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*Original Research*

# Acid-catalyzed isomerization of maleic acid to fumaric acid: synthesis and characterization of a biomedically relevant dicarboxylic acid

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## ABSTRACT

**Background:** Fumaric acid (trans-butenedioic acid) is the thermodynamically stable geometric isomer of maleic acid (cis-butenedioic acid). It serves as the parent compound of dimethyl fumarate (DMF), an FDA-approved immunomodulatory agent used for relapsing-remitting multiple sclerosis and moderate-to-severe plaque psoriasis. Laboratory-scale synthesis of fumaric acid from maleic acid via acid-catalyzed isomerization provides a practical route for studying the physicochemical properties of this compound. **Objective:** This study **aim**ed to synthesize fumaric acid through hydrochloric acid (HCl)-catalyzed isomerization of maleic acid under reflux conditions and to characterize the products by melting point determination and gravimetric yield analysis. **Methods:** Maleic anhydride (2 g) was hydrated in boiling distilled water (5 mL) to produce maleic acid, which was crystallized by cooling. The filtrate containing dissolved maleic acid was treated with concentrated HCl (2 mL) and refluxed for 15 minutes. Fumaric acid was isolated by ice-bath crystallization and gravity filtration. Both products were characterized by gravimetric yield and melting point analysis. **Results:** Maleic acid was obtained with a yield of 25.39% (0.6011 g) and a melting point of 139°C, consistent with the literature range (130-139°C). Fumaric acid was obtained with a yield of 34.64% (0.6119 g) and a melting point of 280°C, slightly below the reported literature range (286-302°C), suggesting the presence of minor impurities. **Conclusion:** The HCl-catalyzed reflux method converted maleic acid to fumaric acid through an addition-rotation-elimination mechanism. The higher melting point of fumaric acid reflects its greater molecular symmetry and stronger intermolecular interactions in the crystal lattice.

**Keywords:** fumaric acid; maleic acid; geometric isomerism; acid-catalyzed isomerization; melting point; dicarboxylic acid

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## 1. INTRODUCTION

Fumaric acid (trans-butenedioic acid) and maleic acid (cis-butenedioic acid) are geometric isomers sharing the molecular formula $C_4H_4O_4$ but differing in their spatial arrangement around a rigid carbon-carbon double bond. This structural difference produces distinct melting points, solubilities, dipole moments, and biological activities (Clayden et al., 2012). Fumaric acid, the thermodynamically more stable trans-isomer, has become a compound of interest in biomedical research.

In mammalian metabolism, fumaric acid is an intermediate of the tricarboxylic acid (TCA) cycle, produced by succinate dehydrogenase and converted to L-malate by fumarase (Berg et al., 2019). Fumaric acid is also the parent molecule of fumaric acid esters (FAEs), particularly dimethyl fumarate (DMF). DMF, marketed as Tecfidera and Skilarence, has been approved by the FDA and the EMA for the treatment of relapsing-remitting multiple sclerosis (RRMS) and moderate-to-severe plaque psoriasis, respectively (Gold et al., 2012; Mrowietz et al., 2018). DMF activates the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidative pathway, suppresses NF-κB signaling, and modulates T-helper cell differentiation (Bresciani et al., 2026; Carlström et al., 2019). Fumaric acid derivatives have also been investigated for anti-tumor properties in in vivo models (Shakoor et al., 2016), and ensitrelvir fumaric acid has shown efficacy as an oral antiviral for SARS-CoV-2 infection (Mukae et al., 2023).

The isomerization of maleic acid to fumaric acid can be achieved through several catalytic approaches, including mineral acid catalysis, photochemical activation, thiyl radical catalysis, and bromide-mediated pathways (Nozaki & Ogg, 1941; Neveselý et al., 2022). Among these, HCl-catalyzed isomerization under reflux conditions is one of the most accessible laboratory methods. The reaction proceeds through electrophilic addition across the double bond, free rotation about the resulting single bond, and elimination to regenerate the double bond in the trans-configuration (Nozaki & Ogg, 1941).

Industrially, fumaric acid is produced by isomerization of maleic acid, which is derived from the hydration of maleic anhydride (Felthouse et al., 2001). Although the synthetic procedure is well established, the simultaneous characterization of both isomers from a single reaction sequence and the comparison of their physicochemical properties provide a useful framework for understanding the relationship between molecular geometry and physical properties.

This study aimed to synthesize fumaric acid through HCl-catalyzed isomerization of maleic acid under reflux conditions, characterize both the cis- and trans-products by melting point and gravimetric yield analysis, and discuss the results in the context of stereochemical principles and the biomedical applications of fumaric acid.

## 2. METHODS

### 2.1 Study Design

This was a laboratory-based experimental synthesis study conducted at the Organic Chemistry Laboratory, Department of Chemistry, Faculty of Sciences and Mathematics, Universitas Diponegoro, Semarang, Indonesia. The study used acid-catalyzed isomerization under reflux to convert maleic acid to fumaric acid, followed by product isolation via crystallization and characterization by melting-point determination and gravimetric yield calculation.

### 2.2 Materials

Maleic anhydride (analytical grade, ≥99% purity) served as the starting material. Concentrated hydrochloric acid (HCl, 37% w/w) was used as the isomerization catalyst. Distilled water was used as the solvent for hydration and crystallization. All reagents were obtained from the laboratory inventory and used without further purification.

### 2.3 Apparatus

The following apparatus was used: reflux apparatus (round-bottom flask with Liebig condenser), Erlenmeyer flask (125 mL), hot plate, analytical balance, filter paper, glass funnel, graduated cylinder, beaker glass, glass stirring rod, pipette, and a melting point determination apparatus (Stuart Scientific SMP10).

### 2.4 Synthesis of Maleic Acid from Maleic Anhydride

Distilled water (5 mL) was measured into a 125 mL Erlenmeyer flask and heated to boiling on a hot plate. Maleic anhydride (2.0000 g, 0.0204 mol) was added to the boiling water with continuous stirring until a clear, homogeneous solution was obtained. The hydration reaction proceeds via nucleophilic attack of water on the electrophilic carbonyl carbon of the anhydride ring, producing maleic acid in a 1:1 molar ratio (Clayden et al., 2012; Felthouse et al., 2001). The resulting solution was cooled gradually using running tap water to promote controlled crystal nucleation and growth (Magoo et al., 2025). The precipitated white crystals of maleic acid were collected by gravity filtration through filter paper, and the filtrate was reserved for the subsequent isomerization step. The crystals were dried at ambient temperature and weighed.

### 2.5 Isomerization of Maleic Acid to Fumaric Acid

The filtrate from the crystallization step, containing dissolved maleic acid, was transferred to a 100 mL round-bottom flask. Concentrated HCl (2 mL) was added under a fume hood. HCl serves as a Brønsted acid catalyst: protonation and chloride addition across the double bond form a saturated intermediate, allowing free rotation about the C-C single bond before elimination of HCl regenerates the double bond in the trans-configuration (Nozaki & Ogg, 1941). The mixture was refluxed for 15 minutes using a Liebig condenser, with the heating mantle set to approximately 150°C. After reflux, the solution was rapidly cooled in an ice bath to induce crystallization of fumaric acid, exploiting its lower aqueous solubility relative to maleic acid. The precipitated crystals were collected by gravity filtration, washed with minimal cold distilled water, and dried at ambient temperature.

### 2.6 Product Characterization

#### *2.6.1 Melting point determination*

The melting points of both maleic acid and fumaric acid crystals were determined using a Stuart Scientific SMP10 melting point apparatus. Finely powdered samples were loaded into capillary tubes, and the temperature at which complete melting was observed was recorded. Melting point is a standard purity indicator for crystalline organic compounds: a pure substance melts sharply within a narrow range, whereas impurities broaden and depress the melting range (Wesolowski & Leyk, 2023). Measurements were performed as single determinations for each compound due to limited sample availability, a limitation discussed in Section 4.5.

#### *2.6.2 Yield calculation*

The percent yield for each product was calculated as: percent yield = (actual mass obtained / theoretical mass) × 100%. The theoretical mass of maleic acid was calculated from the stoichiometric relationship with maleic anhydride (molecular weight of maleic anhydride: 98.06 g/mol; molecular weight of maleic acid: 116.07 g/mol). For fumaric acid, the theoretical yield was based on the moles of maleic acid remaining in the filtrate (determined by subtracting the moles of crystallized maleic acid from the initial moles of maleic anhydride), considering the 1:1 stoichiometric conversion and the identical molecular weight of both geometric isomers (116.07 g/mol).

#### *2.6.3 Comparative data treatment*

## 3. RESULTS

### 3.1 Observations During Synthesis

The sequential steps of the synthesis and their corresponding observations are summarized in Table 1. Hydration of maleic anhydride in boiling water produced a clear, colorless solution. Upon cooling, white crystalline precipitates of maleic acid formed. Reflux of the filtrate with concentrated HCl yielded a clear solution, which, upon ice-bath cooling, produced white crystalline precipitates of fumaric acid.

**Table 1.** Sequential observations during the synthesis of maleic acid and fumaric acid.

| Step | Procedure | Observation |
|---|---|---|
| 1 | Hydration of maleic anhydride (2 g) in boiling water (5 mL) | Clear, colorless solution |
| 2 | Cooling with tap water and filtration | White crystalline |

| | | |
|---|---|---|
| | | precipitate (maleic acid) |
| 3 | Addition of HCl (2 mL) to filtrate and reflux (15 min) | Clear, colorless solution |
| 4 | Ice-bath cooling and filtration | White crystalline precipitate (fumaric acid) |
| 5 | Drying at ambient temperature | Dry white crystals of both products |

Figure 1 presents the reaction scheme illustrating the three mechanistic stages of HCl-catalyzed isomerization: electrophilic addition of $H^+$ and $Cl^-$ across the double bond to form 2-chlorosuccinic acid, free rotation about the resulting C-C single bond, and elimination of HCl to yield the trans-product.

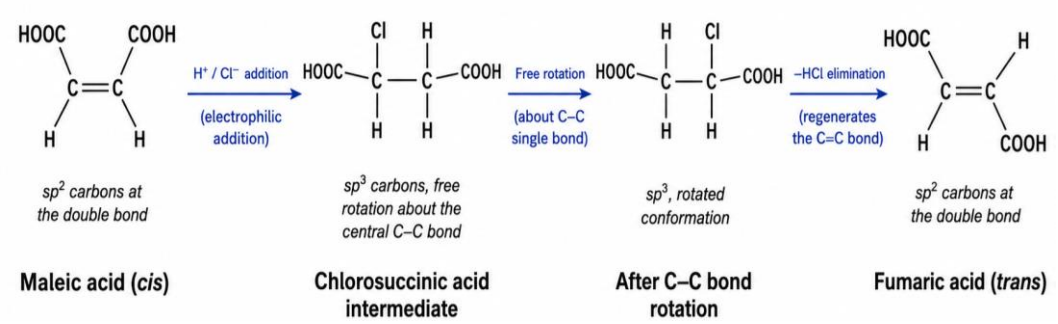


**Figure 1.** Reaction scheme for the HCl-catalyzed isomerization of maleic acid (cis) to fumaric acid (trans) via 2-chlorosuccinic acid intermediate.

## 3.2 Gravimetric Yield Analysis

The gravimetric data and calculated yields are presented in Table 2. From 2.0000 g (0.0204 mol) of maleic anhydride, 0.6011 g of maleic acid crystals were recovered, corresponding to a yield of 25.39% relative to the theoretical yield of 2.3673 g. The fumaric acid product weighed 0.6119 g, corresponding to a yield of 34.64% relative to the theoretical yield of 1.7662 g (based on 0.0152 mol of maleic acid remaining in the filtrate after crystallization).

**Table 2.** Gravimetric yield data for maleic acid and fumaric acid synthesis.

| Parameter | Maleic Acid | Fumaric Acid |
|---|---|---|
| Starting moles (mol) | 0.0204 | 0.0152 |
| Theoretical mass (g) | 2.3673 | 1.7662 |
| Filter paper mass (g) | 0.3796 | 0.3796 |
| Product + paper mass (g) | 0.9807 | 0.9915 |
| Actual product mass (g) | 0.6011 | 0.6119 |
| Percent yield (%) | 25.39 | 34.64 |

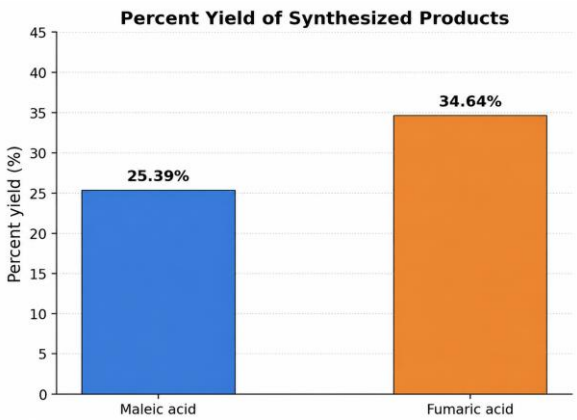


**Figure 2.** Percent yield of maleic acid and fumaric acid crystals obtained from the synthesis

The fumaric acid yield (34.64%) exceeded that of maleic acid (25.39%) by approximately 9 percentage points. This difference is consistent with the lower aqueous solubility of fumaric acid, which favors its

preferential crystallization upon ice-bath cooling.

### 3.3 Melting Point Analysis

The experimentally determined melting points are compared with literature values in Table 3 and visualized in Figure 3. Maleic acid melted at 139°C, within the accepted literature range of 130-139°C, with a percent relative deviation (%RD) of 3.3% from the literature midpoint (134.5°C). Fumaric acid melted at 280°C, slightly below the literature range of 286-302°C, with a %RD of 4.8% from the literature midpoint (294°C).

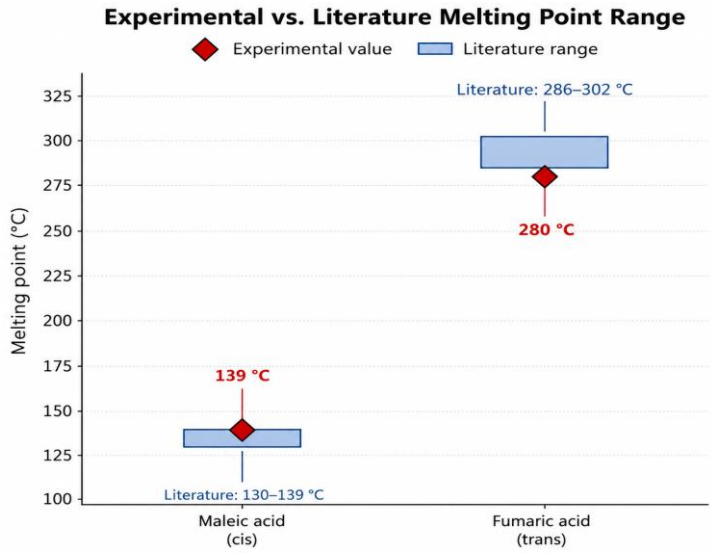


**Figure 3.** Experimental melting points (red diamonds) relative to literature reference ranges (blue bars) for maleic acid and fumaric acid.

**Table 3.** Melting point comparison of synthesized products with literature values.

| Compound | Experimental (°C) | Literature (°C) | Literature Midpoint (°C) | %RD | Configuration |
|---|---|---|---|---|---|
| Maleic acid | 139 | 130-139 | 134.5 | 3.3 % | cis (Z) |
| Fumaric acid | 280 | 286-302 | 294.0 | 4.8 % | trans (E) |

The melting point of fumaric acid (280°C) was 141°C higher than that of maleic acid (139°C), consistent with the greater molecular symmetry and stronger intermolecular forces of the trans-isomer.

## 4. DISCUSSION

### 4.1 Stereochemical Basis of the Isomerization

The conversion of maleic acid to fumaric acid involves the transformation of a cis-configured alkene to its trans-isomer. The carbon-carbon double bond in maleic acid does not permit free rotation under normal conditions; a catalyst is required to transiently remove the pi bond, allow rotation, and re-establish the double bond in the more stable trans-geometry (Clayden et al., 2012).

HCl catalyzes this transformation through three sequential steps. First, electrophilic addition of $H^+$ and $Cl^-$ across the double bond forms the saturated intermediate 2-chlorosuccinic acid. Second, free rotation about the resulting C-C single bond allows the two carboxyl groups to adopt a trans arrangement, which is thermodynamically favored because it minimizes steric repulsion. Third, elimination of HCl regenerates the double bond in the trans-

configuration, yielding fumaric acid (Nozaki & Ogg, 1941).

The thermodynamic driving force is the lower energy of the trans-isomer. In the cis-configuration, the two carboxyl groups are on the same side of the double bond, producing steric repulsion and unfavorable electrostatic interactions. In the trans-configuration, the carboxyl groups are on opposite sides, reducing steric strain and allowing more efficient crystal packing (Smith & March, 2020).

### 4.2 Melting Point Analysis and Purity Assessment

The melting point of maleic acid (139°C) was within the accepted literature range (130-139°C), indicating satisfactory purity. The melting point of fumaric acid (280°C) was 6°C below the lower bound of the literature range (286-302°C). Several factors may account for this deviation. First, residual maleic acid in the fumaric acid crystals would act as an impurity, depressing the melting point according to colligative principles (Pavia et al., 2015). Second, incomplete drying at ambient temperature may have left trace moisture. Third, the single-point determination without replicate measurements introduces measurement uncertainty.

The 141°C difference in melting points between the two isomers is a direct consequence of their differing molecular symmetries. Fumaric acid, with its centrosymmetric trans-configuration, packs more efficiently in the solid state. The trans-geometry allows the formation of extended intermolecular hydrogen-bonding networks that require more thermal energy to disrupt (Smith & March, 2020). Maleic acid, by contrast, can form intramolecular hydrogen bonds between its proximal carboxyl groups, which partially satisfies its hydrogen-bonding capacity and weakens intermolecular interactions in the crystal lattice.

### 4.3 Yield Analysis

The yield of maleic acid (25.39%) was low, which is expected because the crystallization step was designed to recover only a portion of the dissolved maleic acid while leaving the remainder in solution for isomerization. The high aqueous solubility of maleic acid at elevated temperatures and the small solvent volume (5 mL) limit the amount that crystallizes upon cooling.

The fumaric acid yield (34.64%) was modest but consistent with reported yields for this laboratory-scale procedure, in which product losses occur during filtration, transfer, and incomplete crystallization (Russell & Becker, 1975). The sensitivity of gravimetric recovery to the specific isolation technique employed has been documented for other organic compounds as well; for example, comparison of Soxhlet extraction and simple boiling for caffeine isolation from tea leaves showed that method selection alone can produce marked differences in recovery (Huda & Prayogo, 2025). The lower aqueous solubility of fumaric acid in cold water (approximately 0.63 g/100 mL at 25°C, compared to 78.8 g/100 mL for maleic acid) facilitates its preferential crystallization, and this solubility difference is the physicochemical basis for separating the trans-isomer from the reaction mixture (Haynes, 2016).

### 4.4 Biomedical Context

Fumaric acid is a TCA cycle intermediate involved in cellular energy metabolism (Berg et al., 2019). Its pharmacological relevance stems from its ester derivative DMF, which upon oral administration is hydrolyzed to its active metabolite monomethyl fumarate (MMF). MMF activates the Nrf2 pathway by modifying cysteine residues on KEAP1, releasing Nrf2 to induce expression of cytoprotective genes such as HO-1 and NQO1 (Carlström et al., 2019). DMF also suppresses NF-κB-dependent pro-inflammatory signaling and inhibits NLRP3 inflammasome activation (Bresciani et al., 2026).

In clinical trials, DMF (240 mg twice daily) reduced annualized relapse rates by approximately 50% compared to placebo in patients with RRMS (Gold et al., 2012; Fox et al., 2012). For psoriasis, fumaric acid esters have been used in European clinical practice since the 1990s with demonstrated efficacy in reducing PASI scores (Mrowietz et al., 2018). In vitro cytotoxicity studies on other bioactive compounds, such as plant-derived extracts tested against colon cancer cell lines, similarly reflect the growing interest in identifying small molecules with anti-tumor potential (Anam et

al., 2026). Beyond fumaric acid, several other naturally occurring or semi-synthetic compounds have been reviewed for comparable pharmacological properties; astaxanthin, a carotenoid from *Haematococcus pluvialis*, has been explored for its antioxidant and cytoprotective effects in various biomedical contexts (Prayogo et al., 2025). More recently, ensitrelvir fumaric acid has shown clinical efficacy as an oral antiviral for SARS-CoV-2 (Mukae et al., 2023). Although the present study did not assess any biomedical properties directly, the efficient synthesis of high-purity fumaric acid remains a necessary precursor step for pharmaceutical applications of fumarate-based compounds.

### 4.5 Limitations

Several limitations should be acknowledged. First, melting point measurements were single determinations without replicates, limiting data precision. Triplicate measurements with mean and standard deviation reporting would strengthen confidence in the values. Second, product characterization was limited to melting point and gravimetric yield; spectroscopic confirmation by FTIR or NMR was not performed, and such data would be needed for definitive structural verification. Third, a commercially available fumaric acid standard was not included for comparative melting point analysis. Fourth, the reflux time (15 minutes) and catalyst concentration were not varied systematically; optimization of reaction parameters could improve both yield and purity.

## 5. CONCLUSION

This study demonstrated the synthesis of fumaric acid (trans-butenedioic acid) from maleic acid (cis-butenedioic acid) via HCl-catalyzed isomerization under reflux conditions. Maleic acid was obtained with a melting point of 139°C (within the literature range of 130-139°C) and a yield of 25.39%. Fumaric acid was obtained with a melting point of 280°C (slightly below the literature range of 286-302°C) and a yield of 34.64%. The 141°C difference in melting points between the two isomers reflects the greater molecular symmetry, stronger intermolecular hydrogen bonding, and more efficient crystal packing of the trans-configuration. Future studies should include spectroscopic characterization and systematic optimization of reaction parameters to improve product purity and yield.

## DECLARATION

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### Conflict of Interest

The authors declare no conflict of interest.

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### Author Contributions

M.B.H.: Conceptualization, methodology, investigation, formal analysis, writing - original draft, supervision. F.A.P.: Data curation, visualization, writing - review and editing. Both authors read and approved the final manuscript.

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