

Dehydro-aromatization of cyclohexene-carboxylic acids by sulfuric acid: critical route for bio-based terephthalic acid synthesis

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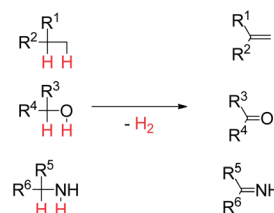
A novel dehydro-aromatization reaction under mild reaction conditions was successfully developed using sulfuric acid as a cost-effective and efficient oxidant. This reaction simplified the synthesis of terephthalic acid (TA, an important aromatic monomer precursor) from biomass-derived isoprene and acrylic acid.

In response to the diminishment of oil reserves and the rise of green chemistry, there is growing interest in the development of bond construction strategies for synthesizing chemicals that are currently derived from oil from renewable resources.¹ For example, aromatic molecules, as core structures of commodity chemicals from pharmaceuticals² to polymers,³ can be synthesized from renewable materials through a diversified bond construction route. Dehydrogenation⁴ is a common method to create unsaturated bond from saturated bond, such as the synthesis of aldehydes or ketones, nitriles, and alkenes from alcohols, amines, and alkanes, respectively (Scheme 1). Dehydrogenation reaction is also an important and widely-used synthetic approach to form aromatic rings by removing one or more pairs of hydrogen atoms from ring hydrocarbons. Herein we report an efficient dehydro-aromatization⁵ method that removes hydrogen from six-membered alicyclic compounds to form aromatic molecules under mild reaction conditions. To the best of our knowledge, this is the first time to elaborate dehydro-aromatization mechanism of cyclohexene-carboxylic acids using sulfuric acid as an oxidant. Furthermore, this methodology is capable to simplify the process to synthesize bio-based terephthalic acid (TA).

Recently, enormous efforts have been devoted to seeking efficient and cost-effective catalysts for dehydro-aromatization reactions under mild conditions (atmospheric pressure and low temperature). Common catalysts for dehydro-aromatization are oxidizing chemicals including elemental sulfur,⁶ selenium,⁷

selenium dioxide,⁸ nitrobenzene, peroxide,⁹ manganese dioxide,¹⁰ iodine(v),¹¹ and graphite oxide.¹² These reactions require very harsh reaction conditions. Although the quinones with high oxidation potential, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)¹⁰ and trityl salts,¹³ can accomplish the dehydrogenation reaction under milder conditions, they have much lower selectivity than those requiring harsh reaction conditions. In addition, the dehydrogenation reaction suffers from high price of reagents and/or low atom economy. Therefore, instead of using single oxidant as the catalyst, researchers have paid more attention to the oxidation catalyst systems, which usually comprise of both an active catalyst and an oxidant. Metal catalysts,^{4c,14} such as rhodium,¹⁵ nickel,¹⁶ copper,¹⁷ iridium,^{4b,18} platinum,¹⁹ ruthenium,²⁰ and palladium (or Pd/C),^{19b,21} as well as their metal-ligand complexes are known as the effective catalyst systems for dehydrogenation reactions. Although a number of extremely active catalysts and eco-friendly oxidants have been developed, their applications have been limited because the synthesis of catalysts is complicated and the dehydrogenation process needs a high temperature and/or a special reactor. Therefore, it is essential to explore an efficient and cost-effective oxidant for dehydro-aromatization reactions under mild conditions.

Inorganic acid, *e.g.* sulfuric acid, demonstrates strong dehydrating and oxidizing capability, but it has never been described particularly as a dehydro-aromatization reagent.²² Considering that the hexavalent sulfur is more oxidative than elementary sulfur, the former could be applied to the



Scheme 1 Dehydrogenation of saturated bonds to unsaturated ones.

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dehydrogenation of saturated bonds to generate aromatic molecules. In this study, sulfuric acid and other similar inorganic compounds were investigated as the oxidants for dehydro-aromatization of cyclohexenes to corresponding aromatic rings. A plausible mechanism was further proposed for the dehydro-aromatization reaction using sulfuric acid as oxidant. This newly-developed dehydrogenation method has great potential to prepare a series of aromatic carboxylic acids, such as terephthalic acid (TA), phthalic acid (PA), isophthalic acid (IA), and trimellitic acid,²³ since there is lack of simplified approach to produce these useful aromatic acids from aliphatic ones.

At the onset of our study, using 3,4-dimethyl-cyclohex-3-enecarboxylic acid **1d** (Table 1) as a model substrate, we examined the dehydro-aromatization reaction using a series of inorganic acids with different oxidation capabilities, which include phosphoric acid, sulfuric acid, and nitric acid as both the oxidizing reagents and solvents. Two previously reported dehydrogenation agents (DDQ and MnO₂) were used for comparison. The results in Table 1 indicated that DDQ and MnO₂ could not effectively catalyze the dehydro-aromatization of **1d** (entries 1 and 2). Phosphoric acid and nitric acid could not aromatize **1d** (entries 3, 4 and 8) either. Only sulfuric acid was capable to effectively dehydro-aromatize **1d** with a yield of 83%. It was also observed that elevating reaction temperature could significantly reduce reaction time, while the product yield kept the same at both conditions (83%). At the reaction temperature of 100 °C and under mediation of sulfuric acid, dehydro-aromatization of **1d** could be finished in 15 minutes (entry 6), while it took 40 minutes at 55 °C (entry 7) or 16 hours at room temperature (entry 8).

In order to further elucidate the dehydro-aromatization reaction of 3,4-dimethyl-cyclohex-3-enecarboxylic acid **1d** using sulfuric acid as the oxidant, a series of similar cyclohexene-carboxylic acids (**1a–e**) and anhydrides (**1f** and **g**), either purchased or synthesized by Diels–Alder reaction between dienes and dienophiles in lab, were further investigated. The results of their aromatization reactions are summarized in Table 2. A number of aliphatic acids **1a–d** were dehydrogenized to their corresponding aromatic products **2a–c** in moderate to

Table 2 Dehydrogenation of cyclohexene-carboxylic acids and its anhydrides with sulfuric acid

Entry	Substrate	Product	Time (min)	Yield ^a (%)
1			15	37
2			60	52
3			15	90
4			15	83
5			40	80
6			15	16
				24
7			15	24
				73 ^b
				49

^a Isolated yield. ^b The product is a mixture of two acid, their respective yields were determined by ¹H NMR.

Table 1 Survey of reaction conditions

Entry	Reagent	Time	Temp. (°C)	Yield ^a (%)
1 ^b	DDQ (4.0 equiv.)	12 h	rt, 50	0, 0
2 ^b	MnO ₂ (4.0 equiv.)	12 h	rt, 50	0, 0
3	H ₃ PO ₄ (85 wt%, 3 mL)	16 h	rt	0
4	H ₃ PO ₄ (85 wt%, 3 mL)	3 h	100	0
5	H ₂ SO ₄ (98 wt%, 3 mL)	16 h	rt	83
6	H ₂ SO ₄ (98 wt%, 3 mL)	15 min	100	83
7	H ₂ SO ₄ (98 wt%, 3 mL)	40 min	55	83
8	HNO ₃ (67 wt%, 3 mL)	16 h	rt	0

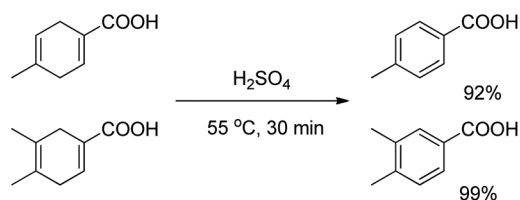
^a Isolated yield. ^b CHCl₃ was used at the solvent.

high yields. Different from other carboxylic acids, the dehydrogenation of substrate **1b** required a relatively longer reaction time (60 min) (entry 2) to obtain a moderate yield (52%). It was found that, the substrates with the methyl group, such as **1c**, **1d**, and **1e**, could reach higher yields than those (**1a** and **b**) without the methyl group. This can be explained that the electron-donating group (methyl group) is beneficial to the formation of carbocations, which might be intermediates in these reactions. The same dehydrogenation methodology was applied to acid anhydrides. Two types of acid anhydrides (**1f** and **g**) were used as the model substrates and the corresponding aromatization products were produced in moderate yields. It was observed that acid anhydrides produced two aromatic products: monocarboxylic acid and dicarboxylic acid, which indicated that decarboxylation probably occurred during the reaction.

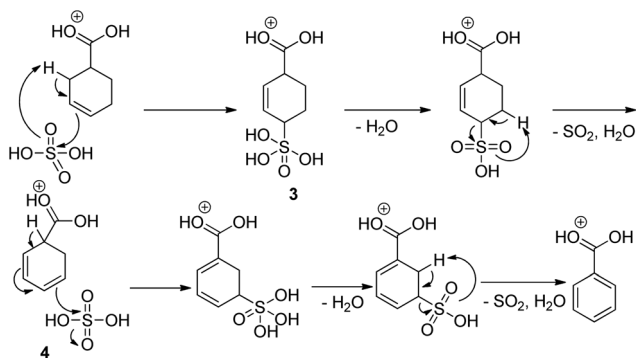
To elucidate the mechanism of dehydro-aromatization and further explore its possible applications, the reaction was applied to cyclohexadiene acids. As shown in Scheme 2, 4-methylcyclohexa-1,4-dienecarboxylic acid and 3,4-dimethylcyclohexa-1,4-dienecarboxylic acid could be effectively dehydro-aromatized by sulfuric acid under mild conditions (55 °C, 30 minutes) to the desired aromatic products in extremely high yields. The results from Table 2 and Scheme 2 demonstrated that both cyclohexenes and cyclohexadienes with similar structures formed the same products. Based on this result, it is reasonable to make a hypothesis that cyclohexadienes might be the intermediate during the conversion of cyclohexenes to their phenyl products.

Plausible mechanism of dehydro-aromatization of cyclohexene carboxylic acids is proposed in Scheme 3. In the presence of sulfuric acid, oxonium ion was formed by protonation, and then the substrate was cleaved through the ene reaction to provide a sulfonic acid **3** via dehydration. Then cyclohexadiene intermediate **4** was obtained by intra-molecular elimination. Based on the aforementioned result shown in Scheme 2, cyclohexadiene acids **4** could continue to react with sulfuric acid through similar dehydration mechanism and elimination reaction. Eventually the aromatic product was obtained successfully. The release of sulfur dioxide is an indicator, which provides further evidence for this proposed mechanism. During the reaction, a filter paper dampened with potassium dichromate was hung above the neck of flask. The paper turned to bluish green from orange when hexavalent chromium was reduced by SO₂.

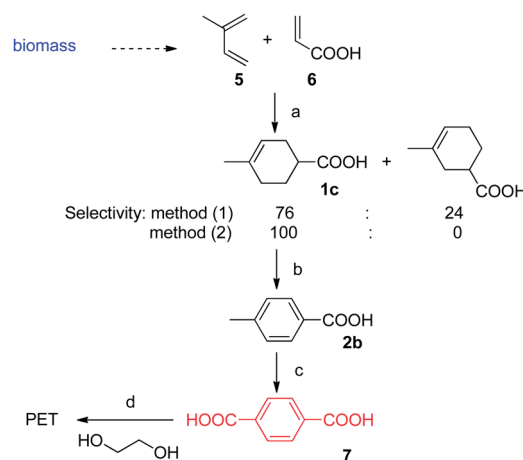
Terephthalic acid (TA), the most widely used aromatic carboxylic acid, is a monomer precursor for synthesizing polyethylene terephthalate (PET) or other polyesters such as



Scheme 2 Dehydro-aromatization of cyclohexadiene-carboxylic acids with sulfuric acid.



Scheme 3 Proposed reaction mechanism.



Scheme 4 Preparation of PET from bio-based chemicals. Conditions: (a) (1) 95 °C, in seal tube 4 h, 65% yield; (2) 0.15 eq. BH₃-THF, CH₂Cl₂, 0-rt, 24 h 80% yield. (b) H₂SO₄, 100 °C, 45 min, 91% yield, (c) K₂Cr₂O₇/NaOH, reflux, 2 h, 95% yield, (d) polycondensation.

polypropenediol terephthalate (PPT) and polybutylene terephthalate (PBT), which have broad applications from drink bottles to polyester fibers.²⁴ TA accounts for approximately 70 wt % of PET, and its total production in the world exceeds 10 billion pounds per year.²³ However, there has been no satisfactory synthesis route to produce biomass-derived TA. The dehydro-aromatization method developed in this study can be used to prepare 4-methylbenzoic acid (**2b**), the key intermediate in the synthesis route to produce bio-based TA. As shown in Scheme 4, bio-based TA could be synthesized using isoprene and acrylic acid as starting materials. It has been proven that isoprene could be prepared by the fermentation of biomass sugars (*e.g.* glucose), and the production of bio-based isoprene was commercialized by Genencor in 2012.²⁵ Bio-based acrylic acid could be synthesized either from dehydration of glucose-based lactic acid or dehydration and oxidation of glycerol through 3-hydroxypropionaldehyde.²⁶ The dehydro-aromatization reaction above therefore is an essential step to simplify the entire synthesis route to produce solely biomass-derived TA and PET under mild conditions. The synthesis route consists of a sequential Diels-Alder reaction (a),²⁷ dehydro-aromatization (b), oxidation (c), and polycondensation (d), as shown in Scheme 4.

Conclusions

In summary, a novel dehydro-aromatization reaction was successfully developed for the synthesis of aromatic carboxylic acid from cyclohexene-carboxylic acids. Sulfuric acid could be used as an efficient oxidizing-aromatization reagent under mild reaction conditions to dehydrolyze cyclohexene-carboxylic acids and its anhydrides. The possible mechanism was reasonably revealed. This aromatization reaction greatly simplified the synthesis of terephthalic acid (TA) from biomass-derived isoprene and acrylic acid. This reaction can be further applied to production of more useful chemicals from renewable starting materials.

Experimental section

Typical procedure for dehydrogenation of cyclohexene-carboxylic acids: 3,4-dimethylcyclohex-3-enecarboxylic acid (**1d**, 308 mg, 0.2 mmol) and H₂SO₄ (98 wt%, 3 mL) were added to a flask with a magnetic stirring bar. The reaction mixture was stirred at 100 °C for 15 min and then poured into excess ice water (5 mL) with stirring. The precipitated raw product was collected by filtration and washed with cool water for three times. The resultant product **2c** was white solid (249 mg, 0.166 mmol, and yield: 83%).

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