

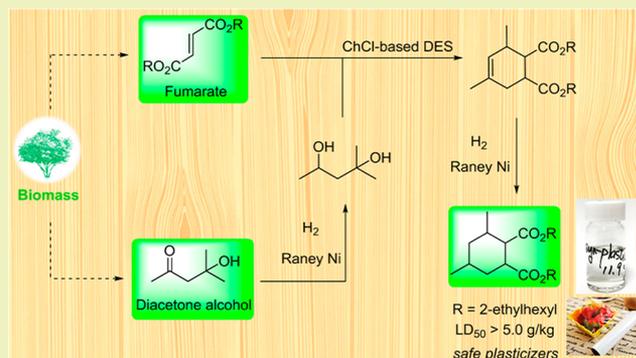
Production of 1,2-Cyclohexanedicarboxylates from Diacetone Alcohol and Fumarates

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Supporting Information

ABSTRACT: 1,2-Cyclohexanedicarboxylates, which are one of the most commonly used plasticizers in the poly(vinyl chloride) (PVC) industry, are generally prepared via the oxidation/esterification/hydrogenation of *o*-xylene (or naphthalene). Herein, we develop an alternative route toward cyclohexane-based plasticizers using diacetone alcohol and fumarates as the starting materials. The process includes a mild Raney Ni-catalyzed hydrogenation of diacetone alcohol, a one-step dehydration/Diels–Alder reaction of resulting 2-methyl-2,4-pentandiol and fumarates in a choline chloride (ChCl) based deep eutectic solvent (DES), and a further Pd/C-catalyzed hydrogenation. The toxicological tests indicate that the as-synthesized di(2-ethylhexyl) 3,5-dimethylcyclohexane-1,2-dicarboxylate can serve as a safe plasticizer for PVC materials.

KEYWORDS: Plasticizers, Diacetone alcohol, Fumarates, Dehydration/Diels–Alder reaction, Hydrogenation, 1,2-Cyclohexanedicarboxylate



INTRODUCTION

Plasticizers are important additives that can improve the flexibility, durability, and workability of poly(vinyl chloride) (PVC), thus enabling their applications in various aspects, including construction materials, consumer goods, transportation, packaging, wires and cables, furnishings, and medical devices.¹ As estimated, the global consumption of plasticizers in 2014 reached up to 8 million metric tons.² So far, phthalates (e.g., di(2-ethylhexyl)phthalate, DEHP/DOP) dominate the plasticizers market.³ However, because of the volatility of phthalates, it was found that exposure to phthalate-containing plastics can cause adverse health effects on humans, children, and infants in particular.⁴ In this respect, many countries have already banned phthalates in those products with close human contact, such as medical tubing, intravenous bags, plastic wrap, childcare articles, toys, and vinyl flooring.⁵ The stringent regulations and increasing health concerns from the consumers, have led to a high demand of safe substitutes for traditional phthalates. According to IHS Markit's latest plasticizers report, global consumption of nonphthalate plasticizers will grow at an average annual rate of 5.8% in the next few years.⁶ Among

those nonphthalate plasticizers, 1,2-cyclohexanedicarboxylates (e.g., diisononyl 1,2-cyclohexanedicarboxylate, DINCH) are one of the most commonly used alternatives in the PVC industry.⁷ These compounds are industrially prepared by oxidation/esterification/hydrogenation of petroleum-derived *o*-xylene (or naphthalene) (Scheme 1).

In recent years, biomass, as an abundant, inexpensive, and carbon-neutral natural resource, has proved to be a promising feedstock for the production of value-added chemicals,^{8–21} which can provide alternatives to the widely used fossil-based chemical processes. In this regard, exploiting potential bioroutes to 1,2-cyclohexanedicarboxylates is highly appealing. Very recently, our group reported a two-step procedure for the preparation of 1,2-cyclohexanedicarboxylates from formaldehyde, crotonaldehyde, and fumarates.²² Later, Lu and Xu et al. disclosed that erythritol and fumarates could undergo a sequential deoxydehydration/Diels–Alder (D-A) reaction/

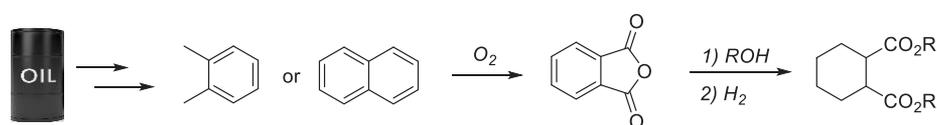
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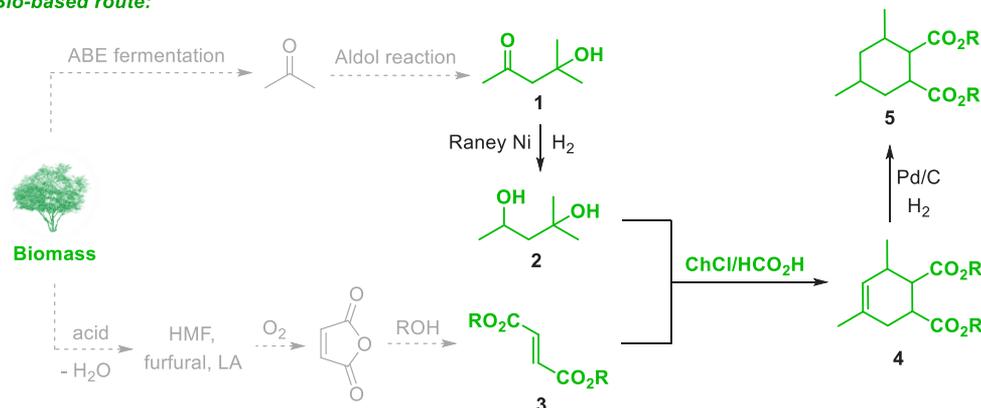
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Scheme 1. Fossil- and Bio-based Routes to 1,2-Cyclohexanedicarboxylates

Fossil-based route:



Bio-based route:



hydrogenation process to deliver 1,2-cyclohexanedicarboxylates.²³

Herein, we develop an alternative approach for the synthesis of 1,2-cyclohexanedicarboxylates using diacetone alcohol and fumarates, which can be derived from biomass, as the starting materials (Scheme 1). Diacetone alcohol can be prepared by the self-aldol reaction of acetone²⁴ from the acetone–butanol–ethanol (ABE) fermentation²⁵ of biomass. Fumarate is an esterification product of maleic anhydride (MA) from the oxidation of bio-based levulinic acid (LA),²⁶ furfural,²⁷ and 5-hydroxymethylfurfural (HMF).²⁸ Besides, biological conversion of sugars can also afford fumaric acid,²⁹ which is a precursor of fumarate. In the first step, diacetone alcohol (compound 1) is efficiently transformed to 2-methyl-2,4-pentandiol (compound 2) by Raney Ni-catalyzed hydrogenation. Subsequently, by employing choline chloride (ChCl)-based deep eutectic solvent (DES)³⁰ as reaction medium, 2-methyl-2,4-pentandiol (compound 2) and fumarates (compound 3) undergo a domino dehydration/D-A reaction to yield dimethyl-substituted cyclohex-4-ene-1,2-dicarboxylates (compound 4). A final Pd/C-catalyzed hydrogenation of the C=C bond in compound 4 leads to the desired product dimethyl-substituted 1,2-cyclohexanedicarboxylates (compound 5) that may serve as safe plasticizers for PVC materials.

RESULTS AND DISCUSSION

Initially, the hydrogenation of diacetone alcohol (compound 1) to 2-methyl-2,4-pentandiol (compound 2) over inexpensive Raney metals was investigated (Figure 1). When the reaction was performed in ethanol (EtOH) at 100 °C under 2.0 MPa of H₂ using Raney Ni as a catalyst, the desired compound 2 was obtained in 91% yield. The hydrogenation also occurred in the presence of Raney Cu or Raney Co, although the yields of compound 2 over these catalysts are slightly lower than that over Raney Ni. In contrast, Raney Fe showed a very low catalytic activity. Based on these results, we believe that Raney Ni was a promising catalyst for the hydrogenation of diacetone alcohol (compound 1) to 2-methyl-2,4-pentandiol (compound

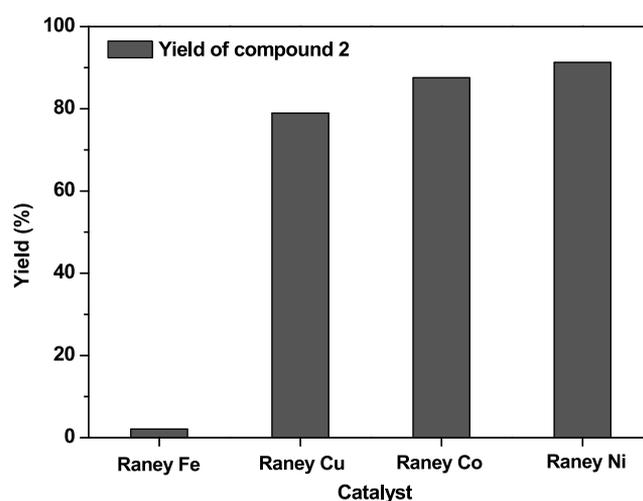


Figure 1. Yield of compound 2 over different Raney metal catalysts. Reaction conditions: diacetone alcohol (compound 1, 10 mmol, 1.16 g), EtOH (5.9 mL, 4.64 g), catalyst (10 wt %, 116.0 mg), H₂ (2.0 MPa), 100 °C for 12 h.

2). A screening of the temperature indicates that the hydrogenation can proceed with a high efficiency (97% yield) at 40 °C (Figure S1 in the Supporting Information). Notably, the Raney Ni catalyst can be reused three times without significant decline in the hydrogenation activity (Figure 2). Furthermore, we also compared the XRD patterns of fresh and used Raney Ni. Based on the results illustrated in Figure S3 in the Supporting Information, no evident change was observed after the catalyst was used for the hydrogenation of diacetone alcohol, which confirmed that Raney Ni was stable under the investigated conditions.

Having established the production of 2-methyl-2,4-pentandiol (compound 2), we envisioned that acid-catalyzed dehydration of compound 2 could lead to the formation of 1,3-diene, which easily reacted with fumarate to afford D–A adduct under thermal conditions. Bearing this in mind, efforts were directed toward one-step synthesis of diethyl 3,5-

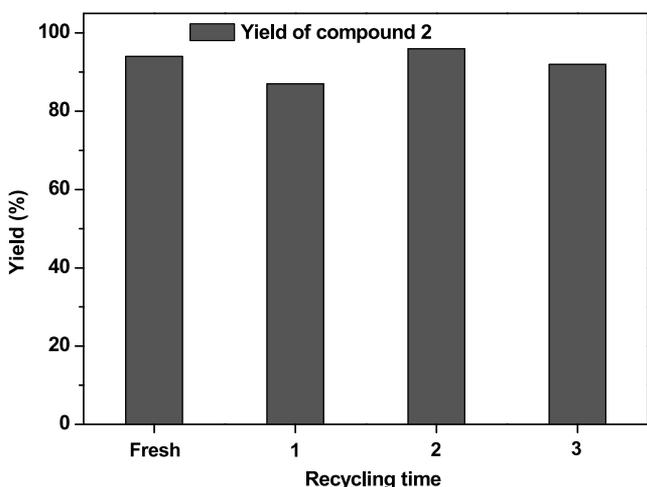


Figure 2. Yield of compound 2 over Raney Ni, as a function of recycling time. Reaction conditions: diacetone alcohol (compound 1, 10 mmol, 1.16 g), EtOH (5.9 mL, 4.64 g), Raney Ni (10 wt %, 116.0 mg), H₂ (2.0 MPa), 40 °C for 12 h.

dimethylcyclohex-4-ene-1,2-dicarboxylate (compound 4a) through domino dehydration/D-A reaction of compound 2 and diethyl fumarate (compound 3a). The strong solid acid Amberlyst-15 was chosen as the catalyst to test our hypothesis. When the reaction was performed in toluene at 120 °C, the target compound 4a was indeed detected, albeit with a low yield (Table 1, entry 1). Other aprotic solvents (e.g., THF and NMP) and protic solvents (e.g., EtOH and H₂O) did not give better results (Table 1, entries 2–5). In these systems, most of diol 2 still remained after stirring at 120 °C for 12 h. It has been proved by our group^{31–33} and others^{34–37} that 1-ethyl-3-methylimidazolium chloride ([Emim]Cl) and choline chloride (ChCl)-based deep eutectic solvents (DESs)³⁰ are efficient media for the dehydration of diols and carbohydrates, in which Cl[−] ions can stabilize the critical carbenium ion intermediate to increase the reactivity. Consequently, these two types of solvents were examined. To our delight, the yield of compound 4a can be improved to 77% using [Emim]Cl as the reaction medium (Table 1, entry 6). ChCl-based DES is simply obtained by mixing ChCl with alcohol or carboxylic acid at 100 °C for 30 min.³⁰ The reactions in DESs such as ChCl/glycerol and ChCl/ethylene glycol (EG) proceeded smoothly as well, providing compound 4a in 70% and 76% yield, respectively (Table 1, entries 7 and 8). Since [Emim]Cl is a nonrenewable solvent, while ChCl and EG can be obtained from biomass,^{8,30} ChCl/EG was selected as the green medium. The catalytic performances of other solid acids were also surveyed (Table 1, entries 9–13). The commonly used H-type zeolites including H-BEA (Si/Al = 25), H-USY (Si/Al = 3), and H-MOR (Si/Al = 24) showed low catalytic performances (Table 1, entries 9–11). NH₃-TPD experiments demonstrated that the sequence of the amount of acid sites over various catalysts is Amberlyst-15 (3.397 mmol/g) > H-USY (1.318 mmol/g) > H-BEA (1.044 mmol/g) > H-MOR (0.876 mmol/g), which is basically consistent with that of their catalytic activities. One exception was Nafion (2.123 mmol/g), which also gave a high yield of 4a (Table 1, entry 12). This is because Nafion bears an electron-deficient polyfluoro-substituted sulfonic group, which makes it have higher acid strength than Amberlyst-15. As a consequence, we can see that both the acid amount and the strength of catalyst contribute to the reactivity. It is noteworthy

Table 1. Screening the Reaction Conditions for One-Step Synthesis of Compound 4a^a

entry	catalyst	temperature, T (°C)	solvent ^b	yield of 4a ^c (%)
1	Amberlyst-15	120	toluene	38
2	Amberlyst-15	120	THF	37
3	Amberlyst-15	120	NMP	39
4	Amberlyst-15	120	EtOH	42
5	Amberlyst-15	120	H ₂ O	27
6	Amberlyst-15	120	[Emim]Cl	77
7	Amberlyst-15	120	ChCl/glycerol (1:1)	70
8	Amberlyst-15	120	ChCl/EG (1:1)	76
9	H-BEA	120	ChCl/EG (1:1)	46
10	H-USY	120	ChCl/EG (1:1)	45
11	H-MOR	120	ChCl/EG (1:1)	12
12	Nafion	120	ChCl/EG (1:1)	78
13	Amberlyst-15	120	ChCl/EG (2:1)	77
14	Amberlyst-15	120	ChCl/EG (1:2)	76
15	Amberlyst-15	100	ChCl/EG (1:1)	86
16	Amberlyst-15	80	ChCl/EG (1:1)	67
17 ^d	Amberlyst-15	100	ChCl/EG (1:1)	97
18 ^e	Amberlyst-15	100	ChCl/EG (1:1)	84

^aReaction conditions: compound 2 (5.0 mmol, 0.59 g), compound 3a (5.0 mmol, 0.86 g), solvent (2.36 g), catalyst (10 wt %, 59.0 mg), T (°C) for 12 h. ^bThe ratio in parentheses is the molar ratio of choline chloride (ChCl) to the other component. ^cDetected by GC using tridecane as the internal standard. ^dOnly compound 2 was 7.5 mmol (0.89 g, 1.5 equiv) and the yield was calculated based on a 5.0 mmol scale. ^eOnly compound 3a was 7.5 mmol (1.29 g, 1.5 equiv), and the yield was calculated based on a 5.0 mmol scale. NMP = N-methyl-2-pyrrolidone; [Emim]Cl = 1-ethyl-3-methylimidazolium chloride; EG = ethylene glycol.

that when AlCl₃ (a typical Lewis acid) was used as the catalyst, the reaction also proceeded with good efficiency (Figure S5b in the Supporting Information); therefore, Lewis acids may also play a role in the dehydration step.

The molar ratio of ChCl and EG had a negligible impact on the outcome (Table 1, entries 13 and 14). The yield of 4a increased to 86% when the reaction was conducted at 100 °C (Table 1, entry 15). A further decrease of the temperature led to an inferior result (Table 1, entry 16). Gratifyingly, subjecting 1.5 equiv of diol 2 to the standard conditions resulted in compound 4a in 97% yield (Table 1, entry 17). In contrast, increasing the amount of diethyl fumarate had no positive effect on the reaction (Table 1, entry 18). Note that the dimerization of the resulting 1,3-diene was observed as the main side reaction (Figure S9 in the Supporting Information). Thus, to compensate the side reaction, the excessive diol was essential for the complete consumption of diethyl fumarate.

The influence of the catalyst loading on the outcome was subsequently evaluated. As shown in Figure 3, the yield of 4a remained high (95%) when the loading of Amberlyst-15 decreased to 4 wt % of compound 2. Further decreasing catalyst loading resulted in a decline of the product yield. The turnover number (TON) and turnover frequency (TOF) of Amberlyst-15 under the standard conditions are determined as 59.4 and 0.12 min^{−1}, respectively.

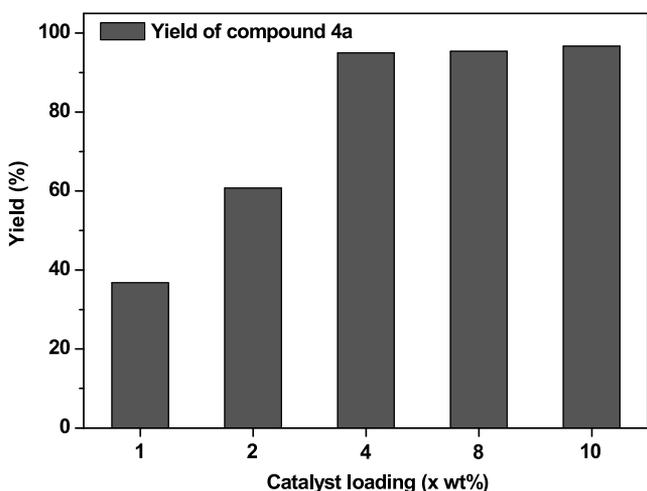


Figure 3. Yield of compound **4a** over Amberlyst-15, as a function of catalyst loading. Reaction conditions: compound **2** (7.5 mmol, 0.89 g), compound **3a** (5.0 mmol, 0.86 g), ChCl/EG (1:1, 2.36 g), Amberlyst-15 (*x* wt %, based on 5.0 mmol scale of compound **2**), 100 °C for 12 h.

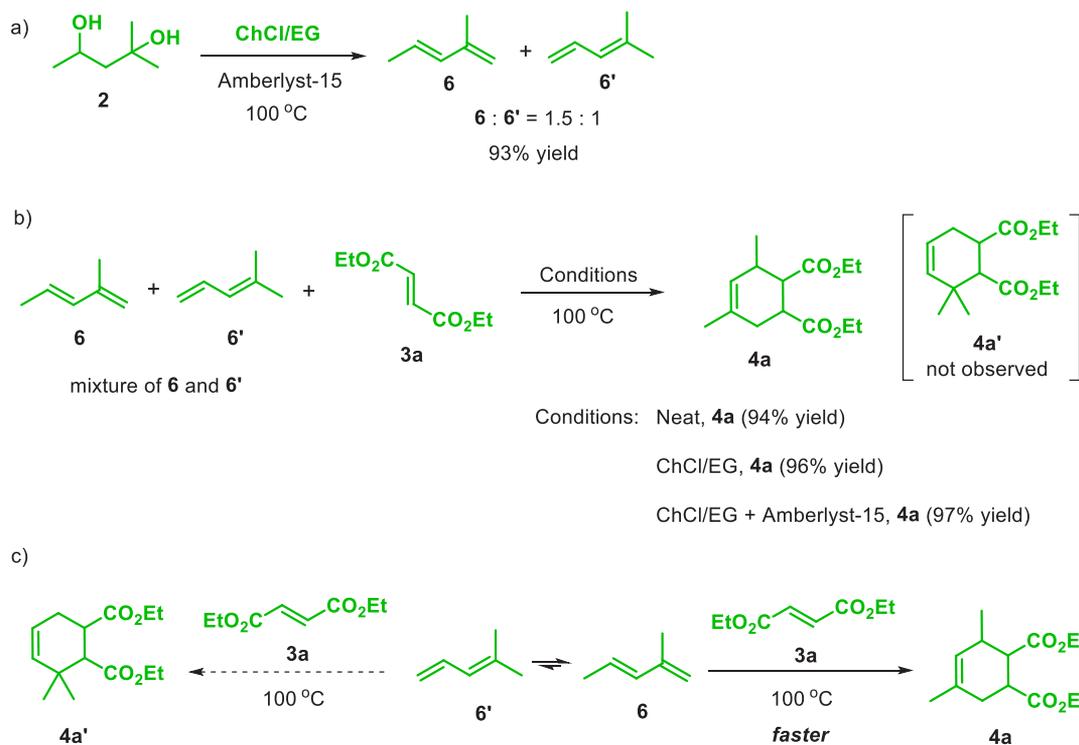
To elucidate the mechanism for this cascade process, some control experiments were conducted (Scheme 2). We first attempted the dehydration of diol **2** in the absence of diethyl fumarate **3a**. Treatment of diol **2** with Amberlyst-15 in ChCl/EG at 100 °C furnished a mixture of (*E*)-2-methylpenta-1,3-diene (compound **6**) and 4-methylpenta-1,3-diene (compound **6'**) with a molar ratio of 1.5:1 (Scheme 2a). Theoretically, the following D-A reaction of 1,3-dienes with **3a** should afford a mixture of compounds **4a** and **4a'**, which was not consistent with the experimental results. Accordingly, this process was then investigated in detail. It is found that the separated 1,3-

dienes (**6**:**6'** = 1.5:1) and compound **3a** could undergo D–A reaction spontaneously at 100 °C without solvent or catalyst to provide compound **4a** as the sole product and compound **4a'** was not observed (Scheme 2b). In addition, the D–A reactions in ChCl/EG and ChCl/EG/Amberlyst-15 exclusively delivered **4a** in comparable yields. Based on these results, two conclusions can be drawn:

- (1) ChCl/EG and Amberlyst-15 are responsible for the dehydration of diol **2**.
- (2) The D–A reaction between **6** and **3a** is faster than that of **6'** and **3a**, thus shifting the equilibrium from **6'** to **6** (Scheme 2c).

Another advantage of the process is the facile separation of the product. Initially, when stirring at 100 °C, diol **2** and fumarate **3** merged into ChCl/EG and a colorless liquid was formed. With the increase in reaction time, the monophasic liquid spontaneously switched to biphasic (Figure S4 in the Supporting Information). After cooling to room temperature, the upper yellow layer was the product **4a** that can be easily separated just by decantation and no further distillation was required. The lower layer was composed of Amberlyst-15, ChCl/EG, and the byproduct water. After drying at 60 °C under vacuum, the reusability of Amberlyst-15/ChCl/EG was examined. Unfortunately, the result was not good. When subjected to the second run, the yield of **4a** dramatically decreased (Figure S6 in the Supporting Information). On the basis of NH₃-TPD results, the acid amount of used Amberlyst-15 significantly decreased from 3.397 mmol/g (fresh one) to 0.374 mmol/g. These results were presumably due to the coke formation on the surface of the catalyst. Compared to NMR spectrum of fresh EG, that of used EG contained some new unidentified peaks (Figures S17 and S18 in the Supporting Information), suggesting that EG was unstable under the investigated conditions. According to literature reports,³⁸ the

Scheme 2. Control Experiments for Mechanistic Studies



strong solid acids could lead to polymerization of EG at high temperature, which may be one reason for the deactivation of Amberlyst-15 resin.

Our previous works³¹ showed that acidic DES formed with ChCl and HCO₂H could also promote the dehydration of diols and featured good reusability. Thus, we further attempted the reaction of 2-methyl-2,4-pentandiol (compound 2) with diethyl fumarate (compound 3a) in ChCl/HCO₂H in the absence of Amberlyst-15. Gratifyingly, when stirring at 120 °C for 12 h, the system also automatically divided into two phases (Figure S4). A simple decantation of the upper layer furnished the desired product 4a in 98% yield. Notably, after removing the byproduct water in the lower layer, ChCl/HCO₂H can be used for three times with no evident change in the activity (Figure 4). The turnover number (TON) of HCO₂H is

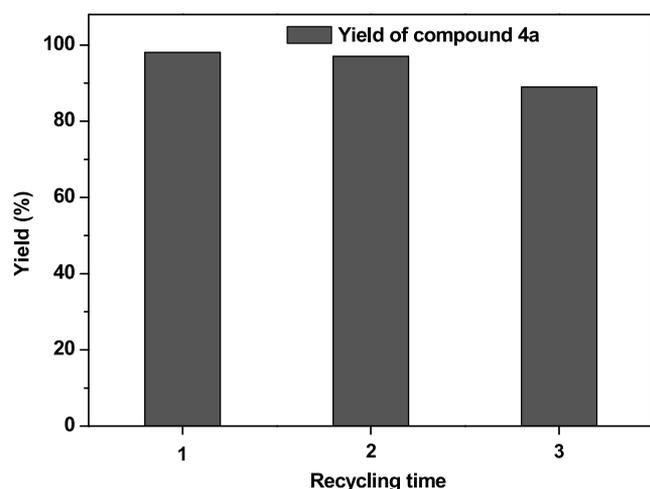


Figure 4. Yield of compound 4a in ChCl/HCO₂H, as a function of recycling time. Reaction conditions: compound 2 (7.5 mmol, 0.89 g), compound 3a (5.0 mmol, 0.86 g), ChCl/HCO₂H (1:1, 2.36 g), 120 °C for 12 h. The lower layer was dried at 60 °C under vacuum for 1 h after each use.

determined as 1.05. As we can see from Figures S21 and S22 in the Supporting Information, the ¹H NMR spectra of the used ChCl/HCO₂H DES is almost identical to that of fresh one, indicating that ChCl/HCO₂H was stable under the investigated conditions.

Finally, an array of catalysts were screened for the hydrogenation of the C=C bond of compound 4a, and the results were presented in Figure 5. Noble-metal catalysts, including Pd/C, Pt/C, and Ru/C can efficiently promote the hydrogenation at 100 °C, delivering diethyl 3,5-dimethyl-1,2-cyclohexanedicarboxylate (compound 5a) in good yields. In the case of non-noble metal catalyst Raney Ni, a slightly lower yield of compound 5a was obtained. However, when the temperature increased to 150 °C, the hydrogenation of compound 4a over Raney Ni also led to compound 5a in a comparable yield. We then tested the stability of Pd/C and Raney Ni for the hydrogenation. Pd/C maintained good catalytic performance with the increase of recycling time (Figure 6). The XRD pattern of the used Pd/C was almost the same as that of the fresh one (Figure S11 in the Supporting Information), demonstrating that Pd/C was stable under the investigated conditions. In contrast, evident deactivation was observed over used Raney Ni, which is possibly because active nickel was oxidized after the first usage.

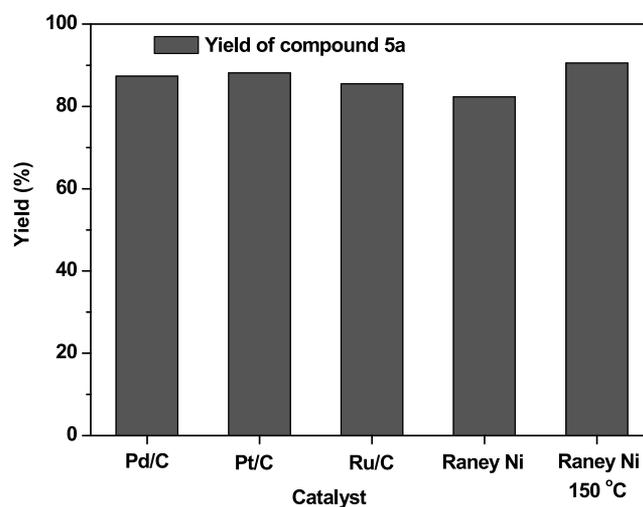


Figure 5. Yield of compound 5a over different catalysts. Reaction conditions: compound 4a (5.0 mmol, 1.27 g), catalyst (10 wt %, 127.0 mg), EtOH (6.4 mL, 5.08 g), 100 °C for 10 h.

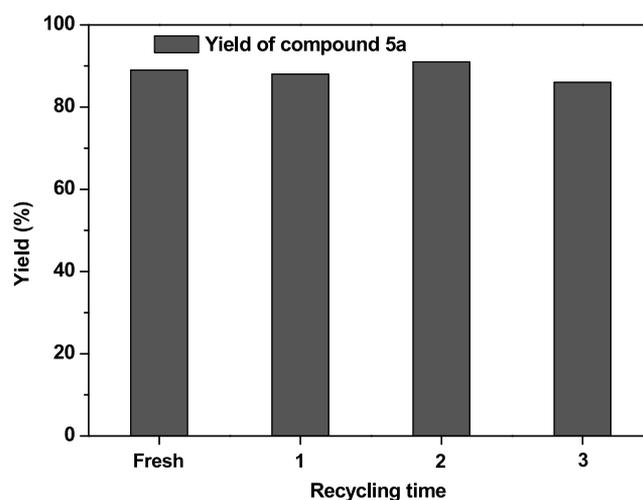
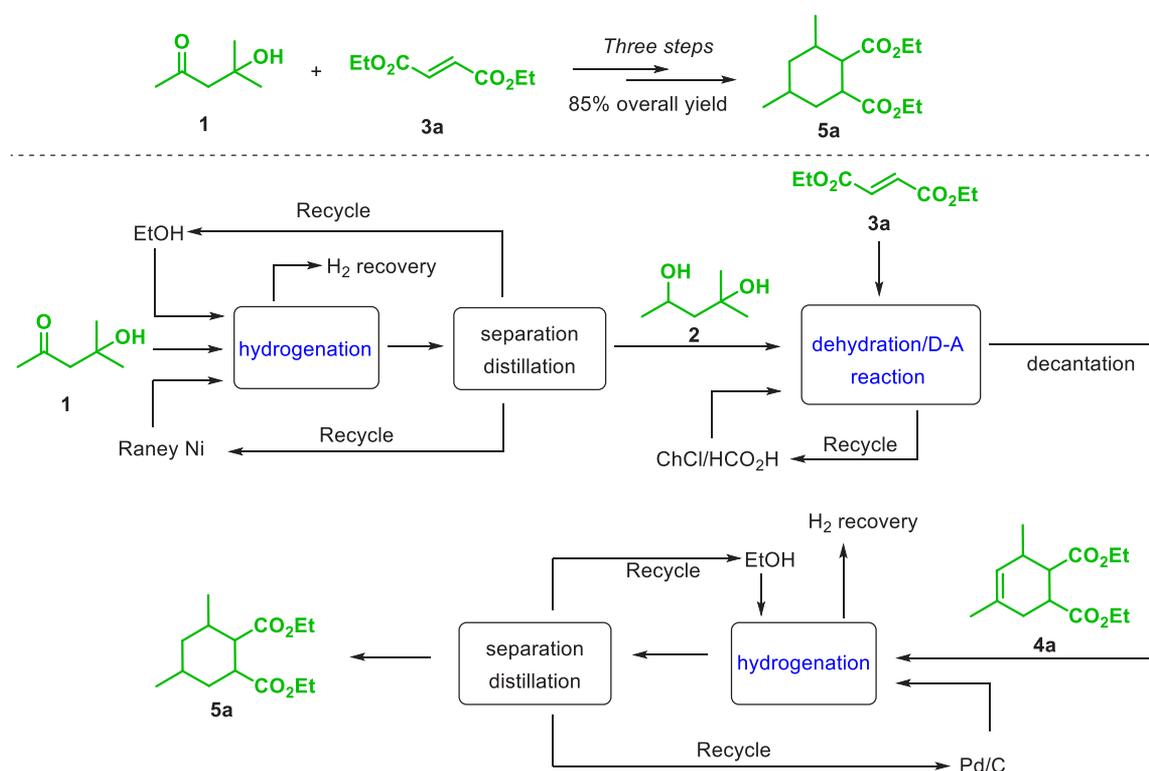


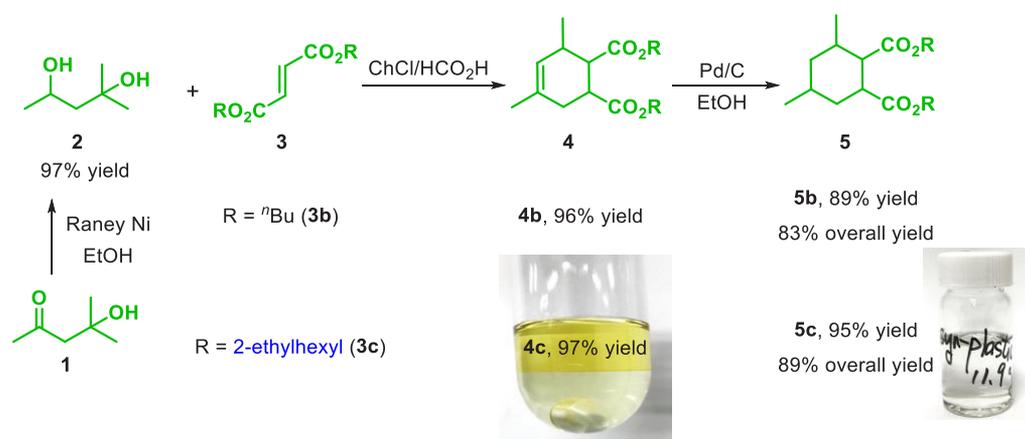
Figure 6. Yield of compound 5a over Pd/C as a function of recycling time. Reaction conditions: compound 4a (5.0 mmol, 1.27 g), Pd/C (10 wt %, 127.0 mg), EtOH (6.4 mL, 5.08 g), 100 °C for 10 h.

Scheme 3 shows a block flow diagram for the process. The diacetone alcohol and EtOH were fed to the hydrogenation reactor containing Raney Ni catalyst. After stirring for 12 h, the excess H₂ was released and recovered. Raney Ni was filtered, and the organic phase was distilled to afford 2-methyl-2,4-pentandiol (compound 2, 97% yield) by removing EtOH. Raney Ni and EtOH can be recycled back to the reactor. In the second reactor, one-step dehydration/D-A reaction of compound 2 and diethyl fumarate occurred in ChCl/HCO₂H system. The upper layer (product 4a) was separated by a simple decantation (98% yield), and the lower layer ChCl/HCO₂H was recycled after a desiccation treatment. Compound 4a and EtOH together with H₂ were fed to the third reactor, where the hydrogenation of the C=C bond occurred over Pd/C at 100 °C. The excess H₂ was recovered. Pd/C was filtered, and a final distillation produced diethyl 3,5-dimethyl-1,2-cyclohexanedicarboxylate (compound 5a, 89% yield) by removing EtOH. Pd/C and EtOH could be recycled back to the reactor. As a result, the overall yield was 85% starting from diacetone alcohol and diethyl fumarate.

Scheme 3. Block Flow Diagram for the Synthesis of 1,2-Cyclohexanedicarboxylate Starting from Diacetone Alcohol and Fumarate



Scheme 4. Synthesis of 1,2-Cyclohexanedicarboxylates with Long Alkyl Groups



Since the length of alkyl side chain in plasticizers typically ranges from four to nine carbons, other biomass-derived fumarates with longer alkyl groups were further studied. Dibutyl fumarate, which is an ester of biobutanol³⁹ with MA, could also participate in the process, providing dibutyl 3,5-dimethyl-1,2-cyclohexanedicarboxylate (compound 5b) in 83% overall yield (Scheme 4). 2-Ethylhexanol is a long-chain alcohol that can be prepared by sequential aldol condensation and hydrogenation of biomass-based *n*-butyraldehyde.⁴⁰ Its esterification product di(2-ethylhexyl) fumarate was an ideal feedstock as well, leading to the formation of di(2-ethylhexyl) 3,5-dimethyl-1,2-cyclohexanedicarboxylate (compound 5c) in 89% overall yield (Scheme 4).

We further evaluated the toxicity of compound 5c to illustrate its potential application in the plasticizer industry. The genotoxicity of compound 5c, and two widely used

plasticizers (DEHP and DINCH) was first assessed. Hypoxanthine-guanine phosphoribosyltransferase (HPRT or HGPRT) is an enzyme encoded by the HPRT1 gene, a housekeeping gene located on the X chromosome. The enzyme HPRT regulates purinergic signaling in pluripotential stem cell in humans,⁴¹ and mutations in the gene will produce a deficiency of HPRT, leading to inherited diseases, such as Lesch–Nyhan syndrome.⁴² HPRT1 has been identified as the best single reference gene of 13 frequently used housekeeping genes in cellular maintenance, and measurement of the enzyme expression is an accurate and economic assay of genotoxicity.⁴³

Three plasticizers (DINCH, DEHP, and compound 5c) and ethylmethanesulfonate (EMS) were prepared. DEHP has been reported to possibly damage fertility,⁴⁴ and EMS is teratogenic and possibly carcinogenic,⁴⁵ and they were selected to be positive control substances. Because of limited solubility of the

plasticizers in an aqueous solution, acetone was selected as the vehicle. HPRT expression levels of the three samples were converted to concentrations; results are summarized in Figure 7. The non-drug-treated control sample contained HPRT at a

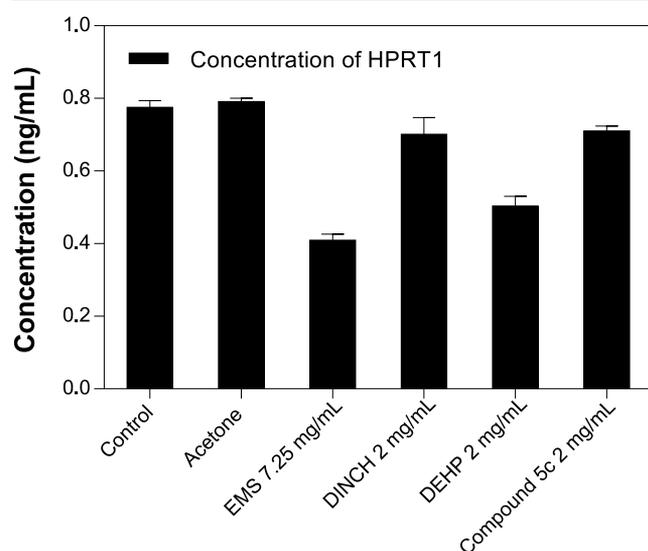


Figure 7. ELISA result of HPRT expression in CHO-K1 cells. Concentrations of HPRT in each sample were presented in a bar graph. Compared to the control, acetone the vehicle and negative control brought no influence to the HPRT expression. Enzyme concentrations of the culture samples incubated with DINCH and compound 5c slightly decreased, still close to the control. Positive controls, DEHP and EMS, largely reduced the enzyme expression levels.

concentration in the neighborhood of 0.8 ng/mL. The acetone-added cells had a similar expression level of HPRT to the control, suggesting that acetone was a suitable vehicle in this experiment, because it did not influence the enzyme expression or the measurement. For DINCH, the HPRT concentration slightly decreased but it was still close to the control. However, DEHP and EMS treatment largely reduced the expression levels, by ~35% and ~50%, indicating the influence/toxicity of the two negative substances. The HPRT1 gene might not be much impacted during the 24-h exposure, but the HPRT expression was clearly affected. Their performances were in agreement with previous reports on toxicity.^{44,45} HPRT concentration of cells that were incubated with compound 5c declined, not considerably, compared to the control, and it was at the same level as that of the DINCH sample, implying that, under the experimental conditions of this assay, (1) compound 5c showed no toxic activity in vitro in the CHO-K1 cells, and (2) this substance acted as DINCH did, which was a reported safe material to human health.^{7,46}

Furthermore, acute toxicity of compound 5c in vivo was also tested. The purpose of the acute toxicity test is to speculate on the acute toxicity of the new compound to humans. The acute toxicity test mainly observes the symptoms and extent of toxicity to experimental animals after one-time administration.

In the 14-day experimental period, both male and female rats gained weight steadily. The male rats weighed 263.1 ± 4.424 at day 0, 343.7 ± 4.372 at day 8, and 389.8 ± 8.975 at day 14. The female rats weighed 224.6 ± 2.849 at day 0, 251.7 ± 4.485 at day 8, 261.6 ± 5.467 at day 14 (Figure S16 in the Supporting Information). Behaviors, furs, feces, secretions,

perineum, and eyes of the rats were observed every day and no abnormalities were found. A pathological section of liver tissue and kidney tissue were made to determine if any damage occurred. The results showed that there was no damage to the liver and kidney (Figure 8). According to OECD Guideline

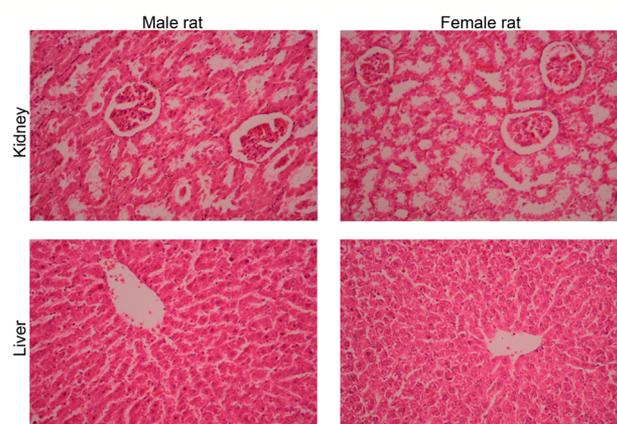


Figure 8. Hematoxylin and eosin (HE) staining of liver and kidney. Histopathological examination of liver and kidney showed no abnormal changes both in male and female rats.

For Testing Of Chemicals 423: Acute Oral Toxicity, dosages above 5 g/kg are not recommended. Therefore, after testing at 5 g/kg, no higher doses were attempted. According to the in vitro and in vivo results, no acute reproductive toxicity was observed at dosages of 2 mg/mL and 5 g/kg, respectively. Hence, the median lethal dose (LD_{50}) of compound 5c after oral application was found to be greater than 5 g/kg of body weight for the male and female rats. Based on the GB15193.3 National Food Safety Standard: Acute Oral Toxicity Test, a level of $LD_{50} > 5$ g/kg can be considered to be practically nontoxic. Therefore, compound 5c can be considered to be a safe plasticizer to humans.

CONCLUSION

In summary, we have developed an alternative three-step route for the production of 1,2-cyclohexanedicarboxylates using diacetone alcohol and fumarates as starting materials. The process features a mild Raney Ni-catalyzed hydrogenation of diacetone alcohol, one-step dehydration/D-A reaction of resulting 2-methyl-2,4-pentandiol and fumarates in a choline chloride (ChCl)-based deep eutectic solvent (DES), and a further Pd/C-catalyzed hydrogenation of D-A adduct. The toxicological tests indicate that the as-synthesized di(2-ethylhexyl) 3,5-dimethylcyclohexane-1,2-dicarboxylate can serve as a safe plasticizer for PVC materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.8b04310.

Experimental details; copies of GC chromatograms and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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