *in situ* an active reagent). A certain amount of alcohol species in the solvent is required to perpetuate higher yields of the corresponding di-/mono-esters. The alcohol concentration in the solvent should be at least about 5% to about 10% by wt. of the solution.

A mixed solvent of alcohol and non-alcoholic species can produce a good yield of esters. The non-alcoholic component of the solvent can include an organic solvent, such as: carbonate/CO_2, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, tetrahydrofuran (THF), acetone, N-methyl-2-pyrrolidone (NMP), chloroform, ethyl acetate, provided that the organic acids are at least partially soluble within them at the temperatures of the reaction.

For instance, when a mixed-solvent or blended system of DMF/alcohol, such as methanol, is used in a 1:1 ratio, such as in Examples 7 and 20 of Table 3, the mixed solvent blend can help enhance substrate solubility for carbonate species that have a high molecular weight. In another
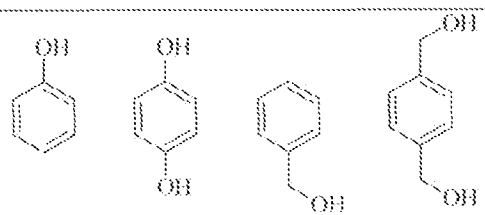
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example, a reaction mixture is prepared with CO_2 and methanol with a heterogeneous catalyst to generate a reaction product containing DMC and methanol. This reaction product can be part of a cost efficient and self-sustaining reagent system, and allows one to avoid the need to synthesis pure DMC. (For more detail about this process of converting CO_2 and methanol to DMC, see: Michael A. Pacheco, *et al.*, *"Review of Dimethyl Carbonate (DMC) Manufacture and Its Characteristics as a Fuel Additive."* ENERGY & FUELS 1997, 11, 2-19; Masayoshi Honda, *et al.*, *"Catalytic Synthesis of Dialkyl Carbonate from Low Pressure CO_2 and Alcohols Combined with Acetonitrile Hydration Catalyzed by CeO_2,"* CATALYSIS A: GENERAL 384 (2010) 165-170; or Masayoshi Honda, *et al.*, *"Ceria-Catalyzed Conversion of Carbon Dioxide into Dimethyl Carbonate with 2-Cyanopyridine."* CHEMSUSCHEM, v.6, issue 8, pp. 1341-1344 Aug. 2013, the contents of each are incorporated herein by reference.)

Any liquid alcohol with R-groups having one to 12 carbons, or more, can serve as the solvent (reagent). The R-groups can be saturated, unsaturated, or aromatic. Alcohols such as methanol, ethanol, propanol, or butanol are more typical in view of their common availability, inexpensiveness, and mechanistic simplicity in the esterification reaction. Table 1 shows non-limiting examples of some unsaturated and aromatic alcohols, which represent alternative species including their various permutations and derivatives. These alkene, alkyne, and aromatic alcohols are commercially available and relatively inexpensive.
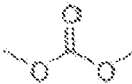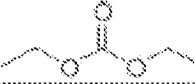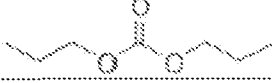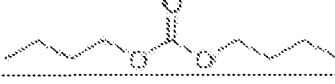
TABLE 1. – Unsaturated & Aromatic Alcohols

The particular choice of alcohol species can determine the kind of ester species generated. In certain embodiments, the alcohol may have an R-group different from that of the alkyl group in the dialkylcarbonate. For instance, when the alkyl group in the diakylcarbonate is a methyl group and the alcohol is an ethyl group. Alternatively, the alcohol species can have an R- group with an identical number of carbon atoms as that of the diaklylcarbonate, such as ethanol reacting with diethylcarbonate.

Various alkylcarbonate species can be used in the esterification reaction according to the present process. The alkyl group in the dialkylcarbonate may have any number of carbon atoms, for instance, from 1 or 2 to 18 or 20 carbon atoms, typically between 1 and 15 carbon atoms, more typically between 1 and 10 carbon atoms. Preferably, the alkyl group has 1 to 6 carbon atoms. The alkyl group may, for example, be methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, pentyl, isopentyl, hexyl, or isohexyl. Preferably, the alkyl is methyl or ethyl. Table 2 provides non-limiting examples of common dialkyl carbonate species, such as dimethylcarbonate (DMC), diethylcarbonate (DEC), dipropylcarbonate (DPC), or dibutylcarbonate (DBC), and their respective molecular weights and boiling points. For reasons of cost, common availability and ease of handling, dimethylcarbonate or diethylcarbonate are the carbonate species employed typically, but other dialkylcarbonate species may also be used.

TABLE 2. - Carbonates

Dialkylcarbonate	Boiling Pt.	Molecular Wt.	Structure
Dimethylcarbonate (DMC)	90°C	90.08 g/mole	
Diethylcarbonate (DEC)	126°C – 128°C	118.13 g/mole	
Dipropylcarbonate (DPC)	167°C – 168°C	146.18 g/mole	
Dibutylcarbonate (DBC)	207.2°C at 760 mmHg 95°C at 15 mm Hg	174.24 g/mole	

One can use a variety of different organic acids, for example, selected from: a) monocarboxylic acids: formic acid, acetic acid, propionic acid , lactic acid, butyric acid, isobutyric acid, valeric acid, hexanoic acid, heptanoic acid, decanoic acid, lauric acid, myristic acid, and C14-C18 fatty acids; b) dicarboxylic acids: 2,5-furandicarboxylic acid (FDCA), fumaric acid, itaconic acid, malic acid, succinic acid, maleic acid, malonic acid, glutaric acid, glucaric acid, oxalic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, dodecanedioic acid, glutaconic acid, ortho-phthalic acid, isophthalic acid, terephthalic acid; or c) tricarboxylic acids: citric acid, isocitric acid, aconitic acid, tricarballylic acid, and trimesic acid. Desirably, the organic acid is a dicarboxylic or tricarboxylic acid. In certain preferred embodiments, the carboxylic acid can be selected from one or more of the following: succinic acid, malic acid, citric acid, levulinic acid, or adipic acid. As used herein an organic acid may be either a carboxylic acid or an amino acid.

The amount of reagents used in each reaction is adjusted to meet the requirements of the different organic acids. In other words, a mono-acid will need one equivalent of reagents, while a di-acid will use two equivalents, and a tri-acid will use three equivalents.

Typically, the reactions are performed within a time period not exceeding about 24 hours, often not exceeding about 10 or 12 hours, or preferably within about 6 or 8 hours, and more preferably within about 4 or 5 hours. For about each hour of increase in the duration of the reaction, the amount yield of ester product can improve about 5-10%.

The temperatures at which the esterification reaction is conducted may vary considerably, but usually the reaction temperature is in a range from about 130°C to about 230°C, depending on the species of organic acid and dialkylcarbonate used in the reaction, in an inert atmosphere such as N₂. Typically, the temperature is in a range from about 140°C or 150°C to about 215°C or 220°C. In certain embodiments the carboxylic acid and carbonate are reacted at a temperature between about 150°C or 160°C to about 208°C or 215°C. Particular examples involve reactions at a temperature between about 165°C or 168°C to about 205°C or 212°C. In other examples, the temperature is in a range from about 170°C or 175°C to about 200°C or 210°C; particularly, from about 180°C or 185°C to about 190°C or 195°C.

Since the temperatures required to obtain good results in reasonable reaction times from an industrial point of view are generally higher than 120°C, and since the dialkylcarbonate (e.g., DMC, DEC, DPC, DBC) boils under such temperature ranges, the alkylation reactions are executed in an apparatus capable of bearing the required pressures.

The pressures at which the reaction is conducted are similarly susceptible to variation. Atmospheric and super-atmospheric pressures are generally applied, depending on the vapor pressure of the particular solvent at a particular temperature in the operative temperature range. Typically, the pressure is in a range from about 145 psi to about 950 psi; more typically from about 150 psi or 155 psi to about 900 psi or 920 psi (gauge). In certain examples the pressure is between about 160 psi and about 650 psi, or about 180 psi to about 620 psi. For instance, the vapor pressure of methanol is about 293.9 psi or 587.8 psi, respectively, at about 167.8°C or 203.5°C. Ethanol, for example, has a vapor pressure of about 295 psi and 580 psi, respectively, at about 185°C and 212°C.

According to the present process, one is able to achieve at least 50% conversion of a particular carboxylic acid to its corresponding mono-, di-, or tri-esters. Typically, the acid conversion rate is at least about 55%. More typically, the acid conversion rate is between about 60% and about 100%. Desirably, one is able to achieve at least 70% conversion. In some reactions, at least 50% of the organic acid is converted to a combined yield of monoesters and di-esters. Usually, the combined monoester and di-ester conversion rate is about 65% or greater. With optimization, complete conversions of carboxylic acids to their corresponding mono- and/or di-esters can be accomplished under the reaction conditions. The reaction can be performed in either a batch or continuous reaction process.

A principal advantage of the present method of esterification derives from the circumvention of added catalyst to effect complete acid or ester conversions. A corollary to this benefit is the simplification of downstream separation process for the reaction products in comparison to

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conventional techniques. One can eliminate a conventionally necessary downstream step of pH adjustment prior to purification. Moreover, the avoidance of either an extrinsic acidic or alkaline catalyst with the present synthesis process, one need not worry about the effects that acids or bases present in the distillation columns and one can recycle the distillation bottoms product back into the reaction.

The different organic acid esters produced in the esterification reaction can be isolated from the reaction mixture using various techniques such as by means of distillation or acid-base extraction. For instance, one can separate the mono and diesters, which tend to have boiling point of about 200°C or greater, from lower boiling solvents by means of simple distillation, or use an acid-base extraction to precipitate the carboxylate, and then regenerate the organic acid with a strong acid (pKa <0, e.g., HCl).

Section II – Examples

According to the present esterification process, it is probable that in reactions involving diacids formation of monoesters would dominate during the initial stages of the reaction primarily due to statistics. Equation (1) represents an example of this mechanism involving a reaction of succinic acid with a diethylcarbonate in ethanol. According to the mechanism, if one di-acid molecule collides with two molecules of the carbonate, the di-ester would form. Statistically, however, it would be more likely that one molecule of the di-acid collides with one molecule of the carbonate, thus generating the monoester. Over time, the monoester would convert to corresponding di-esters.

Eq. (1)
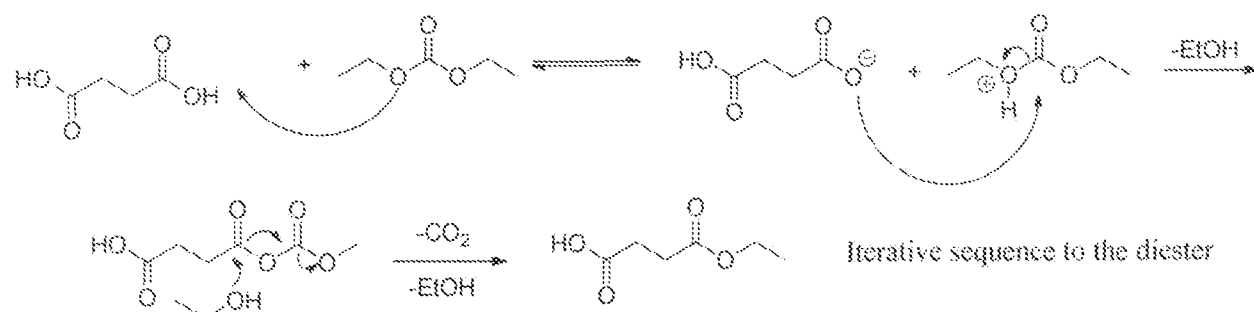
The ratio of monoesters to diesters produced can vary depending on the duration and temperature of the esterification reaction. Early in the reaction (i.e., 0-1 hours), the ratio significantly favors the monoester species (e.g., about 95:0.5). The ratio is about 4:1 after about 3-4 hours, and about 1:1-1:2.5 (depending on the acid and conditions) after 5 hours. This ratio would be about 1:3 or 1:4 after about 6-7 hours and about 0.5:95 after about 8-10 hours. Repeating these reactions will generate the di-ester or tri-ester of the corresponding di- or tri-acids.

Table 3 summarizes a number of comparative examples and inventive examples. In Comparative Examples 1 and 2, when an organic acid (e.g., succinic acid or levulinic acid) is reacted

with an alcohol solvent alone, virtually no ester is produced, and the acid remains largely unreactive. When the organic acid is reacted with a dialkyl carbonate in DMF solvent, as in Comparative Examples 3 and 4, the acid was again largely unreactive and generated a yield from about 0 wt.% to about 17 wt.% of ester.

When the esterification reaction is run without the presence of an alcohol, we observe very little to no conversion of the carboxylic acid to its corresponding mono-ester, di-ester, tri-ester, or polyester. In the comparative examples, esterification reactions conducted neat in carbonate solvent resulted in negligible conversions of acid to ester product, such as in Comparative Examples 5 and 6 (i.e., levulinic acid ~10% wt. methyl esterification with DMC; ~1.1% wt. ethyl esterification with DEC). Hence, alcohols appear to be an important reagent in the reaction so as to obtain a high-yielding esterification process (e.g., diester yield of ≥ 35%).

In contrast, the present esterification method can work well with a variety of different organic acids. In the examples conducted according to the present esterification reactions, we demonstrate that one can produce mono-, di- or tri-esters by means of reacting a corresponding carboxylic acid and dialkyl carbonate in an alcoholic solvent. Reacting five different carboxylic acids (i.e., mono-, di- and tri-acids: levulinic, succinic, malic, adipic, and citric acids) and a combination of dialkyl carbonate species, the examples show that esters from each acid and carbonate combination can be prepared in relatively good yields (e.g., ≥ 45% or 50%) and with specificity (e.g., up to about ~79% ± 3% diester). The amount of ester produced and conversion of the acid are significantly greater than, e.g., 90%-100% conversion, up to about 80% yield vis-à-vis that of the comparative examples. Depending on particular reaction parameters, such as the temperature, pressure and duration of the esterification reaction, esters were produced with yields between about 43% or 45% and 75% or 80% by weight (e.g., 50% or 60% by wt.). With optimization of the process one can achieve even more favorable conversation rates and yields (e.g., about 90%, 95%, 97%, or 98% by weight).

TABLE 3. - Experimental Results with Various Acid Species

Example	Acid	Carbonate	Solvent	Ester	Ester Yield (%)	Acid Remaining (%)
Comp.1	Succinic	None	methanol	Dimethylsuccinate	0.0	90.8
Comp.2	Succinic	None	ethanol	Diethylsuccinate	0.0	95.4
Comp.3	Succinic	DEC	DMF	Diethylsuccinate	0.0	84.1
Comp.4	Succinic	DMC	DMF	Dimethylsuccinate	16.3	52.3
Comp.5	Levulinic	DMC	DMC (neat)	Methyllevulinate	10.0	0.0
Comp.6	Levulinic	DEC	DEC (neat)	Ethyllevulinate	1.1	17.2
1	Succinic	DMC	Methanol	Dimethylsuccinate	59.7	0.0
2	Succinic	DMC	Ethanol	Diethylsuccinate	56.5	8.7
3	Succinic	DMC	Ethanol	Diethylsuccinate	60.2	0.0
4	Succinic	DEC	Ethanol	Diethylsuccinate	53.9	0.0
4	Succinic	DEC	Methanol	Dimethylsuccinate	57.4	8.9
6	Succinic	DEC	Methanol	Dimethylsuccinate	61.5	0.0
7	Succinic	DMC	Methanol/DMF	Dimethylsuccinate	77.0	0.0
8	Malic	DMC	Methanol	Dimethylmalate	78.5	0.0

9	Malic	DEC	Ethanol	Diethylmalate	69.4	0.0
10	Malic	DMC	Ethanol	Diethylmalate	77.6	0.0
11	Levulinic	DMC	Methanol	Methyllevulinate	70.5	29.3
12	Levulinic	DEC	Ethanol	Ethyllevulinate	46.8	50.8
14	Levulinic	DPC	Ethanol	Ethyllevulinate	45.6	54.7
15	Citric	DMC	Methanol	Trimethylcitrate	71.3	0.0
16	Citric	DEC	Ethanol	Triethylcitrate	45.6	0.0
17	Citric	DMC	Ethanol	Triethylcitrate	55.8	0.0
18	Adipic	DMC	Methanol	Dimethyladipate	39.8	0.0
19	Adipic	DEC	Ethanol	Diethyladipate	35.1	0.0
20	Adipic	DMC	Methanol/DMF	Dimethyladipate	43.3	0.0

DMC = Dimethylcarbonate
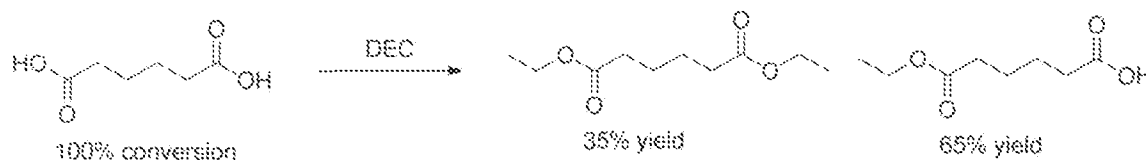DEC = Diethylcarbonate
DPC = Dipropylcarbonate
DMF = Dimethylformamaide

Reaction conditions: 20 g. acid, 5 molar equivalents of DMC/DEC/DPC (2.5 molar eq. in case of levulinic acid), 300 g. solvent reacted at 180°C, 5 h., 200 psi N₂.

The following describe the preparation and reaction of some of the comparative and inventive examples in Table 3 in greater detail.

Example A: Synthesis of Diethyladipate from Adipic Acid, Diethylcarbonate, and Ethanol

Twenty grams adipic acid, 83 mL of diethylcarbonate, and 300 g of ethanol were charged to a stainless steel, 1L Parr reactor body. While stirring mechanically at 1100 rpm, the internal headspace was pressurized to 200 psi N₂ and heated to 180°C for 5h. After this time, the reactor body was cooled in a water bath until reaching room temperature and pressure released. The homogeneous solution was poured into a storage flask and a sample of this quantitatively analyzed for diethyladipate, mono-methyladipate and adipic acid.

Example B: Synthesis of Dimethylmalate from Malic Acid, Dimethylcarbonate, and Methanol
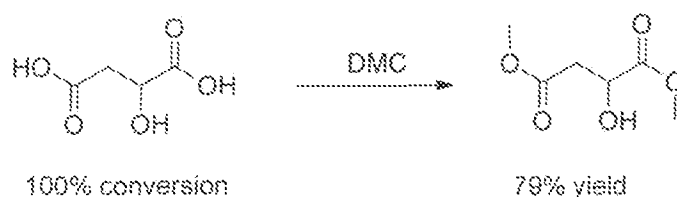
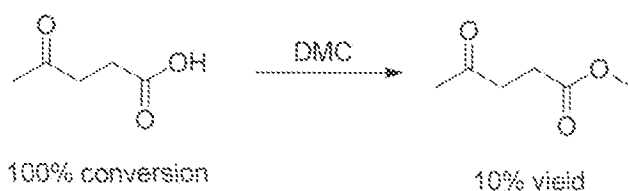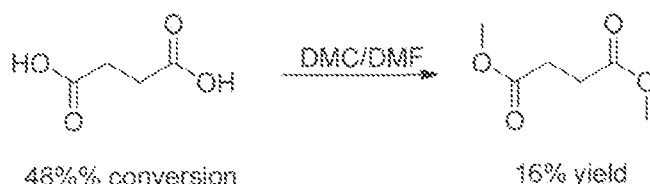Twenty grams malic acid, 63 mL of dimethylcarbonate, and 300 g of methanol were charged to a stainless steel, 1 L Parr reactor body. While stirring mechanically at 1100 rpm, the internal headspace was pressurized to 200 psi N₂ and heated to 180°C for 5h. After this time, the reactor body was cooled in a water bath until reaching room temperature and pressure released. The homogeneous
5   solution was poured into a storage flask and a sample of this quantitatively analyzed for dimethylmalate and malic acid. Based on findings with adipic acid, the absence of malic acid in the product mixture and 79% yield of diester adduces the remaining 21% of product mixture as the corresponding mono-ester.

10   **Example C:** Synthesis of Methyllevulinate from Levulinic acid and Dimethylcarbonate

100% conversion   10% yield

Twenty grams levulinic acid and 300 g dimethylcarbonate were charged to a stainless steel, 1 L Parr
15   reactor body. While stirring mechanically at 1100 rpm, the internal headspace was pressurized to 200 psi N₂ and heated to 180°C for 5h. After this time, the reactor body was cooled in a water bath until reaching room temperature and pressure released. The homogeneous solution was poured into a storage flask and a sample of this quantitatively analyzed for methyllevulinate and levulinic acid.

20   **Example D:** Synthesis of Dimethylsuccinate from Succinic acid, Dimethylcarbonate, and Dimethylformamide

48%% conversion   16% yield

25   Twenty grams succinic acid, 72 mL dimethylcarbonate and 300 g of DMF were charged to a stainless steel, 1 L Parr reactor body. While stirring mechanically at 1100 rpm, the internal headspace was pressurized to 200 psi N₂ and heated to 180°C for 5h. After this time, the reactor body was cooled in a water bath until reaching room temperature and pressure released. The homogeneous solution was poured into a storage flask and a sample of this quantitatively analyzed for dimethylsuccinate and
30   succinic acid.

        The accompanying Tables 4-7 summarize examples of the synthesis of di-esters from dimethyl carbonate and diethyl carbonate using succinic acid and either methanol or ethanol solvent.

In Table 4, succinic acid is reacted with dimethylcarbonate in ethanol at a temperature of about 180°C in an inert nitrogen atmosphere at a pressure of 500 psig. The di-ester product is predominately diethylsuccinate at about 56.5% yield with minimal dimethylsuccinate at 0.1% yield. A small amount of succinic acid remained unreacted. In contrast, in Table 5, succinic acid is reacted with diethylcarbonate and methanol at 190°C under similar conditions. The di-ester product is overwhelmingly dimethylsuccinate at about 57.64% yield, with minimal diethylsuccinate at 0.0% yield. Table 6 presents a reaction of succinic acid with diethylcarbonate in ethanol at 190°C for 5 hours, which produced diethylsuccinate at about 52.5% conversion. Table 7 summarizes the results of a reaction between citric acid and diethylcarbonate in ethanol at a temperature of 190°C for about 5 hours in an inert atmosphere at a pressure of about 500 psig. The reaction produced triethylcitrate at about 38% conversion. All of the citric acid was consumed. As the examples show in these tables, esterification conducted under mild conditions according to the present process produces various kinds di-esters and tri-esters from different organic acids at relatively good conversion rates. The ester yields will improve with adjustments to increase the reaction time and/or temperatures for optimal results.

Figure 3 presents a series of methyl esterification reactions using various kinds of carboxylic acids with dimethylcarbonate in methanol. Each reaction used 20 g. carboxylic acid, 5 molar equivalents of dimethylcarbonate (DMC) (2.5 equivalents for levulinic acid), 300 g. of absolute methanol, at 180°C, 5h, 200 psi N₂. All acids, except levulinic acid, completely converted in the reaction. Each exhibited high selectivity (e.g., 40%) of the fully esterified target (diester) species. Figures 3A and 3B represent esterification of succinic acid and malic acid, respectively, which produced about a yield of about 60% and 79%, respectively, of the corresponding di-esters. In Figure 3C, about 71% of levulinic acid was consumed in the reaction to produce about 70% yield of the ester. The esterification reaction with adipic acid produced a mixed product of the corresponding mono-ester and di-ester, respectively, at about 60% and 40% yield.

Similar to the reactions in Figure 3, Figure 4 presents a number of reactions in which different ethyl esters of carboxylic acids are prepared with diethylcarbonate in ethanol. The each of the reactions was performed with 20 g. carboxylic acid, 5 molar equivalents of diethylcarbonate (DEC) (2.5 equivalents for levulinic acid, 300 g. ethanol, at 180°C, 5h, 200 psi N₂. Again all acids, except levulinic acid, manifested complete conversion during the respective reactions. The selectivity for each of the esterified targets was very good, at about 35% or greater. Figure 4A shows the esterification of succinic acid, which produced a yield of about 54% of the corresponding di-ester. In Figure 4B, malic acid is also completely consumed and produced a yield of about 69% of the corresponding di-ester. In Figure 4C, about 50% of the levulinic acid is consumed to yield about 47% of the corresponding ester. In Figure 4D, citric acid completely converted to produce about 46% of the tri-ester. Figure 4E shows the reaction of adipic acid to make a mixed product of the

corresponding monoester and di-ester, about 65% and 35%, respectively. The remaining product in each case, excepting levulinic acid, presumably is the mono-ester.

Figures 5A and 5B illustrate comparative examples (entries 5 and 6 of Table 3) in which levulinic acid is reacted, respectively, with diethylcarbonate and dimethylcarbonate without any other solvent being added. The reactions were performed with 50 g. carboxylic acid, 300 g. of diethylcarbonate (DEC) / dimethylcarbonate (DMC) (respectively 5.9, 7.7 molar equivalents), at 180°C, 5h, 200 psi N_2. The reactions in the comparative examples both exhibited relatively high conversion (~80%) of the organic acid, but low yield of ester, which indicates an ineffective method of esterification. The reactions generated a very small amount of ester (~1%) when using DEC, and made a slightly better but still minor amount of ester (≤10%) when using DMC. The difference in yield obtained between the reactions that employed DMC versus DEC is likely a result of steric hindrance to the bimolecular substitution in the reaction.

The present invention has been described in general and in detail by way of examples. Persons of skill in the art understand that the invention is not limited necessarily to the embodiments specifically disclosed, but that modifications and variations may be made without departing from the scope of the invention as defined by the following claims or their equivalents, including other equivalent components presently known, or to be developed, which may be used within the scope of the present invention. Therefore, unless changes otherwise depart from the scope of the invention, the changes should be construed as being included herein.

TABLE 4 – Esterification of Succinic Acid with Dimethylcarbonate in Ethanol

Example:	1
Mass of Succinic Acid (g):	20
Molecular weight succinic acid (g/mol):	118.04
Moles of Succinic Acid	0.17
Molar equivalents of Dimethylcarbonate	5
Mass of Dimethylcarbonate (g)	76.31
Molecular weight Dimethylcarbonate (g/mol)	90.08
Moles of Dimethylcarbonate	0.85
Density of Dimethylcarbonate (g/mL)	1.07
Volume of Dimethylcarbonate (mL)	71.32
Mass of Ethanol (g)	300
Density of Ethanol (g/mL)	0.789
Volume of Ethanol (mL)	380.23
Total Volume (mL)	~451.55
Total Mass (g)	396.31
Reaction Temperature (°C)	180
Reaction Time (h)	5
Initial N$_2$ Pressure (psig)	200
N$_2$ Pressure at 180°C (psig)	500
Molecular weight dimethyl succinate (g/mol)	146.14
Molecular weight diethyl succinate (g/mol)	174.19

Results are in g/L	Dimethylsuccinate (g/L) 0.041	Mass dimethyl succinate (g) 0.0185	Moles dimethyl succinate 0.0001	% Conversion 0.1%
Results are in g/L	Diethylsuccinate (g/L) 36.9	Mass diethylsuccinate (g) 16.6622	Moles diethyl succinate 0.0957	%Yield 56.5%
Results are in g/kg	Succinic Acid Remaining (g/kg) 4.41	Mass Succinic Acid (g) 1.7477	Moles Succinic Acid 0.0148	% Succinic Acid Remaining 8.7%

TABLE 5 – Esterification of Succinic Acid with Diethylcarbonate in Methanol

Example:	1
Mass of Succinic Acid (g)	20
Molecular weight succinic acid (g/mol)	118.04
Moles of Succinic Acid	0.169
Molar equivalents of Diethylcarbonate	5
Mass of Diethylcarbonate (g)	100.31
Molecular weight of diethylcarbonate (g/mol)	118.13
Moles of Diethylcarbonate	0.847
Density of Diethylcarbonate (g/mL)	0.975
Volume of Diethylcarbonate (mL)	103
Mass of Methanol (g)	300
Density of Methanol (g/mL)	0.792
Volume of Methanol (mL)	378.79
Total Volume (mL)	~481.79
Total Mass (g)	420.31
Reaction Temperature (°C)	190
Reaction Time (h)	5
Initial N_2 Pressure (psig)	200
N_2 Pressure at 180°C (psig)	500
Molecular weight diethyl succinate (g/mol)	174.19
Molecular weight dimethyl succinate (g/mol)	146.14

Results are in g/L	Diethylsuccinate (g/L) 0.00	Mass diethyl succinate (g) 0.0014	Moles diethyl succinate 0.0000	% Conversion 0.0%
Results are in g/L	Dimethylsuccinate (g/L) 29.40	Mass dimethylsuccinate (g) 14.1646	Moles dimethyl succinate 0.0969	%Yield 57.64%
Results are in g/kg	Succinic Acid Remaining (g/kg) 4.22	Mass Succinic Acid (g) 1.7737	Moles Succinic Acid 0.0150	% Succinic Acid Remaining 8.9%

TABLE 6 -- Esterification of Succinic Acid with Diethylcarbonate in Ethanol

Example:	1
Mass of Succinic Acid (g)	20
Molecular weight succinic acid (g/mol)	118.04
Moles of Succinic Acid	0.169
Molar equivalents of Diethylcarbonate	5
Mass of Diethylcarbonate (g)	100.31
Moles of Diethylcarbonate	0.847
Density of Diethylcarbonate (g/mL)	0.975
Volume of Diethylcarbonate (mL)	103
Mass of Ethanol (g)	300
Density of Ethanol (g/mL)	0.789
Volume of Ethanol (mL)	380
Total Volume (mL)	~490
Total Mass (g)	420.31
Reaction Temperature (°C)	190
Reaction Time (h)	5
Initial N₂ Pressure (psig)	200
N₂ Pressure at 190°C (psig)	500
Molecular weight diethyl succinate (g/mol)	174.19

	Diethylsuccinate (g/L)	Mass diethyl succinate (g)	Moles diethyl succinate	% Conversion
Results are in g/L	32.00	15.46	0.0888	52.5%

	Succinic Acid Remaining (g/kg)	Mass Succinic Acid (g)	Moles Succinic Acid	% Succinic Acid Remaining
Results are in g/kg	2.3	0.966713	0.0082	4.8%

TABLE 7 – Esterification of Citric Acid with Diethylcarbonate in Ethanol

Example:	1
Mass of Citric Acid (g)	20
Molecular weight succinic acid (g/mol)	192.12
Moles of Citric Acid	0.104
Molar equivalents of Diethylcarbonate	6
Mass of Diethylcarbonate (g)	73.78
Moles of Diethylcarbonate	0.625
Density of Diethylcarbonate (g/mL)	0.975
Volume of Diethylcarbonate (mL)	75.68
Mass of Ethanol (g)	300
Density of Ethanol (g/mL)	0.789
Volume of Ethanol (mL)	380
Total Volume (mL)	~455
Total Mass (g)	393.78
Total Mass (kg)	0.39378
Reaction Temperature (°C)	190
Reaction Time (h)	5
Initial N_2 Pressure (psig)	200
N_2 Pressure at 190°C (psig)	500
Molecular weight diethyl succinate (g/mol)	118.13

Results are in g/L	Triethylcitrate (g/L)	Mass triethylcitrate (g)	Moles triethylcitrate	% Conversion
	32.00	15.46	0.0888	38.0%
Results are in g/kg	Citric Acid Remaining (g/kg)	Mass Citric Acid (g)	Moles Citric Acid	% Citric Acid Remaining
	0	0	0.0000	0.0%

CLAIMS

We Claim:

1. A method of preparing esters, the method comprises: reacting in a reaction mixture an organic acid with a dialkyl-carbonate in the presence of an alcohol-containing solvent without an extrinsic catalyst.

2. The method according to claim 1, wherein said method further comprises isolating said esters by at least fractional distillation, chromatography, or both from said reaction mixture.

3. The method according to anyone of the foregoing claims, wherein said esters are individually monoester, diesters or triesters, or mixtures thereof in various combinations.

4. The method according to anyone of the foregoing claims, wherein said organic acid is selected from: formic acid, acetic acid, propionic acid , lactic acid, butyric acid, isobutyric acid, valeric acid, hexanoic acid, heptanoic acid, decanoic acid, lauric acid, myristic acid, and C_{11}-C_{18} fatty acids, 2,5-furandicarboxylic acid (FDCA), fumaric acid, itaconic acid, malic acid, succinic acid, maleic acid, malonic acid, glutaric acid, glucaric acid, oxalic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, dodecanedioic acid, glutaconic acid, ortho-phthalic acid, isophthalic acid, terephthalic acid, citric acid, isocitric acid, aconitic acid, tricarballylic acid, and trimesic acid.

5. The method according to anyone of the foregoing claims, wherein said organic acid is a dicarboxylic or tricarboxylic acid.

6. The method according to anyone of the foregoing claims, wherein said dialkyl-carbonate is at least one of the following species: dimethylcarbonate (DMC), diethylcarbonate (DEC), dipropylcarbonate (DPC), or dibutylcarbonate (DBC).

7. The method according to anyone of the foregoing claims, wherein said alcohol-containing solvent is: a single alcohol species, or a mixture of different alcohols, or a mixture of an alcohol and other non-alcoholic species.

8. The method according to claim 7, wherein said alcohol in said alcohol-containing solvent is at least saturated, unsaturated, or aromatic.

9. The method according to claim 7, wherein said non-alcoholic species includes at least one of the following: a carbonate/CO_2, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, tetrahydrofuran (THF), acetone, N-methyl-2-pyrrolidone (NMP), chloroform, and ethyl acetate.

10. The method according to anyone of the foregoing claims, wherein said alcohol mediates the formation of said esters.

11. The method according to anyone of the foregoing claims, wherein said alcohol is present in excess of stoichiometric amounts of carbonate.

12. The method according to anyone of the foregoing claims, wherein said organic acid and carbonate are reacted at a temperature between about 130°C to about 230°C, at a pressure in a range from about 145 psi to about 950 psi inert atmosphere.

13. The method according to anyone of the foregoing claims, wherein said organic acid and carbonate are reacted at a temperature between about 160°C to about 215°C.

14. The method according to anyone of the foregoing claims, wherein said organic acid and carbonate are reacted within a time period not exceeding about 24 hours.

15. The method according to claim 14, wherein said organic acid and carbonate are reacted within a time period not exceeding about 12 hours.

16. The method according to anyone of the foregoing claims, wherein said method is able to achieve at least 45% conversion of said carboxylic acid to the ester.

17. The method according to claim 16, wherein said method is able to achieve at least 70% conversion of said carboxylic acid to the ester.

18. A method of esterification comprising: contacting an organic acid and a dialkyl-carbonate in a reaction mixture with an alcohol mediating agent, absent an extrinsic acid or a base catalyst.

19. The method according to claim 18, wherein said alcohol serves as a nucleophile that assists said reaction between said organic acid and said carbonate.

20. The method according to claim 18, wherein at least 45% of said organic acid is converted into a yield of corresponding esters.

21. The method according to claim 20, wherein said esters include either monoesters, diesters, or triesters, or a mixture containing combinations thereof.

22. The method according to claim 18, wherein said organic acid is converted into a corresponding monoester and diester in a ratio of about 95:0.5 to about 0.5:95.

23. The method according to claim 18, wherein a di-ester product is favored.

24. The method according to claim 18, wherein a CO_2 molecule is released from said reaction.

25. The method according to claim 18, wherein said reaction is performed in either a batch or a continuous process.

26. The method according to claim 18, wherein said alcohol is either saturated, unsaturated, aromatic, or a mixture of different alcohol species.

27. The method according to claim 18, wherein said carbonate is at least one: DMC, DEC, DBC, and DPC.

28. An ester compound formed from a reaction of an organic acid with a carbonate in an alcohol-containing solvent without the presence of either an extrinsic acid or base catalyst according to anyone of the foregoing claims.
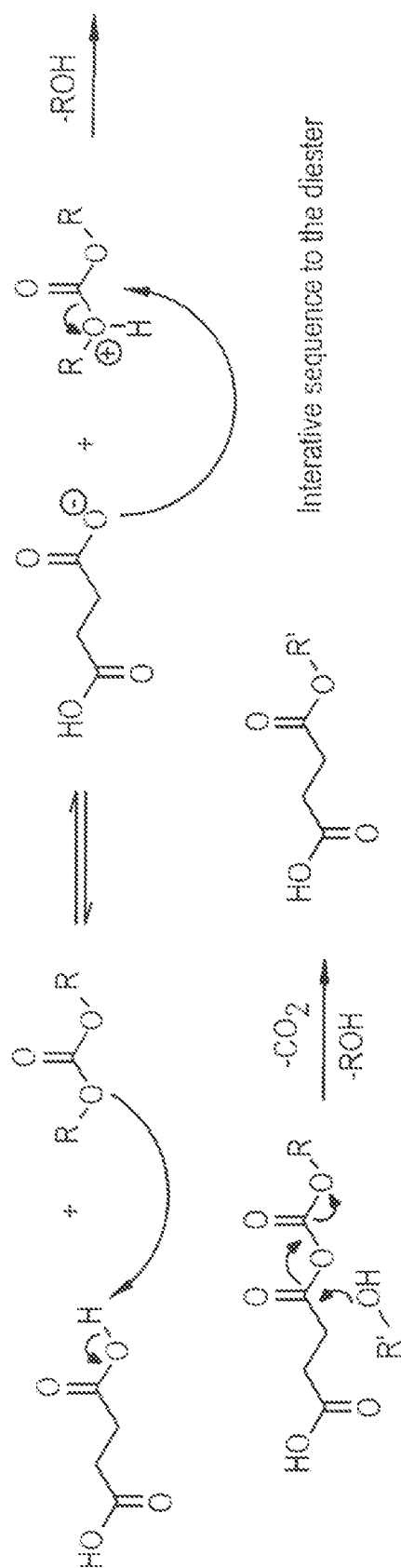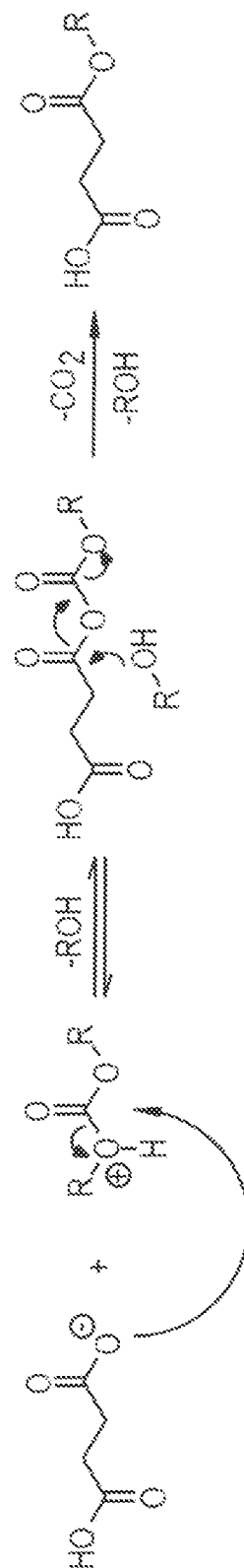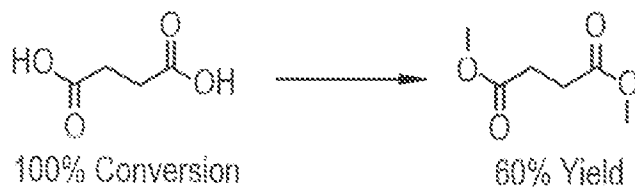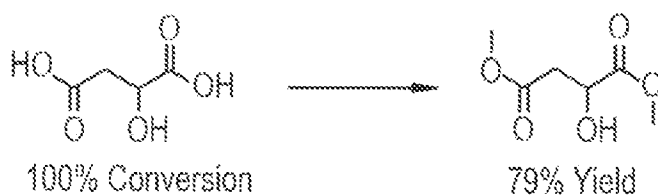
Fig. 1

Fig. 2

A. Succinic Acid
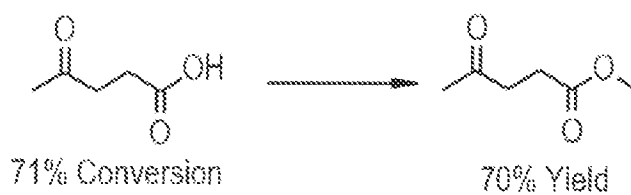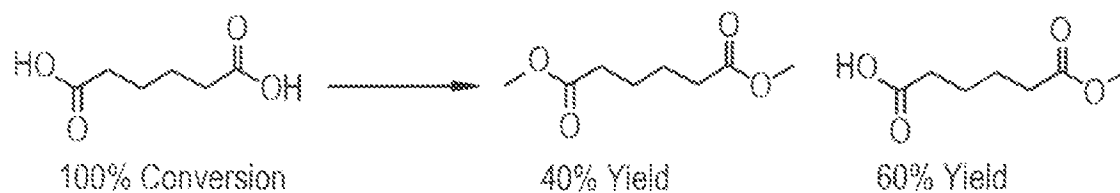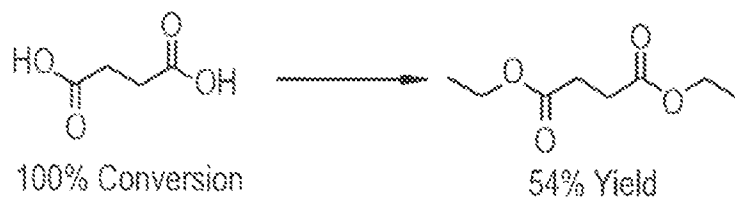
100% Conversion   60% Yield

B. Malic Acid

100% Conversion   79% Yield

C. Levulinic Acid

71% Conversion   70% Yield

D. Adipic Acid

100% Conversion   40% Yield   60% Yield

Fig. 3

A. Succinic Acid

100% Conversion   54% Yield

B. Malic Acid

100% Conversion   69% Yield

C. Levulinic Acid

50% Conversion   47% Yield

D. Citric Acid

100% Conversion   46% Yield

E. Adipic Acid

100% Conversion   35% Yield   65% Yield

Fig. 4

FIG. 5

A.

83% conversion   1% yield

B.

100% conversion   10% yield
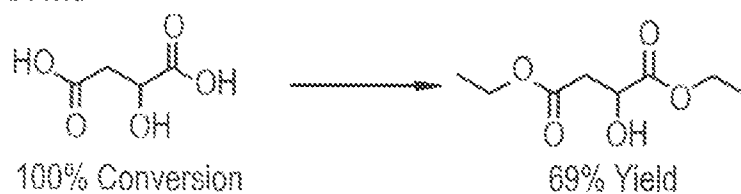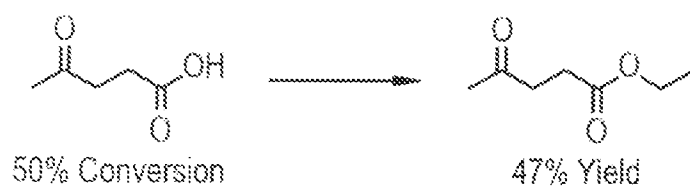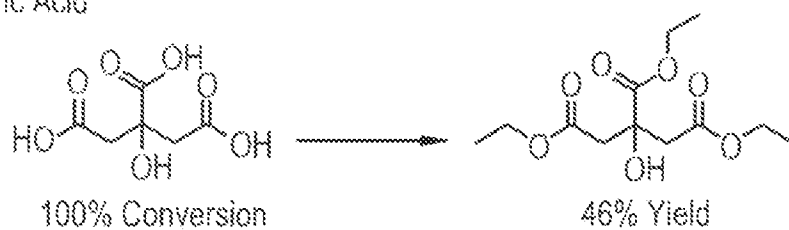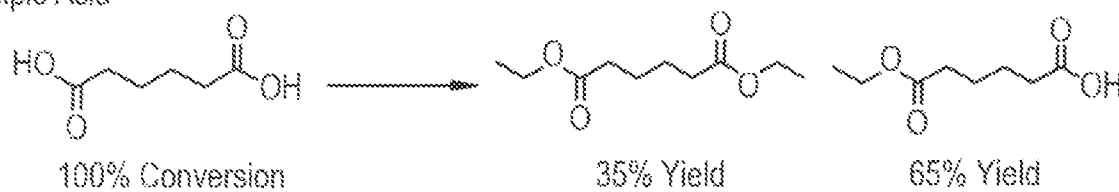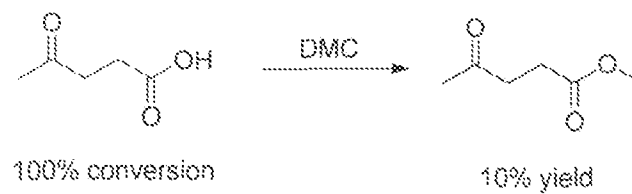
INTERNATIONAL SEARCH REPORT	International application No.
	PCT/US2013/064458

A. CLASSIFICATION OF SUBJECT MATTER

C07C 67/62(2006.01)i, C07C 69/34(2006.01)i

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 67/62; C07C 69/34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: esterification, organic acid, carboxylic acid, dialkylcarbonate, alcohol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WEN-CHUNG SHIEH et al., `Nucleophilic Catalysis with 1,8-Diazabicyclo[5.4.0]undec-7-ene(DBU) for the Esterification of Carboxylic Acids with Dimethyl Carbonate`, J. Org. Chem., Vol. 67, pp. 2188-2191 (2002) See abstract; Scheme 2; and Table 1.	1-3,18-27
A	LETICIA GUERRERO R. et al., `1,2-Dimethylimidazole (DMI) and microwaves in the alkylation of carboxylic acids and phenols with dimethyl and diethyl carbonates`, ARKIVOC, Vol. 2008(xi) pp. 295-306 (2008) See abstract; Scheme 1; and Table 1.	1-3,18-27
A	L. GOOSSEN et al., `Lewis Acids as Highly Efficient Catalysts for the Decarboxylative Esterification of Carboxylic Acids with DialkylDicarbonates`, Adv. Synth. Catal., Vol. 345, pp. 943-947 (2003) See abstract; Scheme 1; Scheme 2 and Table 1.	1-3,18-27
A	ROILA AWANG et al., `Enzymatic Synthesis of Palm Alkyl Ester Using Dialkyl Carbonate as an Alkyl Donors`, Am. J. Appl. Sci., Vol. 7(8), pp. 1083-1086, (2010) See abstract.	1-3,18-27

☐ 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 "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	Date of mailing of the international search report
13 January 2014 (13.01.2014)	**14 January 2014 (14.01.2014)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea Facsimile No. +82-42-472-7140	KIM, Jong Ho Telephone No. +042 481 8657

Form PCT/ISA/210 (second sheet) (July 2009)

Box No. II   Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 8, 9, 15, 17
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
   Claims 8, 9, 15, 17 are unsearchable because they are worded in reference to multiple dependent claims.

3. ☒ Claims Nos.: 4-7, 10-14, 16, 28
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III   Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date

None