

A.1 Single Crystal X-ray Parameters

Single crystal data parameters of all the crystal structure included in the thesis are summarized in Table A.1.

Table A.1 Single crystal X-ray parameters.

Crystal data	8m	37k	37u	37v	66o	69f
Formula unit	C ₉ H ₆ F ₆ N ₂ O	C ₁₇ H ₁₅ NO ₂	C ₂₃ H ₁₉ NO ₂	C ₂₃ H ₁₇ N	C ₂₈ H ₂₈ N ₂ O	C ₂₀ H ₁₉ N
Formula weight (g/mol)	272.16	265.30	341.39	307.38	408.52	273.36
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic	Orthorhombic	Orthorhombic
T [K]	100	100	100	296	100	100
a [Å]	13.97 (10)	10.699 (9)	7.804 (11)	14.183 (3)	7.179 (14)	8.12 (2)
b [Å]	11.33 (9)	24.611 (19)	10.261 (14)	12.855 (3)	46.13 (10)	19.50 (5)
c [Å]	9.52 (8)	11.444 (9)	11.611 (16)	8.841 (19)	6.476 (13)	20.58 (5)
α [°]	90	90	100.60 (13)	90	90	90
β [°]	93.86 (15)	112.40 (19)	102.62 (13)	98.11 (6)	90	90
γ [°]	90	90	94.90 (13)	90	90	90
Volume [Å ³]	1503 (20)	2786.0 (4)	884.0 (2)	1595.7 (6)	2145 (8)	3259 (14)
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> $\bar{1}$	<i>P</i> 2 ₁ / <i>c</i>	<i>Aba</i> 2	<i>Pbca</i>
Z	4	8	2	4	4	8
D _{cal} [g/cm ³]	1.202	1.265	1.282	1.279	1.265	1.114
μ (mm ⁻¹)	0.130	0.083	0.082	0.074	0.077	0.064
Reflns. collected	2532	5470	3418	3136	2275	3092
Unique observed	561	3217	1894	2265	1147	1330
R1 [I > σ(I)]	0.0743	0.0693	0.0569	0.0425	0.0911	0.0795
wR2	0.2650	0.1997	0.1647	0.1161	0.2115	0.2474
CCDC No.	2284849	2219983	2219981	2219982	2284523	2284524

A.2 Oak Ridge Thermal Ellipsoid Plot (ORTEP)

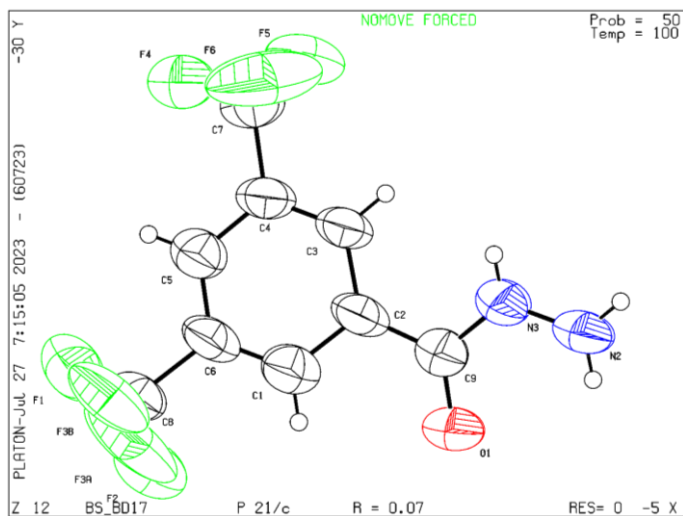


Figure A.1 ORTEP of 8m

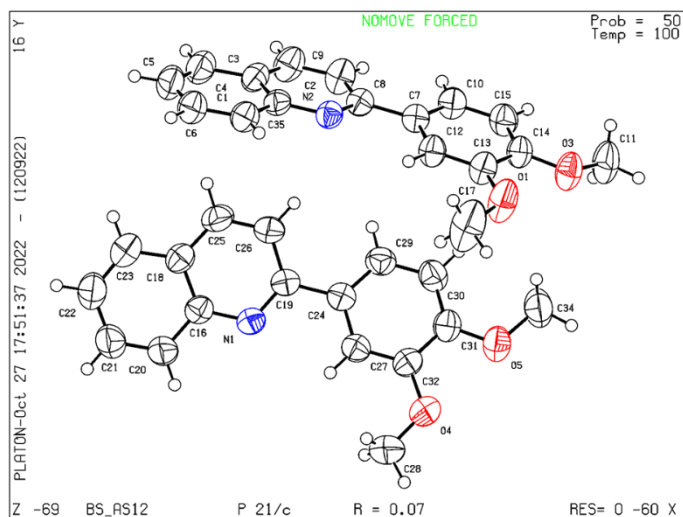


Figure A.2 ORTEP of 37k

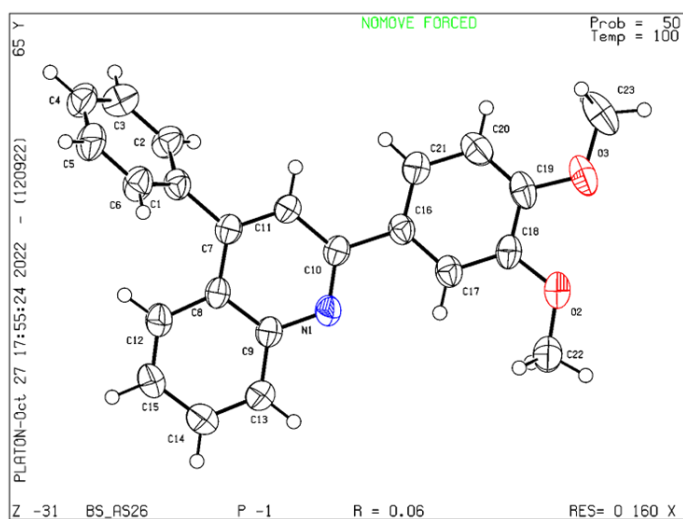


Figure A.3 ORTEP of 37u

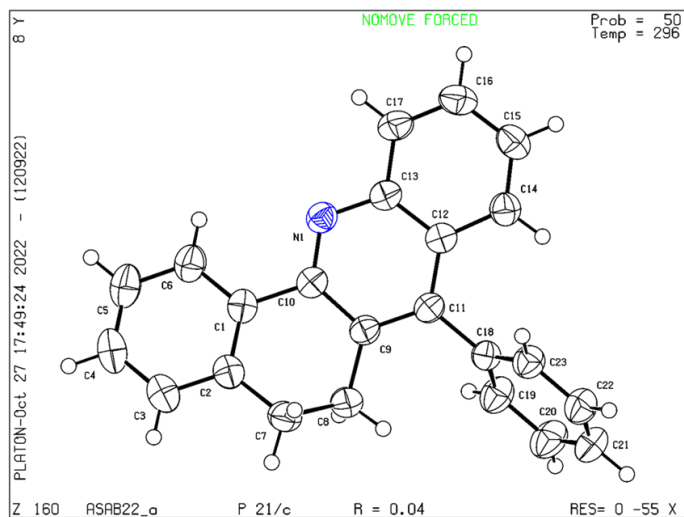


Figure A.4 ORTEP of 37v

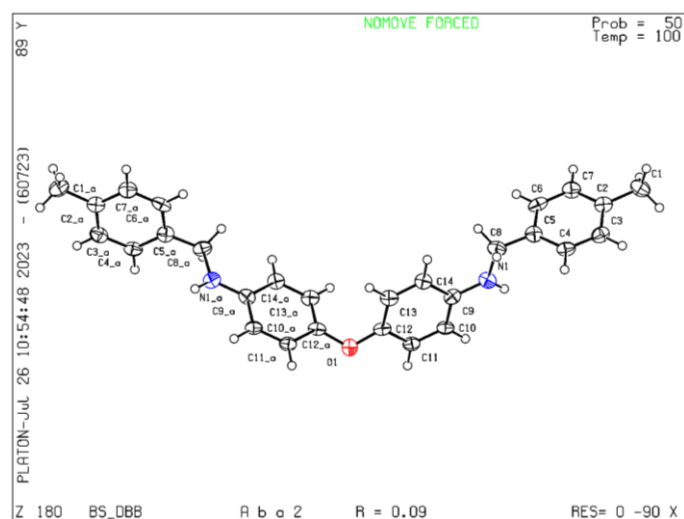


Figure A.5 ORTEP of 66o

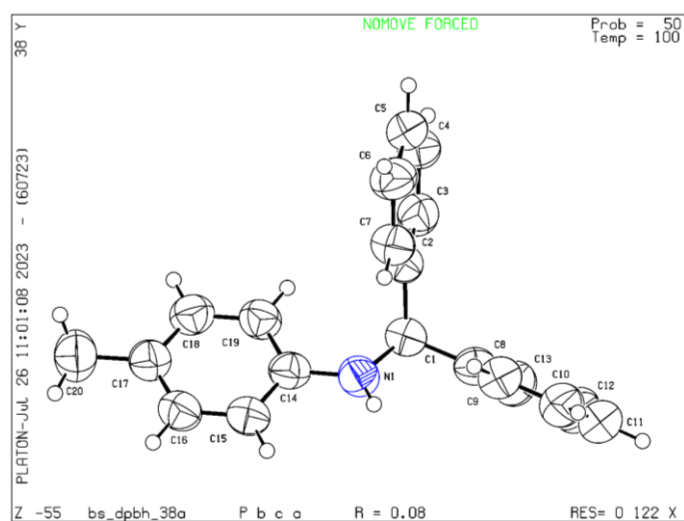


Figure A.6 ORTEP of 69f

A. List of Publications:**In international refereed journals*****Included in thesis***

- [1] **Pathak, D.**, Kalita, B. K., Sarmah, A., Sharma, H., Bora, B., Goswami, T. K., and Sarma, B. Metal-free reusable hollow-spherical triazine microporous organic polymer supported quinolines synthesis *via* hydrogen evolution. *Green Chemistry*, 25:7642-7652, 2023.
- [2] **Pathak, D.**, Khatioda, R., Sharma, H., Guha, A. K., Saikia, L., and Sarma, B. Endorsing organic porous polymers in regioselective and unusual oxidative C=C bond cleavage of styrenes into aldehydes and anaerobic benzyl alcohol oxidation *via* hydride elimination. *ACS Applied Materials & Interfaces*, 13:15353-15365, 2021.
- [3] **Pathak, D.**, Kalita, B. K., Biswakarma, N., Sharma, H., Deka, R. C., and Sarma, B. One-pot *N*-alkylation reaction over reusable Ni(II) decorated triazine porous organic polymer via borrowing hydrogen strategy. (*Under revision*)

Not included in thesis

- [4] Saikia, R. A., Talukdar, K., **Pathak, D.**, Sarma, B., and Thakur, A. J. Utilization of aryl(TMP)iodonium salts for copper-catalyzed *N*-arylation of isatoic anhydrides: an avenue to fenamic acid derivatives and *N,N'*-diaryldiazol-3-ones. *Journal of Organic Chemistry*, 88:3567-3581, 2023.
- [5] Sharma, H., Kalita, B. K., **Pathak, D.**, and Sarma, B. Low molecular weight supramolecular gels as crystallization matrix. *Crystal Growth & Design*, 2023. (*Accepted*)
- [6] Bora, P., **Pathak, D.**, Kalita, B. K., and Sarma, B. Deciphering the role of environmental variables in the nucleation of stoichiometric cocrystals. *Crystal Growth & Design*, 23:1500-1510, 2023.
- [7] Saikia, B., **Pathak, D.**, and Sarma, B. Variable stoichiometry cocrystals: occurrence and significance. *CrystEngComm*, 23:4583-4606, 2021.

- [8] Khatioda, R., **Pathak, D.**, and Sarma, B. Cu(II) Complex onto a pyridine-based porous organic polymer as a heterogeneous catalyst for nitroarene reduction. *ChemistrySelect*, 3:6309-6320, 2018.

B. List of Book Chapters

- [1] Kalita, B. K., **Pathak, D.**, Sharma, H., and Sarma, B. Surfacing hybrid medicines of bioactive molecules: a solid states formulation approach. In Rahman, A. U., editor, *Studies in Natural Products Chemistry (Bioactive Natural Products)*, Vol 78, pages 323-364, ISBN: 978-0-323-91253-2. Elsevier Science Publishers, 2023.
- [2] Bora, P., **Pathak, D.**, and Sarma, B. Polymer therapeutics in drug delivery system: advances & challenges. In Jha, D. K., editor, *Modern Trends in Chemistry*, pages 43-82, ISBN: 978-81-948732-0-4. Purbayon Publication, 2020.
- [3] Khatioda, R., **Pathak, D.**, and Sarma, B. Pore surface engineering in the construction of covalently linked porous organic polymers/frameworks (POPs/COFs) for diverse applications. In Sarma, G. K., editor, *Recent Advances in Material Science*, Vol 1, pages 61-89, ISBN: 978-93-86302-74-8. EBH publishers, 2018.

C. In Conferences/Seminar/Workshops (as abstract):

Oral Presentation

- [1] **Pathak, D.**, Khatioda, R. and Sarma, B. *Unusual Wacker-type Oxidative C=C Cleavage Driven by Metal Free Nitrogen Rich Microporous Organic Polymer*. International Conference on Emerging Trends in Chemical Sciences (ETCS-2020), organized by Department of Chemistry, Gauhati University, Assam, India, 13th-15th February 2020.
- [2] **Pathak, D.**, Khatioda, R. and Sarma, B. *Exploring 2D COF as Remarkable Catalyst for Efficient Reduction of p-Nitrophenol*. UGC Sponsored National Seminar on Recent Trends in Environment Responsive Chemical Process, Organized by Department of Chemistry, D. R. College, Assam, India, 22nd September 2017.

Poster Presentation


- [1] **Pathak, D.** and Sarma, B. *Engineering Framework Surface in Organic Transformation reaction*. 3rd International Conference on Crystal Engineering: From Molecule to Crystal [CE:FMC-2022], organized by University of Kashmir and IISER Kolkata, Pahalgam-Kashmir, India, 31st August-2nd September 2022.
- [2] **Pathak, D.**, Khatioda, R. and Sarma, B. *Organocatalyst for Infrequent Wacker-type Oxidation*. In OrganiX-2018: An International Conference in Chemistry, organized by Tezpur University, India, 20th- 21st December 2018.
- [3] **Pathak, D.**, Khatioda, R. and Sarma, B. *Selective Oxidation of Benzyl Alcohols into Aldehydes on Surface of Organic 2D π -Walls*. In National Workshop on Translational Research on Natural Products for Therapeutic Uses, organized by Institute of Advanced Study in Science Technology (IASST) Guwahati, Assam, India, 21st November 2017.

PAPER



Cite this: *Green Chem.*, 2023, 25, 7642

Metal-free reusable hollow-spherical triazine microporous organic polymer supported quinolines synthesis *via* hydrogen evolution†

Debabrat Pathak,^a Bikash Kumar Kalita,^a Ashish Sarmah,^a Himanshu Sharma,^a Bidisha Bora,^b Tridib K. Goswami ^b and Bipul Sarma ^{*a}

In the synthesis of medicinally and industrially valuable quinoline scaffolds, we report a one-pot greener synthetic route to do away with harsh reaction conditions, low productivity, and unstable substrates associated with the classical methods reported in the literature. Readily available alcohols undergo acceptorless dehydrogenative annulation in basic media over an engineered nitrogen-rich hollow-spherical microporous polymer (**MOP-TA**) devoid of any metal support. This affordable and sustainable route stands up to the test of scalability and green matrices, which are supported by various spectroscopic and microscopic techniques.

Received 17th June 2023,
Accepted 11th August 2023

DOI: 10.1039/d3gc02172f

rsc.li/greenchem

Introduction

The quinoline scaffold is found in a wide range of natural chemicals and pharmacologically active drugs, accounting for a sizable portion of the pharmaceutical industry. The traditional methods for synthesising this heterocyclic skeleton use costly starting materials and high temperatures.¹ Most of the quinoline derivatives are known for their antimalarial, anticancer, anti-Alzheimer's, anti-HIV, and agrochemical activities along with OLED applications in material chemistry (Fig. 1).^{2,3}

The development of several synthetic techniques for effective quinoline synthesis has been sparked by the significance of quinoline scaffolds to date. Commonly known methodologies for quinoline synthesis include Skraup, Pfizinger, Doebner-von Miller, Conrad-Limpach, and Friedländer annulation.¹ Among them, Friedländer annulation is considered the direct classical path for quinoline synthesis with limitations, such as harsh reaction conditions, low stability of the reactants, and multiple steps corresponding to low productivity.⁴ Later, reports suggested a transition metal-driven

system for modified Friedländer quinoline synthesis that included metal complexes of Pd, Ru, Ir, or Rh. Other reported abundant metal complexes contain Fe, Ni, Mn, Cu, Co, *etc.*, ignoring concerns of metal toxicity, stoichiometric catalyst loading, and reusability.^{5,6} However, an environmentally benign, sustainable, metal, and oxidant-free system with affordable efficiency is yet a challenge.

In search of a greener approach for the synthesis of quinoline, Yang *et al.* introduced ethyl lactate as a mediator third component for such synthesis from aldehyde and aniline catalysed by FeCl₃.⁷ However, the stoichiometric use of highly reactive aldehyde brings drawbacks for such transformation reactions because of low stability and easily air oxidizable substrates. In recent years, dehydrogenation of alcohols has

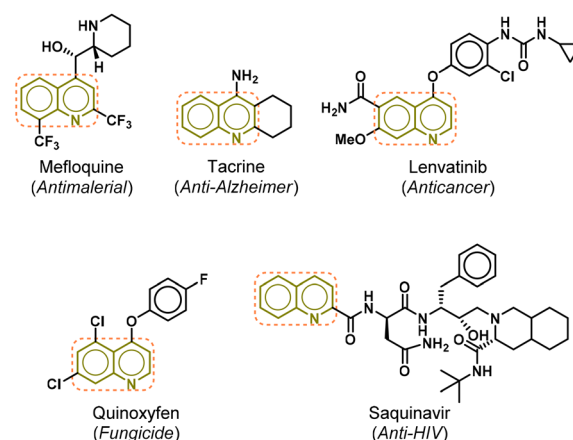


Fig. 1 Examples of bioactive molecules having quinoline moiety.

^aDepartment of Chemical Sciences, Tezpur University, Assam-784028, India.
E-mail: bcsarma@tezu.ernet.in

^bDepartment of Chemistry, Gauhati University, Assam-781014, India

† Electronic supplementary information (ESI) available: Synthesis and experimental sections, ¹H-NMR and ¹³C-NMR spectra, FE-SEM images, TG analysis, FT-IR analysis, P-XRD analysis, green matrices determination, total organic carbon determination, catalytic conversion comparison, determination of hydrogen evolution, single crystal X-ray data, ORTEP, NMR titration, and HRMS data. CCDC 2219981–2219983. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3gc02172f>

Endorsing Organic Porous Polymers in Regioselective and Unusual Oxidative C=C Bond Cleavage of Styrenes into Aldehydes and Anaerobic Benzyl Alcohol Oxidation via Hydride Elimination

Debabrat Pathak, Rajiv Khatioda, Himanshu Sharma, Ankur K. Guha, Lakshi Saikia, and Bipul Sarma*

Cite This: *ACS Appl. Mater. Interfaces* 2021, 13, 15353–15365

Read Online

ACCESS |



Metrics & More



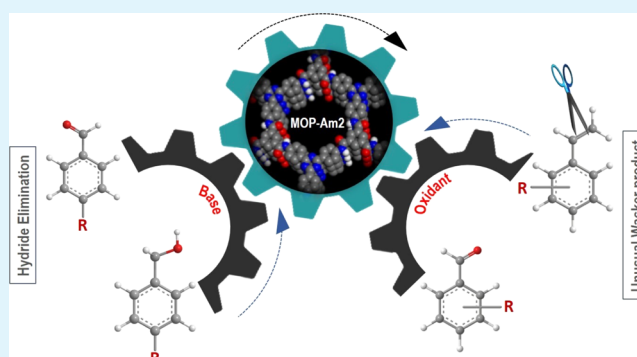
Article Recommendations



Supporting Information

ABSTRACT: Oxidative cleavage of styrene C=C double bond is accomplished by employing a nitrogen-rich triazine-based microporous organic polymer as an organocatalyst. We report this regioselective reaction as first of its kind with no metal add-ons to afford benzaldehydes up to 92% selectivity via an unusual Wacker-type C=C bond cleavage. Such a reaction pathway is generally observed in the presence of a metal catalyst. This polymer further shows high catalytic efficiency in an anaerobic oxidation reaction of benzyl alcohols into benzaldehydes. The reaction is mediated by a base via the *in situ* generation of hydride ions. This study is supported by experiments and computational analyses for a free-radical transformation reaction of oxidative C=C bond cleavage of styrenes and a hydride elimination mechanism for the anaerobic oxidation reaction. Essentially, the study unveils protruding applications of metal-free nitrogen-rich porous polymers in organic transformation reactions.

KEYWORDS: porous organic polymer, Wacker-type oxidation, cleavage of C=C bond, anaerobic oxidation, hydride elimination, carbon balance



INTRODUCTION

Metal-free porous organic polymer (POP) research has emerged if not to its fullest potential but confined to the storage and separation, conductivity, drug delivery, sensing, catalysis, and hazard-free chemistry.^{1–8} Exploration of functionalities for framework connectivity into POPs with a π -conjugated skeleton is limited, but it is envisioned for the selective adsorption of hydrocarbons, toxic molecules via π -complexation, and directional intermolecular interactions.⁹ Since the utilization of palladium-loaded 2D covalent organic framework (COF) by Ding *et al* to carry out Suzuki–Miyaura coupling, it has been attracting the attention of researchers to be exploited in the field of organic reactions.¹⁰ Notable organic reactions such as the Diels–Alder reaction, cascade reactions, Mizoroki–Heck reaction, nitrophenol reduction, carbon dioxide reduction, and so forth have been accomplished in the presence of a 2D COF, mostly having columnar π -arrays and/or conjugated π -electrons, as a heterogeneous catalyst or catalyst promoter. Jiang *et al* demonstrated the Diels–Alder reaction where the columnar π -electronic walls in the imine-linked 2D COF act as a catalytic bed.¹¹ Interestingly, various organic transformation reactions have been accomplished by employing POPs in the presence of a metal, essentially a precious metal. Absence of metals is commonly observed in reactions mediated in the presence of imine functional-linked polymers. The lone pair of electrons on

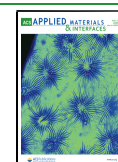
the nitrogen atom of such imine functional polymers allow the interaction sites to amend the rate of the reaction. The scope for exploring polymeric networks having other functionalities such as esters, amides, and so forth thus remains undeveloped. Kitagawa in 2007 illustrated the synthesis of an amide-functionalized porous coordination polymer that exhibited wonderful catalytic activity in performing the Knoevenagel condensation reaction.¹² Thereafter, only a few condensation reactions have been reported with metal-free microporous polymers as heterogeneous catalysts.¹³ The amide-linked POP was first introduced by Zhou *et al* who demonstrated the porous network as a cooperative catalyst in the deacetalization–Knoevenagel condensation reaction.¹⁴

The oxidation of styrenes is important, but selective oxidation to benzaldehyde remains as experiment without using precious and/or toxic metals.^{15,16} Literature evidenced the utility of metals such as Pd for Wacker-type oxidation of terminal alkenes,

Received: February 17, 2021

Accepted: March 15, 2021

Published: March 25, 2021



Utilization of Aryl(TMP)iodonium Salts for Copper-Catalyzed *N*-Arylation of Isatoic Anhydrides: An Avenue to Fenamic Acid Derivatives and *N,N'*-Diarylindazol-3-ones

Raktim Abha Saikia, Khanindra Talukdar, Debabrat Pathak, Bipul Sarma, and Ashim Jyoti Thakur*



Cite This: *J. Org. Chem.* 2023, 88, 3567–3581



Read Online

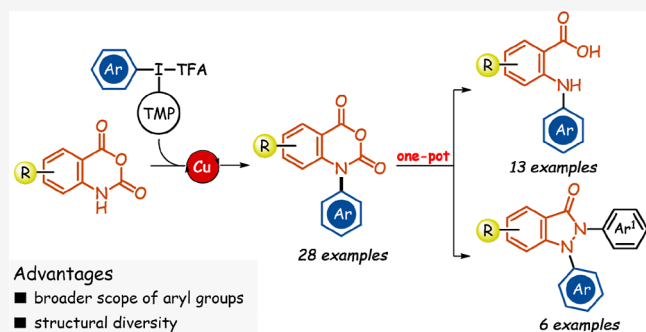
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

ABSTRACT: Herein, we report a general method for copper-catalyzed *N*-arylation of isatoic anhydrides with unsymmetrical iodonium salts at room temperature. The developed catalytic protocol is mild and operationally simple, and aryl(TMP)iodonium trifluoroacetate is employed as the arylating partner. The methodology offers the broad applicability of both structurally and electronically diverse aryl groups from aryl(TMP)iodonium salts to access *N*-arylated isatoic anhydrides in moderate to excellent yields (53–92%). Moreover, the substituted isatoic anhydrides are equally compatible with the protocol too. To demonstrate the synthetic utilities of the *N*-arylation process, we also report an alternative approach for biologically relevant fenamic acid derivatives and *N,N'*-diarylindazol-3-ones in a one-pot step economical system. In addition, the scale-up synthesis of flufenamic acid is also illustrated.



INTRODUCTION

Formulation of a practical strategy for arylation of heterocyclic molecules or heteroatom-based nucleophiles is of paramount importance and a powerful tool to architect the key building blocks in organic synthesis¹ and medicinal chemistry.² In the realm of arylation chemistry,³ the hypervalent iodine arylating compound i.e., diaryl- λ^3 -iodanes,⁴ (well known as diaryliodonium salts) have witnessed a dramatic upsurge as an efficient and versatile aryl-transferring reagent, either in metal-free⁵ or transition-metal-catalyzed methods.⁶ Though the inherent electrophilicity of this aryl donor is immensely applauded in metal-free arylation protocols, the arylation methodologies of diaryliodonium salts under copper catalysis are also quite familiar and illustrate remarkable examples of arylation reactions.⁷ Diaryliodonium salts of both symmetrical⁸ and unsymmetrical types⁹ are well explored in copper catalysis methods; however, the selection of iodonium salts is very crucial and determines the scope and limitations of the method. Of note, unsymmetrical iodonium salts having auxiliaries anisyl (An),¹⁰ mesityl (Mes),¹¹ and 2,4,6-trimethoxyphenyl (TMP)¹² are more beneficial in comparison to their symmetrical counterparts. These unsymmetrical iodonium salts (especially with TMP-iodonium salts) deliver many advantages over symmetrical iodonium salts: (i) wider scope of electronically and sterically variable aryl groups, (ii) ease of preparation, (iii) excellent chemoselective arylation (auxiliary iodide is the leaving group), and (iv) require only one common arene source. However, the application of symmetrical iodonium

salts restrains the arylation methods due to (i) limited scope of the aryl group, (ii) high cost of synthesis for functionalized iodonium salts (require both aryl iodide and aryl boronic acid), (iii) not applicable for expensive and complicated aryl iodides, and (iv) each iodonium salt needs its corresponding arene source. The unsymmetrical aryl(auxiliary)iodonium provides a unified approach of aryl groups to the nucleophile selectivity with a wide range of both electron-donating and electron-withdrawing functional groups, and overall the potential loss is lesser (one functionalized aryl iodide leaves in the case of symmetrical one).¹² Among the popular arylation reactions with iodonium salts under Cu-catalysis, mesityl-iodonium salts {Ar(Mes)I⁺X⁻} have been commonly utilized and they exhibit good chemoselective arylation.¹³ Despite the excellent chemoselectivity and ease of preparation compared to other types, TMP-iodonium salts {Ar(TMP)I⁺X⁻} have been explored mostly in metal-free arylation methods,¹² and very few reports were established in the copper-catalysis methods.¹⁴

2*H*-Benzo[*d*][1,3]oxazine-2,4(1*H*)-diones, also named isatoic anhydrides, featuring an active amidic and an anhydride linkage, are important heterocyclic compounds¹⁵ and key

Received: November 16, 2022

Published: February 24, 2023



Deciphering the Role of Environmental Variables in the Nucleation of Stoichiometric Cocrystals

Pranita Bora, Debabrat Pathak, Bikash Kumar Kalita, and Bipul Sarma*

Cite This: *Cryst. Growth Des.* 2023, 23, 1500–1510

Read Online

ACCESS |



Metrics & More

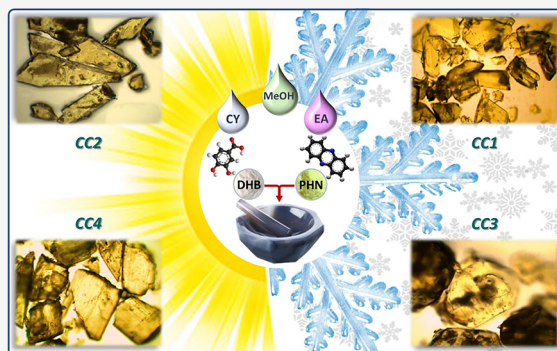


Article Recommendations



Supporting Information

ABSTRACT: The subsistence of dissimilar stoichiometry in cocrystals offers more solid forms with varied therapeutic advantages. Crystallization is a delicate process, and even an insignificant deviation in the process can impact the overall product performance. The significance of seasonal environmental variables in designing such different stoichiometric cocrystals is assessed by nucleating at least six different cocrystals from phenazine and protocatechuic acid. The cocrystals were isolated under continuously changing seasonal environmental variables in a time window of two comprehensive calendar years. The results are concurrent with the imitated *in vitro* laboratory crystallization conditions and are demonstrated. Competitive slurry and mechanochemical grinding experiments are employed to probe the phase relationships between these cocrystal phases.



INTRODUCTION

A cocrystal is now a branded solid formulation in our healthcare system to recover the physiochemical as well as pharmacokinetic properties of a drug suffering from various inadequacies.^{1–5} Cocrystals exhibiting stoichiometric diversity are often discovered either serendipitously or by varying the starting material ratio and solvent of crystallization. Such varied stoichiometric cocrystals can upsurge the number of potential solid forms that pose a serious concern in the development of an active ingredient.⁶ This indeed complicates the control of the cocrystallization process and follow-up interconversions between the phases. With the emergent interest in the field of crystal engineering, understanding the cocrystal polymorphism and variable stoichiometry is on the radar.^{7,8} One of our previous studies reported the synthesis of four different stoichiometric cocrystals of theophylline and *o*-aminobenzoic acid and demonstrated improvement in water solubility and membrane permeation behavior under physiological pH environments.⁹ Li and Matzger further prepared variable stoichiometric cocrystals of carbamazepine and *p*-aminobenzoic acid and studied their dissolution properties. It is indeed the metastable form that showed the highest dissolution profile; thus, efforts should be directed toward cocrystal production by following kinetic growth methods.¹⁰

The role of environmental variables such as relative humidity (RH) and atmospheric temperature on the formation of stoichiometric cocrystals followed by an understanding of their stability relationships is yet to be determined. Only a few studies reported the plausible influences of the crystallization media,¹¹ mechanochemical methods,^{12,13} and conformer stoichiometric ratios⁸ in the crystallization of different stoichiometric cocrystals. Going by the literature, Jones and co-workers

reported the importance of solid-state grinding in producing different stoichiometric cocrystals of caffeine.¹⁴ Nevertheless, the formation of cocrystals by solid-state grinding followed by solution growth techniques is common,^{15,16} while many are selectively prepared only by solid-state grinding or solution growth.¹⁷ To understand the mechanism of formation and/or the kinetics of cocrystallization, it is imperative to understand the various factors that can affect the (i) stability and (ii) phase transformations of the product cocrystals.^{18,19} Reports are available demonstrating the role of solution chemistry,¹³ mechanochemical methods,²⁰ and conformer stoichiometric ratio^{10,21} in the cocrystallization of different stoichiometric cocrystals. Sarma et al. reported the role of π -stacking interactions and hydrogen bond synthons in the alteration of cocrystal stoichiometries.²² As a result, four different stoichiometric cocrystals of phenazine and phloroglucinol were isolated including a hydrate structure. Jayasankar et al. demonstrated the role of moisture in the generation of carbamazepine cocrystals with saccharin and nicotinamide under deliquescence conditions.²³ They established that the mechanism however could not explain how moisture interferes in the solution phase that finally influences the nucleation process of different stoichiometric cocrystals. Paradkar and co-workers demonstrated that by controlling the temperature,

Received: September 27, 2022

Revised: January 10, 2023

Published: January 30, 2023



Catalysis

Cu(II) Complex onto a Pyridine-Based Porous Organic Polymer as a Heterogeneous Catalyst for Nitroarene Reduction

Rajiv Khatioda, Debabrat Pathak, and Bipul Sarma*^[a]

Unlike traditional catalysts, a Cu(II) catalyst incorporated onto a new pyridine based porous organic polymer linked by carboxamide functionality has been developed by impregnation method. Materials are characterized using FT-IR, solid-state NMR, PXRD, SEM, TEM techniques. The uniform confinement effect of the Cu(II) loaded polymer is assured by energy-dispersive X-ray (EDX) elemental mapping, ICP and AAS spectroscopic analysis. The Cu(II) loaded material further employed as a heterogeneous catalyst for nitroarene reduction

and reported as an excellent catalyst with improved performances over those reported using expensive and precious metals (like Au and Pd) on immobilized organic porous materials. The oxidation state of Cu in the catalytic cycle is corroborated with XPS analysis. The present study also emphasizes the role of π -electron rich organic porous polymer as promoter of electronic stature of finely dispersed Cu sites accountable for the excellent catalytic activity towards nitroarene reduction.

Introduction

Catalysis by metals on support matrix such as polymer or silica has accomplished its improved activities and selective reactions. Therefore, the way of doing catalytic reactions has now oriented towards the preparation of heterogeneous supported catalysts. Needless to mention these catalysts have continued to show thermal and chemical stability during the reaction process. Moreover, presence of suitable functional groups, high surface area and porosity in the structure of the support matrix activate the catalytic process through intermolecular interactions. To note, porous carbon materials (PCM) was initially emerged as popular catalyst and catalyst support.^[1,2] Subsequently phosphorus doped carbon based porous material was illustrated as 'green catalyst' and considered as metal free heterogeneous catalyst in selective oxidation of benzyl alcohols in air.^[3] Identical metal free oxidation reaction has also been accomplished by nitrogen doped graphene nanosheets with N serving as an active catalytic center.^[4] Boron nitride nanosheets were also used as support matrix in impregnation of active metals. The successful immobilization of Pd nanoparticles in boron nitride nanosheets and its promising catalytic activity in reduction of nitroarene facilitated by electron push mechanism aided by B and N of the nanosheet has also been demonstrated.^[5] In the recent past porous organic polymers (POPs) have been introduced as superior class of support matrix for transition metal incorporation thereby accomplishing potent

applications as heterogeneous catalyst in photocatalysis; bio-refinery and in biomass refining.^[6-12] Our group has previously demonstrated the role of amide functionality of a porous polymer in gas adsorption and catalytic activity in selective oxidation reactions.^[12] In view of the importance of nitrogen centers with lone pair electrons and amide functionality, an organic porous polymer as support matrix to play important roles in influencing the catalytic performance of the loaded cheaper metals like Cu has been developed and successfully tested for the widely popular nitroarene reduction reaction.

The 4-nitrophenol (4NP) is a widely used but harmful chemical entity especially in agricultural industries. Detoxification of 4NP by conventional water treatment technique is of rising concern owing to its high chemical stability and resistivity towards microbial degradation. Therefore, reduction of 4NP to corresponding 4-aminophenol (4AP), an important precursor compound in pharmaceutical and plastic industries is graded as wise alternate. But, the reduction of 4NP and/or nitroarene does not proceed under ideal conditions in absence of a catalyst, whereas metals can easily reduce 4NP. Conventionally, the reduction of nitro group is performed with iron/acid but the process is not regarded as environmentally benign. During the past few decades 4NP reduction reactions witnessed the involvement of precious noble metals (Au, Pt, Pd, Rh, Ru, etc.) based heterogeneous catalysts.^[13,14] Further reports are also available on the use of bimetallic materials as good candidate in heterogeneous catalysis of organic reactions.^[15,16] For example, Kim *et al.*^[17] synthesized Pd-Pt bimetallic nanoparticles supported by carbon nanotube that exhibits effective and efficient catalytic activity through synergistic effect towards the reduction of 4NP along with chemoselectivity in reduction of other nitroarenes. Immobilized Au nanoparticles rooted in covalently mediated self-assembled polymeric membrane of nanocomposites have further estab-

[a] R. Khatioda, D. Pathak, Dr. B. Sarma
Department of Chemical Sciences
Tezpur University
Napaam - 784028, Tezpur, Assam, India
E-mail: sarmabipul@gmail.com
bcsarma@tezu.ernet.in

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/slct.201801003>

Low Molecular Weight Supramolecular Gels as a Crystallization Matrix

Himanshu Sharma, Bikash Kumar Kalita, Debabrat Pathak, and Bipul Sarma*

Cite This: <https://doi.org/10.1021/acs.cgd.3c01211>

Read Online

ACCESS |



Metrics & More

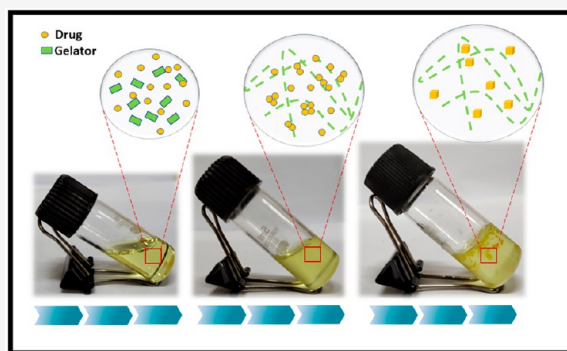


Article Recommendations



Supporting Information

ABSTRACT: Advances in the solid-state formulations of active compounds have shown positive impressions on the drug's properties. Starting from the late appearance of the second form of the anti-HIV drug Ritonavir to the cocrystal-based drug Entresto has been a scientific effort at the crossroads of major subject areas like pharmaceutical development and crystal engineering. Most studies pertaining to the crystallization avenues have been the key choice to understand, predict, and control the solid form and properties, particularly relevant in the case of oral medicines. Crystallization from solution or slow evaporation is studied extensively and is a conventional rolling practice. However, dozens of other impending crystallization approaches encompassing vapor diffusion, precipitation, sublimation and melt crystallization, crystallization in the presence of additives, neat and solvent drop grinding, lyophilization, laser-induced crystallization, sonocrystallization, crystallization by ionic liquids and supercritical liquids, etc. are still being explored. The application of supramolecular gels as a crystallization matrix to nucleate the desired drug's phase preferably metastable forms has been under scientific investigation in the past decade. This Perspective discusses the strategic headway of using supramolecular organogels as a choice of crystallization media for small active molecules. The laboratory-shelved solvent trapped in the designed 3D network of gelator(s) acts as small confined containers to control the nucleation and growth process. Gel fibers act as nucleation-templating surfaces offering epitaxial growth and influencing crystallization outcomes via molecular recognitions and thus are highlighted. Besides highlighting the understanding of the physical properties of organogels, the techniques used to probe their properties and structures, and the thermodynamic concepts involved in gelator aggregation in organic liquids, this Perspective largely emphasizes the basic challenges that the drug manufacturing process faces related to the crystallization of the metastable phase and the role of a gel component(s) versus gel environment on the crystallization output.



1. INTRODUCTION

Heterogeneous nucleation is a common tool to counter the challenges related to the control of the crystallization output in traditional solution state processes. Crystallization is a complex event subject to a wide range of kinetic, thermodynamic, and molecular recognition parameters that proceed via nucleation and growth.^{1–3} In contrast to homogeneous nucleation, primary heterogeneous nucleation involves nucleation onto solid substrates or surfaces of foreign substances.⁴ The feasibility of the process lies in the decrement in the free energy barrier for the generation of the nuclei of critical radii to grow into a stable crystal. The subsequent growth is mostly a diffusion-dependent process of solute molecules depositing onto the surface of the nuclei.⁵ The physical or chemical interaction of the solute with the heterogeneous surface results in the requirement of a smaller number of particles to form the nuclei of critical radii r^* compared to homogeneous nucleation.^{6–8} The scientific literature has numerous models of heterogeneous nucleation like the Fletcher model,⁹ classical flat surface model,¹⁰ Turnbull's patch nucleation model,¹⁰ and double spherical cap model,¹¹ to name a few.

The processing of pharmaceutical compounds in the solid state is the most sought after practice to achieve purity and reproducibility. Polymorphism in this domain is not always a favored phenomenon because of the safety and efficacy issues that are direct manifestations of the structure–function relationship.¹² The timeless example of Ritonavir marketed by Abbott Laboratories in 1996 in form I and its subsequent pull out of the market due to the appearance of form II leading to a failed dissolution test is a concern that still garners scientific and monetary investments. The metastable form I vanished from the entire scenario mysteriously, as the same manufacturing process could never reproduce it. Abbott Laboratories had to withdraw the capsules from the market

Received: October 13, 2023

Revised: October 28, 2023

Accepted: October 30, 2023



Cite this: *CrystEngComm*, 2021, **23**, 4583

Received 4th April 2021,
Accepted 10th June 2021

DOI: 10.1039/d1ce00451d

rsc.li/crystengcomm

Variable stoichiometry cocrystals: occurrence and significance

Basanta Saikia,^{*ab} Debabrat Pathak^a and Bipul Sarma ^{*a}

The occurrence of variable stoichiometry cocrystals offers the prospect to acquire more solid forms of the same system. The control of stoichiometry is extremely important concerning purity and intellectual property (IP) protection. We have analysed structures, synthetic methodologies and properties of the reported variable stoichiometry organic cocrystals reported in the last decade, with discussion of their controlled production for drug formulation plans. This review further fetches an understanding of the accountable reasons for the existence of stoichiometry variation in cocrystals, which essentially results from the disparity in properties with IP coverage.

1. Introduction

The recent development of drug multi-component crystalline systems, particularly cocrystals, has drawn added interest from the pharmaceutical industries for better drug formulation.^{1–9} Cocrystals are a lucrative area of crystal engineering because of their potential ability to modulate material properties on demand.^{10–15} They are evolving as a reliable approach to alter the physicochemical properties of active compounds such as bioavailability,¹⁶ dissolution,^{6,17–23} solubility,^{24–26} stability,^{4,27–30} mechanical properties,^{31–33} etc.,

which are major apprehensions in developing a new drug. Additionally, a new cocrystal can emerge as a contender for a new patent in drug formulation due to its novelty, efficacy, economic feasibility and easy synthetic procedure.^{18,19,34–36} There are reports on drug–drug, drug–nutraceutical and drug–excipient cocrystals with improved properties in the literature and in the near future they may emerge as a viable alternative for traditional medicines.¹⁸ The approval of the cocrystal drug ENTRESTO by the FDA on July 7, 2015, a cocrystal of sacubitril and valsartan, which is a medication for certain types of chronic heart failure, boosted research on cocrystals further.^{37,38} Subsequent approval of more cocrystalline drugs such as ODOMZO, Suglat® STEGLATRO™ etc. added more interest in cocrystal research.^{36–39} The use of cocrystals is emerging as a sustainable alternative to

^a Department of Chemical Sciences, Tezpur University, Tezpur 784028, India.

E-mail: bsaikia1@gmail.com, bcsarma@tezu.ernet.in

^b Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg 39106, Germany



Basanta Saikia

Basanta Saikia was awarded a Ph.D. degree in 2019 under the guidance of Dr. Bipul Sarma from the Department of Chemical Sciences, Tezpur University, India. He was the recipient of the Commonwealth Split-site Ph.D. Program 2017 and performed a part of his Ph.D. work under Prof. Jonathan Steed from the Department of Chemistry, Durham University, United Kingdom. In 2020, he was appointed as a postdoctoral

fellow at Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany. His area of research lies in the field of crystal engineering, nucleation and organogels.



Debabrat Pathak

Debabrat Pathak received a Master of Science (M.Sc.) degree in Chemistry in 2017 from the Department of Chemical Sciences, Tezpur University, Assam, India. He worked on porous organic polymers during his post-graduation under the guidance of Dr. Bipul Sarma and has extended this work to his doctoral research, under him, since 2017. Currently, he is a Council of Scientific & Industrial Research (CSIR), Govt. of India, sponsored

senior research fellow at the Department of Chemical Sciences, Tezpur University. His area of research includes designing porous materials for catalysis and development of separation technology.