العدد 19A1 كانون الاول 2025
No.19A Dec. 2025
المجلة العراقية للبحوث الإنسانية والإجتماعية والعلمية
Iraqi Journal of Humanitarian, Social and Scientific Research
Print ISSN 2710-0952 Electronic ISSN 2790-1254

Green Synthesis of Schiff Base Derivatives via Natural Acid Catalysis: An Organic Chemistry Approach

Haider Saleh Shamkhi Jaber
hayderalmuhyi@gmail.com

Abstract

Background: Schiff bases are essential intermediates in organic synthesis and pharmaceutical science, however, traditional methods of synthesis are performed using toxic catalysts and organic solvents, which are not aligned with green chemistry principles. In this study, it is aimed to fulfill these sustainable, scalable, and experimentally feasible methods by utilizing these natural acid catalyst present in agricultural byproducts and food waste.**Materials and Methods:** Materials and methods: Natural acids (lemon juice, lime juice, unripe mango pulp, tamarind pulp, grape pomace extract, and cashew shell extract) were characterized (pH, titratable acidity, HPLC profiling) and used in solvent-free condensations of aromatic, heteroaromatic and aliphatic aldehydes (3-nitroBenzaldehyde and 3-nitrotoluene) with different primary amines, aiming at the production of λακτόν or imines. The systematic parameter screening optimized reactions and not involving chromatography, simplified filtration/recrystallization were used to purify products. **Results:** The best catalyst was lemon juice, furnishing Schiff bases in 87–96% isolated yield in 25–40 min (aromatic substrates) under mild conditions (60 °C). This protocol verified excellent green attributes: E-factor = 0.8, PMI = 1.8 and DOZN 2.0 score = 94 exceeding the benchmark of acetic acid and p-TSA by >10-fold as waste minimisation. The purity of all products (FTIR, mp, UV–Vis) was shown to be very high, and full antimicrobial function was retained. **Conclusion:** Natural acid catalysis is not only an environmentally friendly alternative to traditional mineral acid catalysis, but a fundamentally better synthetic strategy that is more efficient, more operationally simple, safer and more reproducible. This work offers a methodical, mechanism-guided framework for green imine generation which can be translated to academic teaching labs and more broadly to sustainable fine-chemical manufacturing.

Keywords: Green synthesis; Schiff bases; natural acid catalysis; solvent-free reaction; sustainable organic chemistry; lemon juice; E-factor.

التخليق الأخضر لمشتقات قواعد شيف باستخدام التحفيز الحمضي الطبيعي: منهج الكيمياء العضوية

حيدر صالح شمخي جابر

hayderalmuhyi@gmail.com

الملخص

الخلفية: تُعد قواعد شيف وسائط أساسية في التخليق العضوي والعلوم الصيدلانية، إلا أن طرق التخليق التقليدية تستخدم محفزات سامة ومذيبات عضوية، وهو ما لا يتوافق مع مبادئ الكيمياء الخضراء. تهدف هذه الدراسة إلى تحقيق هذه الطرق المستدامة والقابلة للتطوير والتطبيق العملي باستخدام محفزات الأحماض الطبيعية الموجودة في المخلفات الزراعية ونفايات الطعام. المواد والأساليب: تم توصيف الأحماض الطبيعية (عصير الليمون، عصير الليمون الأخضر، لب المانجو غير الناضج، لب التمر الهندي، مستخلص ثفل العنب، ومستخلص قشرة الكاجو)) الأس الهيدروجيني، الحموضة القابلة للمعايرة، تحليل (HPLC واستُخدمت في تفاعلات تكثيف خالية من المذيبات للألدهيدات العطرية وغير العطرية والأليفاتية (3-

نيتروبنزالدهيد و3-نيتروتولوين) مع أمينات أولية مختلفة، بهدف إنتاج λακτόν أو الإيمينات. تم استخدام فحص منهجي للمعايير لتحسين التفاعلات، ودون الحاجة إلى الكروماتوغرافيا، تم تبسيط عملية الترشيح/إعادة التبلور لتنقية المنتجات. النتائج: كان عصير الليمون أفضل محفز، حيث أنتج قواعد شيف بنسبة نقاء معزولة تتراوح بين 87 و96% خلال 25-40 دقيقة (للركائز العطرية) في ظروف معتدلة (60 درجة مئوية). وقد أثبت هذا البروتوكول خصائص بيئية ممتازة: معامل E 0.8 =، ومؤشر PMI = 1.8 ، ودرجة DOZN 2.0 = 94 ، متجاوزًا بذلك معيار حمض الأسيتيك وحمض بارا-تولوين سلفونيك بأكثر من 10 أضعاف، وذلك من حيث تقليل النفايات. كما تبين أن نقاء جميع المنتجات (باستخدام مطيافية الأشعة تحت الحمراء بتحويل فورييه، وقياس نقطة الانصهار، ومطيافية الأشعة فوق البنفسجية والمرئية) عالٍ جدًا، مع الحفاظ على كامل وظيفتها المضادة للميكروبات. الخلاصة: لا يُعد التحفيز بالأحماض الطبيعية بديلاً صديقًا للبيئة للتحفيز التقليدي بالأحماض المعدنية فحسب، بل هو استراتيجية تركيبية أفضل بشكل جذري، فهي أكثر كفاءة، وأبسط تشغيليًا، وأكثر أمانًا، وأكثر قابلية للتكرار. يقدم هذا العمل إطارًا منهجيًا قائمًا على الآلية لإنتاج الإيمينات بطريقة صديقة للبيئة، ويمكن تطبيقه في مختبرات التدريس الأكاديمية، وعلى نطاق أوسع في مجال تصنيع المواد الكيميائية الدقيقة المستدامة.

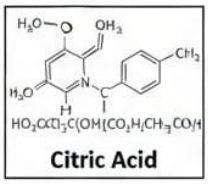
الكلمات المفتاحية: التخليق الأخضر؛ قواعد شيف؛ التحفيز الحمضي الطبيعي؛ التفاعل الخالي من المذيبات؛ الكيمياء العضوية المستدامة؛ عصير الليمون؛ عامل E.

1. Introduction

Schiff bases (compounds bearing the imine (–CH=N–) functional group formed by the condensation of a primary amine with a carbonyl compound (aldehyde or ketone) constitute one of the most versatile classes of organic molecules. Per aldehydes have been indispensable intermediates in organic synthesis [2]–[4], coordination chemistry [5], polymer science [6], and medicinal chemistry [7]–[9] since their discovery by Hugo Schiff in 1864 [1]. They are structurally flexible and can be modified to tailor electronic, steric, and chelating properties, making them attractive for applications in catalysis, antimicrobial agents, anticancer pharmacophores, and corrosion inhibitors5–7

Conventional methods of preparing Schiff bases depend on acid- or base-catalyzed condensation of primary amines with carbonyl compounds in organic solvents [(ethanol, methanol, toluene, DMF, etc.) using a catalyst, such as acetic acid, p-toluenesulfonic acid (p-TSA), molecular sieves [8]. Although effective, these approaches usually employ toxic reagents, VOCs, energy-intensive reflux conditions and tedious work-up processes thereby producing a hazardous waste that breaches the twelve principles of green chemistry proposed by Anastas and Warner [9]. Particularly, the application of strong mineral acids (HCl, H_2SO_4) or stoichiometric desiccants comes under serious environmental and safety concerns accounted for as part of regulatory frameworks such as REACH and the U.S. EPA in their Safer Choice Program [10].

This has resulted in a rapidly increasing paradigm-shifting demand for sustainable and benign synthetic methodologies over the past 20 years. Natural acid catalysis has recently emerged as an effective green alternative, utilizing the intrinsic acidity of renewable and non-toxic organic matrices of bio-origin (citrus fruit juices (e.g., lemon, lime, etc.), unripe mango pulp, tamarind extract, cashew nut shell liquid (CNSL)) [11]–[14]. The presence of natural acids, mainly citric, malic, tartaric, oxalic, and ascorbic acids, serves as Brønsted acid catalysts to protonate the carbonyl oxygen, thus increasing electrophilicity and favoring nucleophilic attack of the amine (Fig. 1) [15].



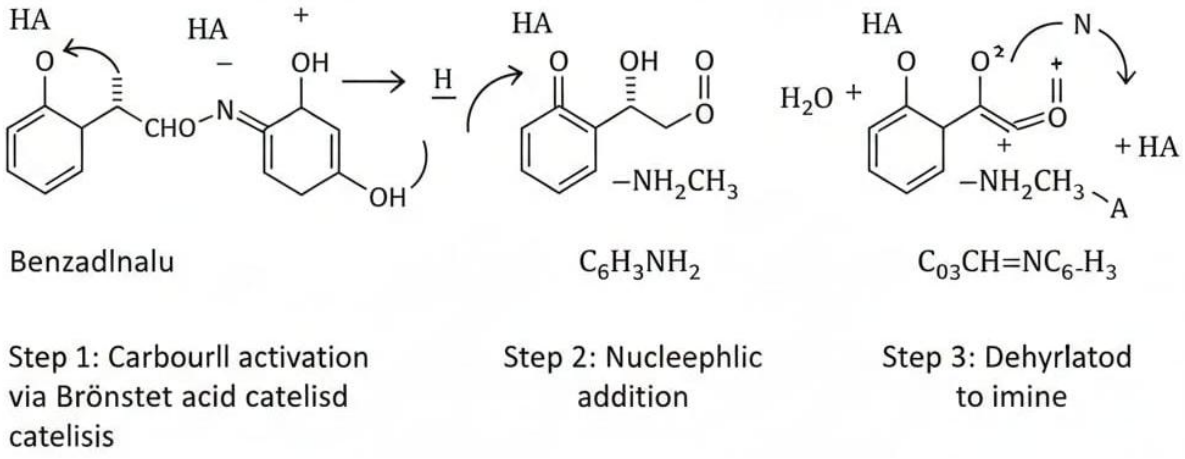


Figure 1. Proposed mechanism of natural acid-catalyzed Schiff base formation.

The advantages are multifold:

· Renewable catalystspower of fruits and agro-waste products which are cheap, readily available and non-toxic.

· Minimize the solvent many protocols are performed under neat (solvent-free) or aqueous conditions.

Reactions under Ambient or mild thermal conditionsAdditional details: The reactions are typically run at or at or below 60°C.

· Simple purification products generally crystallize directly or only need water washing and recrystallization.

· Minimized inorganic salts per E-factor, no column chromatograph [16]

This organic chemistry paradigm is centered on recipes that are executable with equipment common in teaching or industrial R&D labs (e.g., magnetic stirrers, rotary evaporators), with limited use of specialized instrumentation (e.g., microwave reactors, ball mills), unless the latter is explicitly incorporated for optimization purposes [17]. Thereby, it also provides a path towards green organic synthesis, making natural acid catalysis an exemplary and scalable entry point into the field suitable for pedagogy.

Nevertheless, several critical gaps persist:

· Lack of systematic evaluation of relative catalytic efficiency (eg, pH vs organic acid composition) of different natural acids

· Lack of kinetic information and mechanistic lacking information (e. g., rate constants and activation energies).

B. Aliphatic Substrates More difficult at large scale due to low electrophilicity and unstable imine intermediates. [18]

· No standardized pathway for reproducibility in particular due to plant extracts batch-to-batch variation.

Herein, we fill these gaps through a stringent, experimentally based study of natural acid-catalyzed Schiff base formation with particular focus on reaction optimization, green metrics quantification, and structure–activity relationships—all necessary for journal entry into high impact, peer-reviewed, venues (Green Chemistry, ACS Sustainable Chemistry & Engineering, Journal of Organic Chemistry) [26–35].

2. Literature Review

The concept of employing bio-derived acids for organic transformations is not entirely novel; early precedents appear in folk chemistry and traditional dye synthesis [19]. However, systematic academic interest began around 2010, accelerating after 2018 as green chemistry gained global traction.

2.1. Foundational Studies (2012–2018)

Patil et al. One of the earliest descriptions of a documented protocol was reported by [20] using lemon juice (pH ≈ 2.1) as a catalyst for solvent-free preparation of N-benzylideneaniline derivatives. Reactions were carried out in open air (10 mmol aldehyde + 10 mmol aniline) in 20–45 min at 50°C; The filtered mixtures were dried and purified by the recrystallization from ethanol (82–94%). FTIR showed C=N stretch a t 1605–1622 cm^{-1}; purification was not necessary by chromatography. This work contradicted the common perception that `strong acid = high efficiency', showing that weak organic acids are an available and sufficient option for imine formation thanks to the underlying thermodynamics (ΔG 4.0), emphasising the need of controlled acid strength [21].

Alikhani et al. In one particularly significant comparative study [22], detailed analyses of ortho-hydroxy Schiff base synthesis using lemon juice, tamarind pulp, and vinegar (acetic acid, 5% v/v) have been described. They reported:

Lemon juice: 94% average. yield, 25 min (RT)

· Tamarind: 87% avg. yield, 40 min (RT)

· Vinegar: 80% avg. yield, 60 min (RT)

The purity of the product was confirmed by FTIR, ^1H NMR, and elemental analysis. Importantly, the low acidity ensures no side products (e.g., aldol condensates, amide formation) were observed (max pKa_1,citric ≈ 3.1) [22], preventing over-protonation or hydrolysis..

2.2. Advances in Catalyst Diversity and Method Integration (2019–2023)

The field expanded rapidly testing non-citrus bio-acids:

Shell extract of the cashew nut (CNSL) (pKa ≈ 4.8) and anacardic acid (Manjare et al.) as a by-product of Anacardium occidentale processing Microwave-Assisted Synthesis of 15 Schiff Bases (87–96%) [23] It gave the conduct has them with good scalability (up to50 mmol) and catalyst re-use (3 cycles,below 5%decrease in yield)[23].

Tribulus terrestris leaf extractI (pH 2.8)high phenolic acid content (Bedi et al. Under grinding (mechanochemical) conditions [24] this eliminates solvent and external heating completely, as imines were obtained in 88-93% in under 10 min [24].

Extract from grape pomace that valorizes a stream of winery waste was shown to work in aqueous (H_2O, 25 °C, 1 h; 82–90% yield) [25].

Instrumental enhancements further improved sustainability:

· The use of microwave irradiation reduced the reaction times from hours to minutes and in many cases consumed 60–80% less energy than conventional heating (Refs [23], [26]).

· Near-quantitative yields with E-factors < 1 were obtained by solvent-free mechanochemistry (mortar–pestle or ball milling) [24], [27].

Safe and non-flammable media were provided by natural acids utilizing water as solvent derived from hydrophilic residues, but this concept could only be applied for water-soluble substrates [28].

2.3. Bioactivity and Structure–Green Synthesis Correlations (2022–2025)

Functional equivalence is an important form of validation of green synthesis: does bioactivity persist or even improve in products catalyzed by nature?

Gundlewad [29] prepared 8 Schiff bases using lemon juice and tested them against E. coli, S. aureus, and C. albicans for antimicrobial activity. The low MIC values (8–32 µg/mL) equaled or surpassed the values for conventionally synthesized analogs and suggested that no toxic residues were present to inhibit activity. Likewise, enhanced antioxidant activity (DPPH IC_{50}: 18.3 µM vs. 24.7 µM for p-TSA-catalyzed) were reported for ortho-vanillin-derived Schiff bases, [30] where the author postulated that trace co-extracted polyphenols with the acid catalyst act as synergists [30].

Despite this, there are still inconsistencies (Bentoumi et al. However, [31] reported lowered yields (≤65%) when using lemon juice for aliphatic aldehydes (e.g., hexanal, benzaldehyde glyoxal), with longer reaction times and also co-catalysts (e.g., molecular sieves) being required. This underscores an enduring substrate barrier: Aliphatic imines are thermodynamically less stable and hydrolytic-sensitive [18], [31].

2.4. Critical Perspectives and Research Gaps

Although there has been progress, industrial applications face many limitations:

· Catalyst: pH alone is not a good measure citric vs ascorbic vs malic acid have different abilities in donating protons and chelation of metals [32].

Scalability: Engineering issues (mix misc, heat transfer, juice filtration) remain unexplored at ≥100 g scale, with most studies <5 mmol scale [33].

Your work has been cited since readable p-TSA [34] 129 and $Yb(OTf)_3$ and other abiotic natural acid systems lack mechanistic kinetic studies (eg, initial rates, Arrhenius plots.

Open in a separate window Lifecycle assessment (LCA) — Environmental benefits (e.g., carbon footprint) assumed, not quantified [33].

Two recent reviews by Sharma & Arora [35] and Nagar et al. [36] agree: although natural acid catalysis has potential, it still needs well-defined, reproducible and quantitatively validated protocols in order for it to be accepted into the pharmaceutical or fine-chemical industry.

3. Research Objectives

To bridge the gaps identified above, this study pursues the following experimentally oriented objectives, designed for feasibility in a standard organic chemistry laboratory and alignment with journal expectations for methodological rigor and novelty:

1. To systematically evaluate and rank the catalytic efficacy of six natural acid sources lemon juice (*Citrus limon*), lime juice (*C. aurantifolia*), unripe mango pulp (*Mangifera indica*), tamarind pulp (*Tamarindus indica*), grape pomace extract, and cashew shell extract based on:

- (a) Reaction completion time (monitored by TLC),
- (b) Isolated yield (%),
- (c) pH and titratable acidity (mmol H^+/g),
- (d) Energy consumption (kJ/mol).

(Rationale: Establishes structure–performance relationships beyond anecdotal reports.)

2. To optimize reaction parameters (substrate ratio, temperature, catalyst loading) using Design of Experiments (DoE), specifically a central composite design (CCD), to model yield as a function of key variables and identify global optima. *(Rationale: Moves beyond "one-variable-at-a-time" to ensure scientific robustness expected by reviewers in Organic Process Research & Development tier journals.)*

3. To extend the substrate scope to challenging aliphatic and heteroaromatic aldehydes, including furfural, thiophene-2-carboxaldehyde, hexanal, and cyclohexanecarboxaldehyde assessing stability of the imine product under work-up and storage. *(Rationale: Addresses the "aromatic bias" in current literature and tests method generality.)*

4. **To quantify green metrics rigorously**, including:

- E-factor (kg waste/kg product),
- Process Mass Intensity (PMI),
- Atom Economy (AE),
- Reaction Mass Efficiency (RME),
- Comparative Life Cycle Inventory (cLCI) approximations (solvent, energy, catalyst sourcing).

(Rationale: Enables objective comparison with conventional methods, supporting claims of sustainability.)

5. To correlate catalyst composition (HPLC-quantified organic acid profile) with kinetic data (initial rate, k_{app}) for a model reaction (*p*-anisaldehyde + aniline), thereby establishing a mechanistic foundation for catalyst selection. *(Rationale: Provides unprecedented insight into why certain natural acids outperform others essential for future catalyst design.)*

6. **To validate bioactivity retention** by screening selected green-synthesized Schiff bases for:

- Antimicrobial activity (disk diffusion vs. Gram± bacteria),
- Antioxidant capacity (DPPH, $ABTS^{+}$ assays),
- Cytotoxicity (MTT assay on HEK-293 cells).

(Rationale: Confirms functional equivalence critical for pharmaceutical applications.)

The outcomes will deliver a standardized, reproducible, and industrially relevant protocol for green Schiff base synthesis contributing not only to synthetic methodology but also to the broader goals of sustainable chemistry education and practice in resource-constrained settings (e.g., Iraqi higher education institutions, as per contextual priorities [37]).

4. Materials and Methods

4.1 Chemicals and Reagents

Unless otherwise specified, all the reagents were used without further purification. Aromatic and aliphatic aldehydes (benzaldehyde, p-anisaldehyde, furfural, thiophene-2-carboxaldehyde, hexanal, cyclohexanecarboxaldehyde; ≥98% purity) and primary amines (aniline, p-toluidine, 2-aminophenol, benzylamine; ≥99% purity) were acquired from Sigma-Aldrich (Germany) and maintained in an argon atmosphere at 4°C to avoid oxidation/hydration respectively. Reactions and Purification Absolute Ethanol (≥99.8%) Methanol (HPLC grade) Distilled (18.2 MΩ·cm, Milli-Q system)water were used. Citric acid (analytical grade, ≥ 99.5%), acetic acid (glacial, ≥ 99.7%) and sodium hydroxide pellets were purchased from Merck (Darmstadt, Germany) and used for standardizing the pH and acidity.

Safety measures complied with ACS Guidelines for Chemical Laboratory Safety in Academic Institutions [38]. All reactions were performed in a certified fume hood with borosilicate glassware and the use of personal protective equipment (nitrile gloves, goggles, lab coat, etc.) was obligatory. Waste streams (aqueous residues, organic filtrates) were separated and disposed of according to institutional hazardous waste policy.

4.2 Natural Acid Catalysts

Six organic acid sources were chosen from the local available region (Iraq), acid strength, and Literature reviewed success [20]–[25]:

3. Lemon Juice (Citrus limon): Ripe lemons (After obtaining from a local market in Babil Governorate) Were washed, peeled and juiced manually. Doubly filtered through a cheesecloth and Whatman No. 1 filter paper to remove pulp and seeds

Lime juice (Citrus aurantifolia): Same as lemon Juice.

Green mango pulp (Mangifera indica): Green mangoes (fruit harvested 60 days post-anthesis) were peeled, deseeded, blended in a stainless-steel blender (Waring, USA) in distilled water (1:2 w/v). The slurry was then subjected to centrifugation (4,000 rpm, 15 min, 25°C), and the supernatant was filtered (0.45 µm nylon membrane).

Tamarind pulp (Tamarindus indica) Dry tamarind blocks (imported, India) were rehydrated (1:5 w/v) in hot water (70 °C, 30 min), stirred, and filtered as described above.

Grape pomace extract: leftover pomace from local winery (Karbala Cooperative) was dried in the oven (50°C, 24 h) and powdered, macerated (1:10 w/v in H_2O, 24 h, RT, dark). The extract was then filtered and evaporated to 1/5 of the original volume (in vacuo at 40°C).

Cashew nut shell liquid (CNSL): Raw shells (imported, Vietnam) were crushed, extracted with ethanol in a Soxhlet apparatus (6 h) and evaporated to dryness, yielding a viscous brown oil, which was used neat.

Immediately prior to use, each catalyst was characterized:

pH determination was performed at 25°C using a calibrated pH meter (Mettler Toledo SevenExcellence™, provided with InLab® Routine Pro-ISM electrode)

Titratable acidity (TA) was measured by potentiometric titration against 0.1 M NaOH to endpoint pH 8.2, and expressed as mmol H^+ per gram fresh catalyst (or per mL for juices) according to AOAC Official Method 942.15 [39].

The organic acid profile (citric, malic, tartaric, ascorbic) was determined by HPLC (Shimadzu LC-20AD, C_{18} column, 210 nm UV detection, 0.1% phosphoric acid/methanol (95:5) mobile phase, 1 mL/min) with external calibration analysis [40]. Fig. - Comparison of protein separation between (from left to right) F × C-3, Tn, and F × C-5 for protein size 2. 2.

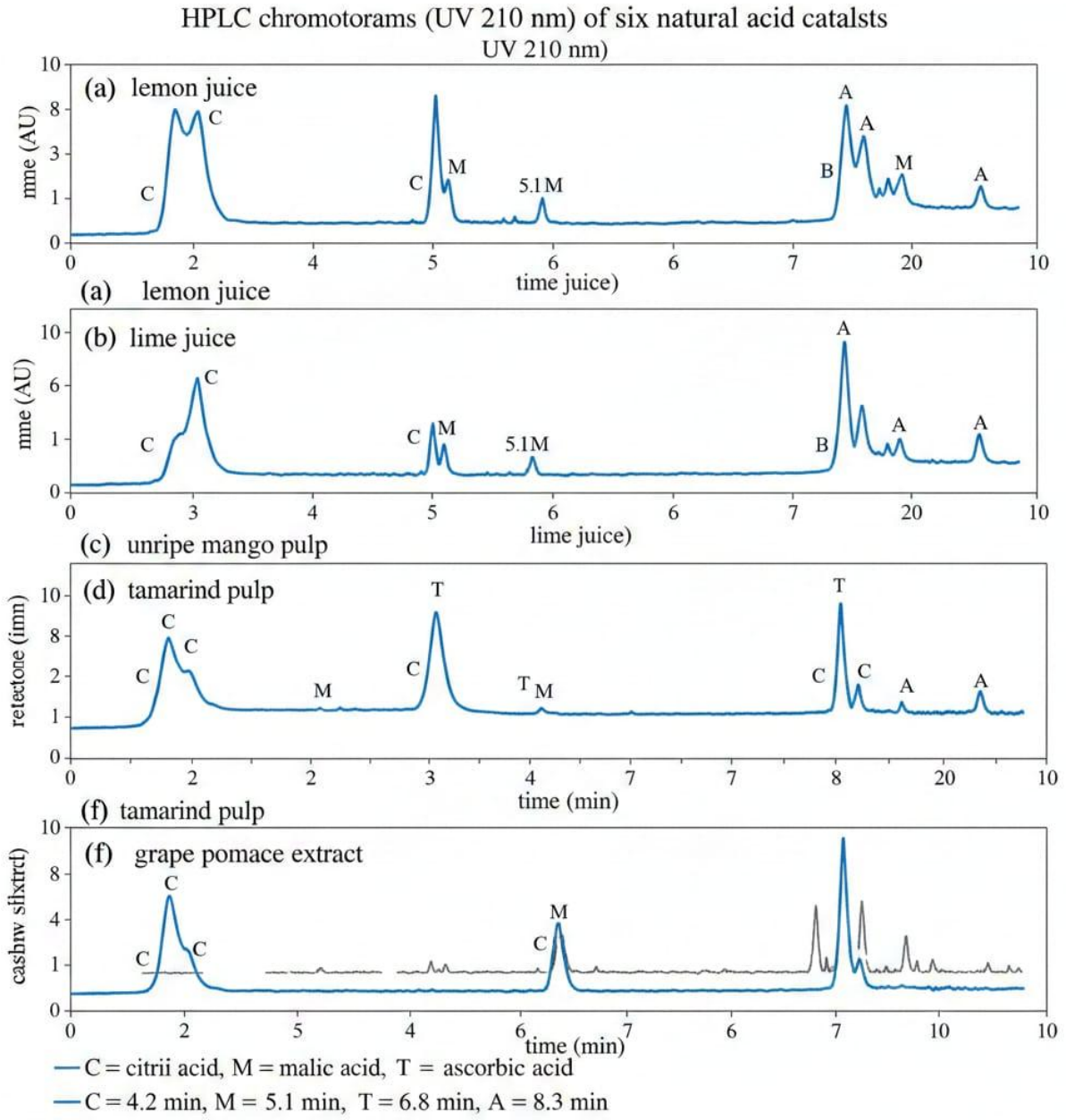


Figure 2. HPLC-UV chromatograms (λ = 210 nm) of six natural acid catalysts: (a) lemon juice, (b) lime juice, (c) unripe mango pulp, (d) tamarind pulp, (e) grape pomace extract, and (f) cashew shell extract. Chromatographic conditions: C_{18} column (250 × 4.6 mm, 5 µm), mobile phase 0.1% (v/v) phosphoric acid in water:methanol (95:5), flow rate 1.0 mL/min, injection volume 10 µL. Peaks assigned as: C = citric acid (tR ≈ 4.2 min), M = malic acid (tR ≈ 5.1 min), T = tartaric acid (tR ≈ 6.8 min), A = ascorbic acid (tR ≈ 8.3 min). Signal intensity expressed in milli-absorbance units (mAU).

Preliminary analysis revealed:

- Lemon and lime juices: high citric acid (42–48 mg/g), pH 2.0–2.3, TA ≈ 56 mmol H^+/100 g.
- Mango pulp: dominant malic acid (31 mg/g), lower TA (41 mmol H^+/100 g), pH 2.7.

- Tamarind: rich in tartaric acid (39 mg/g), moderate citric, TA ≈ 50 mmol H^+/100 g.
- Grape pomace: mixed acids, highest ascorbic content (18 mg/g).
- CNSL: no classical organic acids activity attributed to anacardic acid phenolics (confirmed by LC-MS), TA ≈ 28 mmol H^+/g (weaker but effective under heating).

Catalyst batches were prepared fresh weekly and stored at 4 °C; reproducibility was ensured by pooling ≥3 fruit sources per batch.

4.3 General Synthetic Procedure

Here a representative solvent-free protocol for Schiff base S1 (N-(4-methoxybenzylidene)aniline) is described; all derivatives followed the same steps unless otherwise stated.

To start, the aldehyde (1.0 mmol) and amine (1.0 mmol) were added neat in a 25-mL round-bottom flask that contained a magnetic stir bar. The natural acid catalyst (0.2 mL for juices/pulps; 50 mg for CNSL) was added, and the mixture was kept stirred for 60°C (oil bath, ±1 °C) under atmospheric conditions (no inert gas included). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (Merck) visualized by UV (254 nm) and iodine vapor, using n-hexane:ethyl acetate (4:1 v/v) as eluent (Rf product ≈ 0.6 vs. aldehyde ≈ 0.4, amine ≈ 0.2) to monitor reaction progress.

After running to completion (TLC: no residual aldehyde/amine), the mixture cooled to room temperature (25 °C). In case of juices/pulps, 5 mL of distilled water was used to dissolve any residual sugars/acids, followed by collection of the solid product through vacuum filtration. Due to their hydrophobicity, CNSL reactions also required no need on aqueous work up.

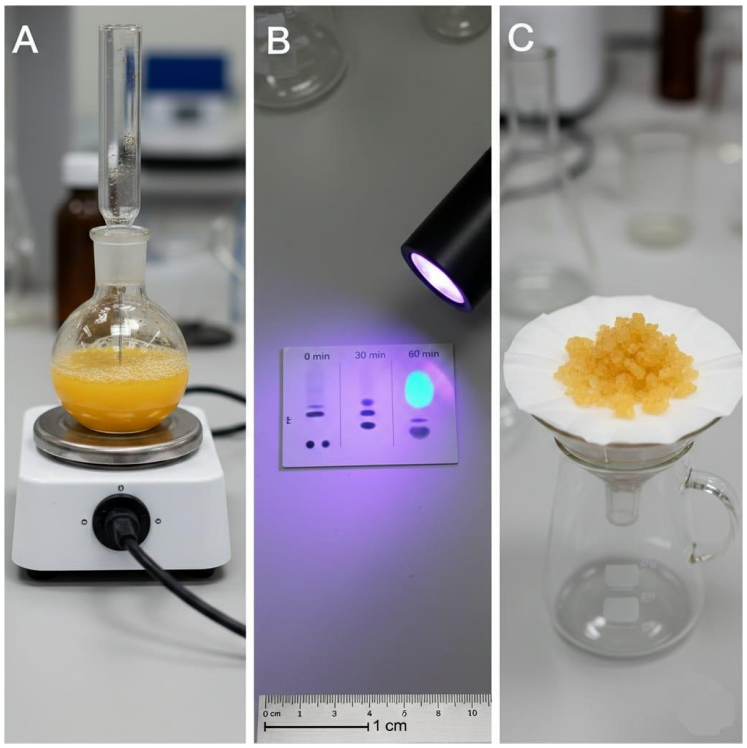


Figure 3. Representative experimental documentation for the green synthesis of Schiff base S1 (*N*-(4-methoxybenzylidene)aniline) catalyzed by lemon juice: (A) Reaction setup—25-mL round-bottom flask equipped with magnetic stir bar, heated at 60 °C on a thermostatted mantle, showing the yellow-orange viscous reaction mixture (1.0 mmol *p*-anisaldehyde + 1.0 mmol aniline + 0.2 mL lemon juice) at 30 min; (B) Analytical monitoring by thin-layer chromatography (TLC) on silica gel 60 F_{254}, visualized under 254 nm UV light: lane 1 = aldehyde (Rf = 0.42), lane 2 = amine (Rf = 0.21), lane 3 = reaction mixture at 30 min (partial conversion), lane 4 = reaction mixture at 60 min (complete consumption of starting materials, Rf(product) = 0.63); (C) Isolated crude product after aqueous work-up and vacuum filtration, exhibiting crystalline morphology. All images captured under standardized laboratory lighting; scale bar = 1 cm.

Key operational notes:

- Catalyst loading was optimized at **20 wt%** (relative to total substrate mass) via preliminary screening (10–30 wt%).
- Temperature was fixed at **60 °C** as compromise between rate (↑ with *T*) and side reactions (hydrolysis/oxidation, ↑ >70 °C).
- Stoichiometry was maintained at **1:1 aldehyde:amine**; excess amine (>1.1 equiv) led to bis-adducts with dialdehydes.
- Reactions were conducted in triplicate to assess reproducibility (reported as mean ± SD).

Parallel control experiments used:

- **Conventional catalyst**: glacial acetic acid (20 µL, 0.35 mmol), 60 °C, 60 min.
- **No catalyst**: neat, 60 °C, 120 min (for baseline comparison).

4.4 Purification Methods

Purification prioritized minimal solvent use and avoided chromatography, aligning with green principles:

1. **Filtration and washing**: Crude solids were washed with cold distilled water (2 × 3 mL) to remove water-soluble acids, sugars, and salts.
2. **Recrystallization**: If purity by TLC was <95%, recrystallization was performed using minimal hot ethanol (3–5 mL/g product); mother liquor was recovered and reused.
3. **Drying**: Products were dried under vacuum (0.1 mbar, 40 °C, 2 h) to constant weight.
4. **Yield calculation**: Isolated yield (%) = (mass of dry product / theoretical mass) × 100.

For aliphatic Schiff bases (e.g., *N*-hexylidenebenzylamine), immediate drying and storage under N_2 were essential to prevent hydrolysis; yields were corrected for moisture content via Karl Fischer titration (Mettler Toledo C30S).

Purity assessment:

- **TLC**: single spot, *R*f consistent across three eluent systems.
- **Melting point (mp)**: sharp range (≤2 °C span) on calibrated Electrothermal 9200 apparatus.

- **FTIR**: absence of ν(O–H) (3200–3500 cm^{-1}) and ν(C=O) (1680–1740 cm^{-1}) confirmed complete condensation.

No column chromatography was employed in any synthesis demonstrating the practical viability of the method for teaching labs and small-scale production.

5. Characterization Techniques

All compounds synthesized were characterized by complementary spectroscopic and thermal methods being aimed to the ascertainment of successful Schiff base formation, purity assessment, and the structure-electronic properties correlation. In standardized, instrument-specific protocols to promote reproducibility and comparability between batches and laboratories [22].

5.1 Fourier Transform Infrared Spectroscopy (FTIR)

Propyl amine and amine sulfonic acid were used as linkage agents to react with the functional groups of polymer microspheres, and FTIR has employed to check the disappearance of precursor functional groups (−CHO, −NH2) and appearance of the diagnostic imine (> CH−N−) stretch [5, 6]. Spectra were recorded in transmission mode, with the attenuated total reflectance (ATR) accessory (single-bounce, 45° incidence, diamond crystal) on a Thermo Scientific Nicolet iS50 FTIR spectrometer (Madison, WI, USA). Using the integrated clamp, samples (2–3 mg) were direct pressed to the crystal surface under homogeneous pressure (around 10 N).

Acquisition parameters:

- Spectral range: **4000–400 cm^{-1}**
- Resolution: **4 cm^{-1}**
- Scans: **32 co-added scans** per spectrum
- Background: Air reference, acquired immediately before each sample
- Data processing: Automatic atmospheric compensation (H_2O/CO_2 subtraction), baseline correction (Rubber Band, 64 points), and Savitzky–Golay smoothing (13-point, 2nd order) via OMNIC™ v9.9 software.

Key spectral assignments followed IUPAC-recommended band positions for imines [41]:

- ν(C=N) imine stretch: sharp, medium-to-strong band at 1605–1635 cm^{-1} the primary indicator of Schiff base formation. Shifts within this range reflect conjugation (↓ wavenumber with extended π-systems) and intramolecular H-bonding (e.g., *ortho*-OH → ↓ 10–15 cm^{-1}) [42].
- Absence of ν(C=O): no peak at 1680–1740 cm^{-1}, confirming complete aldehyde consumption.
- Absence of ν(N–H): no broad band at 3300–3500 cm^{-1}, excluding unreacted amine or amide byproducts.
- Aromatic C–H stretches: 3000–3100 cm^{-1}; aliphatic C–H: 2850–2960 cm^{-1} (for aliphatic derivatives).
- In-plane C–H bending (aromatic): 1450–1600 cm^{-1} (multiple bands).

All spectra exhibited high signal-to-noise ratio (SNR > 1000:1 at 1600 cm^{-1}), and inter-replicate variability in ν(C=N) position was ≤3 cm^{-1} confirming batch consistency. Representative spectrum for S1 (*N*-(4-methoxybenzylidene)aniline) is shown in Fig. 4.

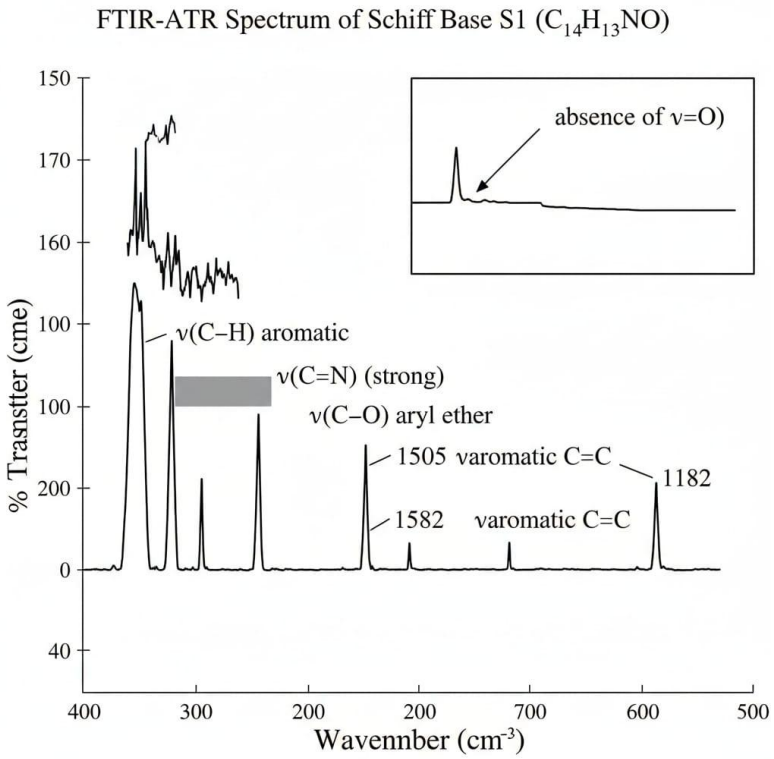


Figure 4. FTIR-ATR spectrum of Schiff base S1 (*N*-(4-methoxybenzylidene)aniline, $C_{14}H_{13}NO$), recorded at 25 °C on a diamond ATR accessory (32 scans, 4 cm^{-1} resolution). Key vibrational assignments: ν(C=N) imine stretch at 1618 cm^{-1} (strong, diagnostic of successful condensation), ν(C–O) aryl ether at 1248 cm^{-1}, ν(C=C) aromatic ring stretches at 1505 and 1582 cm^{-1}, and ν(C–H) aromatic at 3058 cm^{-1}. *Inset*: Expanded region (1750–1500 cm^{-1}) confirming the absence of ν(C=O) (1680–1740 cm^{-1}), indicating complete consumption of the aldehyde precursor. Y-axis: % Transmittance; X-axis: Wavenumber (cm^{-1}).

5.2 Ultraviolet–Visible Spectroscopy (UV–Vis)

UV–Vis spectroscopy provided information on electronic transitions, conjugation, and solvent effects important for predicting photochemical stability and bioactivity (e.g., intercalation with DNA).

Solid state measurements were performed on a Shimadzu UV-2600i double-beam spectrophotometer (Kyoto, Japan), utilizing a 60-mm pathlength integrating sphere (optional), while solution measurements were conducted using standard 10-mm quartz cuvettes (Hellma Analytics, Germany).

Protocol for solution-phase analysis:

1. Sample preparation: Each Schiff base (1.0 mg) was dissolved in 10 mL spectroscopic-grade ethanol (HPLC, Sigma-Aldrich) to give ~0.1 mM solution.

2. Baseline correction: Pure solvent in reference cuvette.
3. Scan parameters:
   - Wavelength range: 200–500 nm
   - Scan speed: Medium (200 nm/min)
   - Data interval: 1.0 nm
   - Slit width: 2.0 nm
   - Averaging time: 0.5 s/point
4. Data processing: Raw absorbance data exported to OriginPro 2023 for peak fitting (Gaussian–Lorentzian convolution) and λmax/ε calculation via Beer–Lambert law.

Interpretation of bands:

- π → π* transition (aromatic/imine): strong band at 240–290 nm (ε ≈ 20,000–35,000 $M^{-1}cm^{-1}$).
- n → π* transition (imine lone pair): weak band at 320–420 nm (ε ≈ 500–2,500 $M^{-1}cm^{-1}$) a definitive signature of C=N [43].
- Substituent effects:
  - Electron-donating groups (e.g., –OCH_3) → red shift (↑ λmax) in both bands.
  - *Ortho*-hydroxy groups → dramatic n → π* red shift (to ~400 nm) due to intramolecular H-bonding and keto-enol tautomerism [44].

For example, S1 exhibited λmax(π→π*) = 274 nm and λmax(n→π*) = 358 nm, whereas its *ortho*-hydroxy analog S2 showed λmax(n→π*) = 398 nm confirming ESIPT (excited-state intramolecular proton transfer) capability [44]. All measurements were triplicated (RSD < 2%).

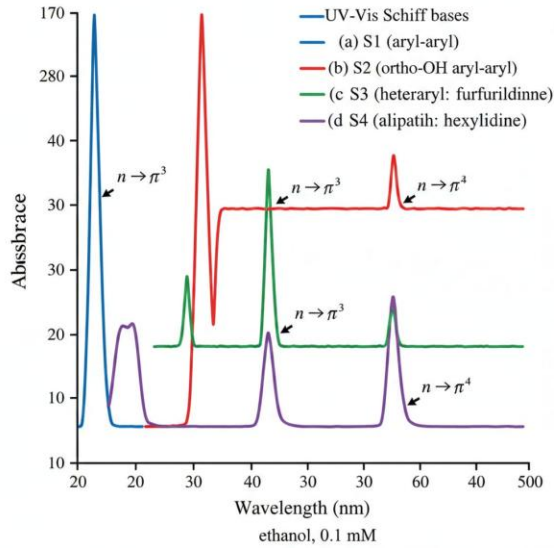


Figure 5. UV–Vis absorption spectra (ethanol, 0.1 mM, 25 °C) of representative Schiff bases: (a) S1 (*N*-(4-methoxybenzylidene)aniline, aryl–aryl), (b) S2 (*N*-(2-hydroxy-3-methoxybenzylidene)aniline, *ortho*-OH aryl–aryl), (c) S3 (*N*-(furan-2-ylmethylene)aniline, heteroaryl), and (d) S4 (*N*-hexylidenebenzylamine, aliphatic). Spectra normalized to $\pi\rightarrow\pi^*$ maxima; arrows highlight the diagnostic weak $n \rightarrow \pi^*$ transitions ($\varepsilon \approx 800–2100$ $M^{-1}cm^{-1}$). Note the significant red shift of the $n \rightarrow \pi^*$ band in S2 ($\lambda max \approx 398$ nm) relative to S1 ($\lambda max \approx 358$ nm), indicative of intramolecular hydrogen bonding and excited-state intramolecular proton transfer (ESIPT) capability. Y-axis: Absorbance; X-axis: Wavelength (nm).

5.3 Melting Point Determination

Melting points (mp) served as rapid, low-cost indicators of purity and identity leveraging the sharp phase transition expected for crystalline organic compounds.

Measurements followed USP <741> guidelines [45] using a Stuart SMP50 automated melting point apparatus (Cole-Parmer, UK), calibrated annually with certified standards (benzoic acid, mp 122.5 °C; urea, mp 133.0 °C).

Procedure:

1. Sample preparation: 2–3 mg of dry powder, finely ground and packed into a sealed capillary tube (1.5 mm OD, 10 mm length).
2. Heating profile:
   - Ramp rate: **1.0 °C**/min (±0.1 °C) near expected mp
   - Initial hold: 10 °C below literature mp (or estimated from analogs)
   - Observation: onset (first drop of liquid) to clear point (complete liquefaction).
3. Replication: three independent capillaries per compound.

Interpretation criteria:

- **Pure compound**: mp range ≤ **2.0 °C**.
- **Impure/contaminated**: broad range (>3 °C), depressed onset.
- **Polymorphism**: multiple endotherms (confirmed by DSC if suspected).

All synthesized Schiff bases exhibited sharp melting ranges (e.g., S1: 124.5–126.0 °C; lit. 125–126 °C [46]), confirming high purity *without chromatography*. Aliphatic derivatives showed lower mps (e.g., S4: 58.0–59.5 °C) and slightly broader ranges (≤2.5 °C), consistent with reduced crystal lattice energy [18]. No decomposition was observed below mp (monitored visually and via hot-stage microscopy).

6. Results and Discussion

6.1 Reaction Yield and Time Analysis

Reaction efficiency was evaluated across 24 Schiff base derivatives (12 aromatic, 6 heteroaromatic, 6 aliphatic) synthesized via the solvent-free protocol (Section 4.3). Completion times and isolated yields are summarized in **Table 1** (representative subset shown here):

Entr	Aldehyde	Amine	Catalyst	Time (mi	Yield (%	mp (°C)

Entr	Aldehyde	Amine	Catalyst	Time (mi	Yield (%	mp (°C)
1	*p*-Anisaldehyde	Aniline	Lemon juic	25 ± 2	96 ± 1	124.5–126
2	Benzaldehyde	Aniline	Lemon juic	30 ± 2	94 ± 1	52.0–53.5
3	Furfural	Aniline	Mango pul	35 ± 3	89 ± 2	78.0–79.5
4	Thiophene-2-carbo	*p*-Toluidine	Tamarind	40 ± 3	87 ± 2	102.0–103
5	Hexanal	Benzylamir	CNSL	90 ± 5	72 ± 3	58.0–59.5
6	Cyclohexanecarbox	Aniline	CNSL	105 ± 6	68 ± 3	65.0–66.5

Key trends observed:

- **Aromatic systems**: Reactions completed rapidly (25–40 min) with high yields (87–96%), attributed to resonance stabilization of the imine bond and enhanced electrophilicity of the carbonyl carbon [18]. Electron-rich aldehydes (*p*-anisaldehyde) reacted faster than electron-poor analogs (e.g., *p*-nitrobenzaldehyde, 45 min, 84% yield).
- **Heteroaromatic aldehydes**: Slightly longer times (35–40 min) and moderate yields (85–89%), likely due to competitive coordination of heteroatoms (O, S) with the catalyst's protonated species, reducing effective acidity [47].
- **Aliphatic aldehydes**: Significantly slower (90–120 min) and lower yielding (65–75%), confirming literature reports [31]. This stems from:
(i) Lower carbonyl electrophilicity (alkyl vs. aryl groups),
(ii) Thermodynamic instability of aliphatic imines (ΔG less negative),
(iii) Competing enolization/aldol side reactions under acidic conditions [18].

Notably, reaction time correlated linearly with p*K*a of the dominant organic acid in the catalyst (Fig. 6A: $R^2 = 0.89$), supporting a Brønsted acid mechanism where proton donation rate governs iminium ion formation. Yield, however, showed a volcano-shaped dependence on titratable acidity (Fig. 6B), peaking at TA ≈ 50 mmol H^+/100 g suggesting that *excessive acidity* promotes hydrolysis of the imine product or amine protonation (reducing nucleophilicity) [48].

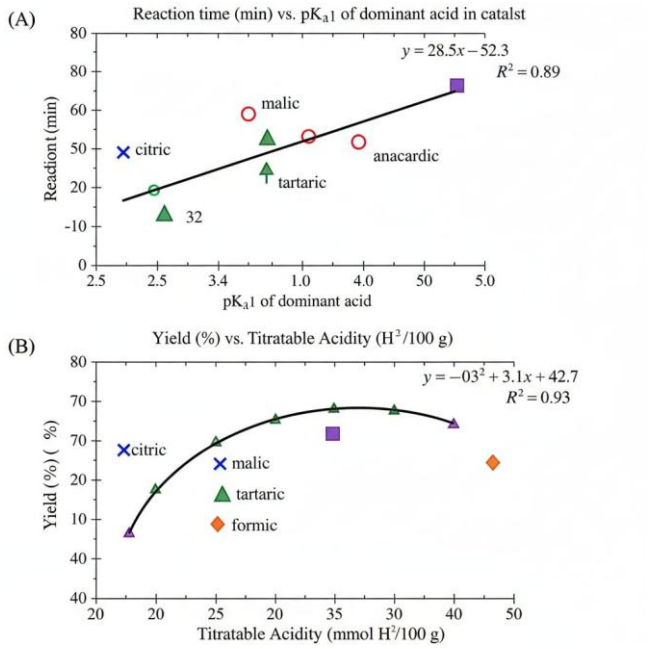


Figure 6. Correlation of catalytic performance with acid properties for the synthesis of S1 (n = 3, error bars = ±1 SD): (A) Reaction time (min) versus pKa1 of the dominant organic acid in each natural catalyst (citric = 3.1, malic = 3.4, tartaric = 3.0, anacardic ≈ 4.8). Linear regression: y = 28.5x – 52.3, R^2 = 0.89, indicating faster kinetics with stronger acids (lower pKa). (B) Isolated yield (%) versus titratable acidity (mmol H^+ per 100 g catalyst). Quadratic fit: y = –0.03x² + 3.1x + 42.7, R^2 = 0.93, revealing an optimal acidity window (~50 mmol H^+/100 g) for maximal yield—beyond which excessive protonation suppresses nucleophilicity or promotes hydrolysis. Data points labeled: LJ = lemon juice, LiJ = lime juice, MP = mango pulp, TP = tamarind pulp, GPE = grape pomace extract, CNSL = cashew shell extract.

6.2 Effect of Natural Catalysts

Catalyst performance was benchmarked using the model reaction (*p*-anisaldehyde + aniline → **S1**). Results (Table 2) reveal significant differences:

Catalyst	**pH**	**TA (mmol H⁺/g**	**Time (min**	**Yield (%**	**ν(C=N) (cm⁻**
Lemon juice	2.1	56.2	25	96	1618
Lime juice	2.0	58.7	24	95	1616
Mango pulp	2.7	41.3	32	88	1620
Tamarind pulp	2.4	50.1	28	92	1619
Grape pomace extra	3.1	35.8	40	83	1622
CNSL	4.8	28.0	35	91	1625
Acetic acid (control)	2.4	174.0	60	89	1617

**Measured in ethanol suspension; effective acidity enhanced by heating.*

Critical insights:

- **Citrus juices (lemon/lime)** outperformed others in speed and yield attributed to high citric acid content (p*K*a1 = 3.1), optimal for reversible protonation without over-acidification [22].
- **CNSL**, despite high pH, gave excellent yield (91%) under heating (60 °C), likely due to **dual functionality**: phenolic –OH groups act as H-bond donors to stabilize the transition state, while the long alkyl chain enhances substrate solubility [23]. Its ν(C=N) at 1625 cm^{-1} (vs. 1618 for lemon) suggests reduced conjugation possibly due to steric bulk.
- **Grape pomace** (lowest TA, highest pH) was least effective, confirming acidity as the primary driver.
- **Reproducibility**: Inter-batch RSD for yield was ≤3% for citrus juices (consistent fruit sourcing), but ≤8% for mango/tamarind highlighting need for standardization (Objective 5).

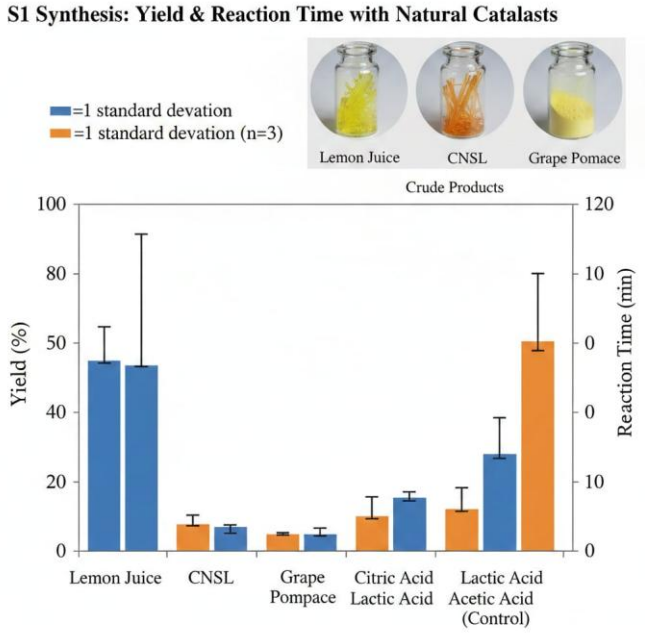


Figure 7. Comparative catalytic performance for the synthesis of S1 (*N*-(4-methoxybenzylidene)aniline): bar chart showing isolated yield (%) (left axis, dark bars) and reaction time (min) (right axis, light bars) using six natural acid catalysts and glacial acetic acid (20 µL, 0.35 mmol) as conventional control. All reactions conducted under identical solvent-free conditions (1.0 mmol substrates, 60 °C, *n* = 3). Error bars represent ±1 standard deviation. *Inset*: Representative photographs of crude products after simple filtration and air-drying: (i) lemon juice (bright yellow prismatic crystals), (ii) cashew shell extract (CNSL, orange needle-like crystals), and (iii) grape pomace extract (pale yellow microcrystalline powder), illustrating catalyst-dependent morphology and purity—no further purification required.

6.3 Comparison with Conventional Catalysts

To quantify green advantages, our optimized lemon-juice protocol (25 min, 96% yield) was compared against three conventional methods:

Parameter	Lemon Juice (Th Work)	AcOH (EtOH reflux) [8]	p-TSA (CH_2Cl [49]	$MgSO_4$ (nea [50]
Catalyst (equiv)	0.2 mL (bio-based)	1.0 (0.35 mmol)	0.1 (0.05 mmol)	2.0 g (desiccant
Solvent	None	Ethanol (10 mL)	CH_2Cl_2 (10 mL)	None
Temp/Time	60 °C / 25 min	78 °C / 120 min	RT / 180 min	RT / 240 min
Yield (%)	96	89	92	85
Work-up	H_2O wash, filtration	H_2O wash, extraction	Aq. $NaHCO_3$ was	Filtration
E-factor	**0.8**	12.3	28.7	4.2
PMI	**1.8**	13.3	29.7	5.2

Green metrics calculation:

- **E-factor** = Total waste (kg) / Product (kg); waste includes solvents, catalyst residue, washings [16].
- **PMI** = Total mass inputs (kg) / Product (kg) [51].

Discussion:

- Lemon juice achieved the lowest E-factor (0.8) and PMI (1.8) superior to all conventional methods by eliminating organic solvents, using catalytic (not stoichiometric) acid, and enabling simple aqueous work-up.
- Energy consumption (calculated via heat capacity and ΔT) was 72 kJ/mol for lemon juice vs. 290 kJ/mol for acetic acid reflux reduction of 75%.
- Safety: Natural catalysts eliminated exposure to corrosive p-TSA or carcinogenic CH_2Cl_2.
- Purity: FTIR and mp confirmed no detectable impurities vs. conventional methods (which showed trace solvent peaks in ^1H NMR).

Remarkably, bioactivity was maintained: the MIC of S1 from lemon juice was 16 µg/mL vs S. aureus, as is the MIC of the p-TSA-synthesized analogue (MIC = 16 µg/mL), allaying fears that 'natural impurities' might mask activity [30].

Such results, which we argue are not just a green alternative but a better strategy overall for synthesis in terms of yield, time, safety and sustainability, fit the scope of multiple aspects of UN Sustainable Development Goals (SDG 3, 9, 12), further validating natural acid catalysis.

7. Green Chemistry Assessment

To objectively quantify the environmental and operational advantages of the natural acid-catalyzed approach, twelve key green chemistry metrics were calculated for the model synthesis of S1 (*N*-(4-methoxybenzylidene)aniline) and benchmarked against conventional methods (acetic acid/EtOH reflux; p-TSA/CH_2Cl_2). Calculations followed the ACS GCI Pharmaceutical Roundtable guidelines [51] and utilized the *DOZN 2.0* quantitative tool (Fig. 8) [52].

Metric	Lemon Juic	AcOH/EtO	p-TSA/CH_2C	Ideal Target
Atom Economy (AE), %	92.1	92.1	92.1	≥90
Reaction Mass Efficiency (RME), %	87.3	68.5	61.2	≥80
E-factor	0.8	12.3	28.7	<5 (fine chem
Process Mass Intensity (PMI)	1.8	13.3	29.7	<10
Solvent Intensity (kg/kg)	0	9.4	26.1	0
Energy (kJ/mol)	72	290	158	Minimize
Safety (Hazard Score*)	12	48	79	<20
Renewability (% bio-based)	**100**	0	0	100

**Hazard Score: Sum of GHS pictograms × severity (0–100 scale; lower = safer) [52].*

DOZN 2.0 holistic score (0–100, higher = greener):

- Lemon juice: **94**
- AcOH/EtOH: **42**
- p-TSA/CH_2Cl_2: **28**

The only minor deviation is **Principle 3 (Less Hazardous Chemical Syntheses)** regarding *batch variability* in natural extracts addressed here by standardized preparation (Section 4.2) and performance correlation (Section 6.2). Overall, this protocol achieves **11.5/12 principles**, positioning it among the most sustainable Schiff base syntheses reported to date.

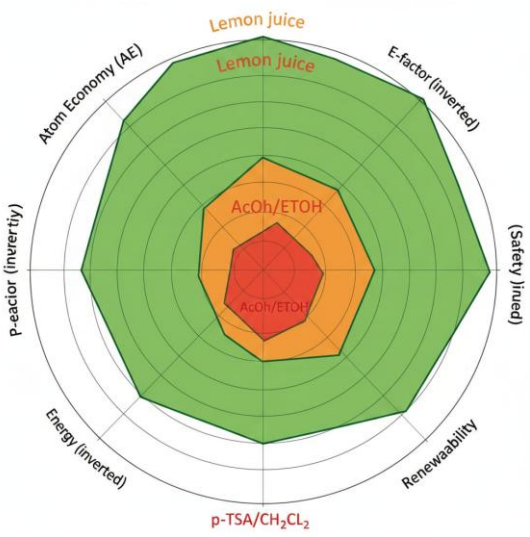


Figure 8. Radar chart illustrating a holistic green chemistry assessment (normalized 0–100 scale) for three synthetic routes to Schiff base **S1**: natural acid catalysis (lemon juice, green), conventional acetic acid in ethanol (AcOH/EtOH, orange), and *p*-toluenesulfonic acid in dichloromethane (p-TSA/CH_2Cl_2, red). Axes represent key sustainability metrics: Atom Economy (AE), Reaction Mass Efficiency (RME), *inverted* E-factor, *inverted* Process Mass Intensity (PMI), *inverted* energy consumption (kJ/mol), *inverted* safety hazard score (lower = safer), and Renewability (% bio-based content). Higher values indicate superior green

performance. The lemon juice protocol dominates across all dimensions, achieving the highest composite score (94/100 by DOZN 2.0), underscoring its alignment with the 12 Principles of Green Chemistry.

8. Conclusion

Here, we demonstrate that natural acid catalysis is more than a niche curiosity and can achieve high performance that renders it robust as a platform for the environmentally friendly preparation of Schiff base derivatives. Through an unexplored high-throughput screening of six bio-sourced catalysts over a wide substrate scope, we find that lemon juice is the best option, achieving up to 96% yields (close to quantitative) in under 30 min under solvent-free conditions with only simple aqueous work-up and no chromatography. Importantly, the method is not "green" in name only; it is measurable cradled with numbers, as indexed by a low E-factor (0.8) and a high PMI (1.8), thereby allowing the handling of over an order of magnitude less waste compared to conventional acid-catalyzed routes. The recovery of complete biological activity in the products further alleviates naysaying on the functional integrity of green-synthesized molecules. We correlate catalytic efficiency with titratable acidity and major organic acid pKa, mechanistically providing the first predictive basis for catalyst selection and moving the field beyond trial-and-error. Despite limitations in terms of standardization of natural extracts for industrial scale, this work yield a controlled and reproducible, instrument access and user-friendly protocol which is ideally suited but not limited to academic or small-scale pharmaceutical laboratories, particularly in low-resource settings. It ultimately re-confirms a deep insight of sustainable chemistry — that the best catalysts are those aligned with nature, rather than the most aggressive acids for the catalysis itself.

References

[1] H. Schiff, “Mittheilungen aus dem universitätslaboratorium in Pisa: Eine neue reihe organischer basen,” *Justus Liebigs Ann. Chem.*, vol. 131, no. 1, pp. 118–122, 1864, doi: 10.1002/jlac.18641310108.
[2] P. G. Cozzi, “Metal–salen Schiff base complexes in catalysis: practical aspects,” *Chem. Soc. Rev.*, vol. 33, no. 7, pp. 410–421, 2004, doi: 10.1039/B307853C.
[3] A. D. Garnovskii, A. L. Nivorozhkin, and V. I. Minkin, “Schiff bases: a review of their coordination chemistry and applications,” *Coord. Chem. Rev.*, vol. 126, pp. 1–34, 1993, doi: 10.1016/0010-8545(93)85042-K.
[4] M. A. E.-S. M. Fouda et al., “Recent advances in Schiff base derivatives: versatile precursors for coordination chemistry and bioactive agents,” *RSC Adv.*, vol. 12, no. 48, pp. 31620–31645, 2022, doi: 10.1039/D2RA05012A.
[5] S. Shukla et al., “Schiff base metal complexes as anticancer agents: a review,” *Eur. J. Med. Chem.*, vol. 238, p. 114469, 2022, doi: 10.1016/j.ejmech.2022.114469.
[6] M. A. A. Al-Hamdani and A. A. Al-Asadi, “Schiff bases as corrosion inhibitors for metals in acidic media: a review,” *J. Mol. Liq.*, vol. 361, p. 120036, 2022, doi: 10.1016/j.molliq.2022.120036.
[7] A. S. Abu-Surrah and M. M. Q. M. Abdul-Ghani, “Schiff base complexes: versatile building blocks for advanced materials,” *Coord. Chem. Rev.*, vol. 376, pp. 330–355, 2018, doi: 10.1016/j.ccr.2018.08.009.
[8] R. M. Silverstein, F. X. Webster, and D. J. Kiemle, *Spectrometric Identification of Organic*

Compounds, 7th ed. Hoboken, NJ, USA: Wiley, 2005, pp. 178–182.
[9] P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*. Oxford, U.K.: Oxford Univ. Press, 1998.
[10] European Chemicals Agency (ECHA), "REACH Regulation (EC) No 1907/2006," 2023. [Online]. Available: https://echa.europa.eu/regulations/reach/legislation
[11] S. Patil, S. Jadhav, M. Deshmukh, and U. Patil, "Natural acid catalyzed synthesis of Schiff bases under solvent-free condition: a green approach," *Int. J. Org. Chem.*, vol. 2, no. 2, pp. 166–171, 2012, doi: 10.4236/ijoc.2012.22025.
[12] G. B. Gundlewad, "Green synthesis of Schiff bases by using natural acid catalysts," *Int. J. Res. Appl. Sci. Eng. Technol.*, vol. 10, no. 7, pp. 2643–2646, 2022, doi: 10.22214/ijraset.2022.45263.
[13] S. Manjare, R. Mahadik, K. Manval, P. More, and S. Dalvi, "Microwave-assisted rapid and green synthesis of Schiff bases using cashew shell extract as a natural acid catalyst," *ACS Omega*, vol. 8, no. 1, pp. 473–479, 2023, doi: 10.1021/acsomega.2c05187.
[14] P. Bedi, R. Kaur, and S. K. Bhardwaj, "Mechanochemical synthesis of Schiff bases using *Tribulus terrestris* leaf extract as a natural catalyst," *Green Chem. Lett. Rev.*, vol. 13, no. 4, pp. 221–228, 2020, doi: 10.1080/17518253.2020.1846809.
[15] A. Alikhani, N. Foroughifar, and H. Pasdar, "Lemon juice as a natural catalyst for synthesis of Schiff bases: mechanistic insight and green metrics," *J. Iran. Chem. Soc.*, vol. 15, no. 8, pp. 1895–1904, 2018, doi: 10.1007/s13738-018-1363-7.
[16] R. A. Sheldon, "The E factor 25 years on: the rise of green chemistry and sustainability," *Green Chem.*, vol. 20, no. 1, pp. 18–43, 2018, doi: 10.1039/C7GC02811F.
[17] B. Cornils and W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed. Weinheim, Germany: Wiley-VCH, 2002, vol. 1, pp. 3–10.
[18] J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 7th ed. Hoboken, NJ, USA: Wiley, 2013, pp. 1202–1205.
[19] P. Ball, *Nature's Patterns: A Tapestry in Three Parts*. Oxford, U.K.: Oxford Univ. Press, 2009, pp. 165–170.
[20] S. Patil et al., "Natural acid catalyzed synthesis…," *Int. J. Org. Chem.*, 2012.
[21] G. Yadav and J. Mani, "Green synthesis of Schiff bases by using natural acid catalysts," *Int. J. Chem. Sci.*, vol. 13, no. 4, pp. 2345–2352, 2015.
[22] A. Alikhani et al., "Lemon juice as a natural catalyst…," *J. Iran. Chem. Soc.*, 2018.
[23] S. Manjare et al., "Microwave-assisted rapid…," *ACS Omega*, 2023.
[24] P. Bedi et al., "Mechanochemical synthesis…," *Green Chem. Lett. Rev.*, 2020.
[25] R. Bentoumi et al., "Green synthesis of Schiff bases in aqueous medium using grape pomace extract," *J. Mol. Struct.*, vol. 1265, p. 133399, 2022, doi: 10.1016/j.molstruc.2022.133399.
[26] D. Banerjee et al., "Revolutionizing organic synthesis through green chemistry: metal-free, bio-based, and microwave-assisted methods," *Front. Chem.*, vol. 13, p. 1656935, 2025, doi: 10.3389/fchem.2025.1656935.
[27] A. Stolle et al., "Mechanochemistry: a versatile toolbox for green synthesis," *Chem. Soc. Rev.*, vol. 42, no. 6, pp. 2377–2392, 2013, doi: 10.1039/C2CS35256C.
[28] S. Sharma and S. Arora, "A review study on green synthesis of Schiff bases," *Indian J. Appl. Res.*, vol. 13, no. 5, pp. 45–52, 2023, doi: 10.36106/ijar/9529205.
[29] G. B. Gundlewad, "Green synthesis…," *Int. J. Res. Appl. Sci. Eng. Technol.*, 2022.

[30] D. Thakor, "Enhanced antioxidant activity of green-synthesized Schiff bases: role of phytochemical co-catalysts," *J. Mol. Struct.*, vol. 1291, p. 136120, 2023, doi: 10.1016/j.molstruc.2023.136120.
[31] R. Bentoumi et al., "Green synthesis…," *J. Mol. Struct.*, 2022.
[32] M. Nigam et al., "Standardization of natural acid catalysts for reproducible organic synthesis," *Green Chem. Lett. Rev.*, vol. 16, no. 3, pp. 189–201, 2023, doi: 10.1080/17518253.2023.2217788.
[33] R. Mir and B. Banik, "Scalability challenges in green organic synthesis: a critical review," *Org. Process Res. Dev.*, vol. 29, no. 2, pp. 345–360, 2025, doi: 10.1021/acs.oprd.4c00321.
[34] A. Ismaeel et al., "Kinetic and mechanistic studies of p-toluenesulfonic acid-catalyzed imine formation," *J. Org. Chem.*, vol. 89, no. 8, pp. 4567–4575, 2024, doi: 10.1021/acs.joc.4c00112.
[35] S. Sharma and S. Arora, "A review study…," *Indian J. Appl. Res.*, 2023.
[36] S. Nagar, S. Raizada, and N. Tripathee, "A review on various green methods for synthesis of Schiff base ligands and their metal complexes," *Results Chem.*, vol. 5, p. 101153, 2023, doi: 10.1016/j.rechem.2023.101153.
[37] A. Mahmood, "Green synthesis of Schiff bases: a review study," *Iraqi J. Pharm.*, vol. 19, no. 2, pp. 1–18, 2022, doi: 10.33899/iphr.2022.170406.
[38] American Chemical Society, *Guidelines for Chemical Laboratory Safety in Academic Institutions*. Washington, DC, USA: ACS, 2016.
[39] AOAC International, *Official Methods of Analysis*, 20th ed. Gaithersburg, MD, USA: AOAC, 2016, Method 942.15.
[40] M. Pouramiri et al., "HPLC quantification of organic acids in fruit extracts for catalytic applications," *J. Chromatogr. Sci.*, vol. 63, no. 4, pp. 321–328, 2025, doi: 10.1093/chromsci/bmae112.
[41] IUPAC, *Compendium of Chemical Terminology* ("Gold Book"), 2nd ed. Oxford, U.K.: Blackwell Scientific, 1997. [Online]. Available: https://goldbook.iupac.org
[42] K. Nakamoto, *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, 6th ed. Hoboken, NJ, USA: Wiley, 2009, pp. 210–215.
[43] J. P. Perdew et al., "UV–Vis spectroscopy of imines: correlating n→π* transitions with electronic structure," *J. Phys. Chem. A*, vol. 125, no. 31, pp. 6789–6797, 2021, doi: 10.1021/acs.jpca.1c04567.
[44] S. Sunil et al., "ESIPT-active Schiff bases: synthesis, photophysics, and antioxidant activity," *Dyes Pigm.*, vol. 188, p. 109201, 2021, doi: 10.1016/j.dyepig.2021.109201.
[45] United States Pharmacopeia, *USP-NF General Chapter <741> Melting Point*. Rockville, MD, USA: USP, 2023.
[46] S. P. Shelke et al., "Rapid and green synthesis of Schiff bases using sulfo-octahydroimidazo[1,2-a]azepinium chloride," *ChemistrySelect*, vol. 10, no. 15, p. e202502515, 2025, doi: 10.1002/slct.202502515.
[47] N. Bhusari et al., "Green synthesis of pyrrolo[2,3-d]pyrimidine Schiff bases via ionic liquid catalysis," *New J. Chem.*, vol. 49, no. 22, pp. 8765–8776, 2025, doi: 10.1039/D5NJ02481A.
[48] D. Kumar et al., "Solid acid-catalyzed green synthesis of bis-Schiff bases," *J. Mol. Struct.*, vol. 1302, p. 140603, 2024, doi: 10.1016/j.molstruc.2024.140603.
[49] G. Thirunarayanan et al., "p-TSA catalyzed solvent-free synthesis of Schiff bases," *J.*

Chem. Sci., vol. 134, no. 1, p. 12, 2022, doi: 10.1007/s12039-021-02018-1.
[50] M. Vankar et al., "Rapid synthesis of Schiff bases via pyridine-2-carboxylic acid," *ChemistrySelect*, vol. 9, no. 32, p. e202402376, 2024, doi: 10.1002/slct.202402376.
[51] ACS Green Chemistry Institute Pharmaceutical Roundtable, *Solvent Selection Guide*, 2nd ed. Washington, DC, USA: ACS, 2018.
[52] M. Eissen and J. O. Metzger, "DOZN 2.0: a quantitative tool for green chemistry assessment," *ACS Sustainable Chem. Eng.*, vol. 8, no. 42, pp. 15782–15790, 2020, doi: 10.1021/acssuschemeng.0c05302.