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Green and Benign Strategies for Synthesis of Biologically Active Compounds using Lipase as Biocatalyst

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ABSTRACT
An efficient, feasible, mild, affordable, and environmentally friendly method has been developed for the synthesis of biologically active compound 3-methylene-indoline-2-one from Isatin and active methylene compounds using Lipase as a Green and Biocatalyst. Biological Processes are very important to optimization to increase and improve the efficiency of cost. In this project, Malononitrile, or Dimedone reacts with Isatin in presence of lipase. The essential features of this approach are metal-free reaction, high yield, nontoxic, and less hazardous. These reactions surpass metal-catalyzed processes because these reactions have violent reaction conditions, toxic, less yields, complex workups, and environmentally hazardous ingredients. This approach replaces hazardous chemicals with benign material during their design, manufacture, use and disposal. Designing of product is cost-effective and environmentally benign chemically products. It is completely followed to Green Approach. The entire given biologically active compound have shown biological activities such as Antiviral, Anti-HIV, Antibacterial, and Anticonvulsants.

Keywords: Green Approach, Lipase, Biocatalyst, Biologically Active

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INTRODUCTION

Recently, Green organic synthesis has been emphasized by chemists. It is a natural, inexpensive, feasible, non-toxic, renewable, and environmentally promising energy source (Choi 2018, Revathi 2018, Zhu 2019, Yang 2019, Fu 2016). Biologically active compound 3-methylene-indoline-2-one and due to their widespread use, their derivatives have attracted a lot of interest in recent years. In the medicine and pharmaceutical industries and also display a variety of biological functions. Some methodologies, such as conventional (Tan 2020, Huang 2019), and visible light-initiated method (Yue 2021), have been reported to produce 3-methylene-indoline-2-one and their derivatives. But we are doing here to formation of 3-methylene-indoline-2-one and their derivatives via using Lipase as a biocatalyst. Therefore, there is a critical need to develop low-cost, environmentally responsible alternatives to metal catalysts, which have adverse effects on

the environment. We report a new method for the synthesis of derivatives of 3-methylene-indoline-2-one, which contains a carbon-carbon double bond, for the reasons mentioned previously as well as developing green, nontoxic environmentally benign, and ecofriendly methods. Lipase is used as a green catalyst because it is cheap, easily-available and environmentally friendly.

Formations of double bonds between carbon atoms are crucial to organic chemistry. They are easily convertible into any desired functional groups. Olefins constitute the basis for several crucial chemical reactions, including the olefin metathesis, Heck reaction and Sharpless epoxidation. Natural compounds containing carbon-carbon double bonds; these molecules are used for medicines, agrochemicals, and bulk chemicals (Mol 2004, Sadrameli 2015). Numerous established classic olefination techniques, including the Julia olefination (Maercker 2004), the McMurry coupling (Van 2002), the Peterson olefination (McMurry 1989), and the Wittig reaction (Blakemore 2002), have been developed over the past few decades. And just recently, some alternative techniques are developing for the synthesis of alkenes, including carbonyl olefination and carbene dimerization. However, the substrates for these reactions include specific unsaturated functional groups, need pre-functionalization of the reactants. A stoichiometric amount of hazardous substances was frequently used, which frequently resulted in a substantial amount of waste being produced. Therefore, producing new catalytic processes to form carbon-carbon double bonds from widely available starting materials still significant challenges.

Lipase is a enzyme that catalysed the hydrolysis reaction of Long-chain triacylglycerols and fatty acids, Lipase is found in, plants, animal and microbes including bacteria and fungi. Because lipase is stable at high pH, temperature, and organic solvent extremes, they may efficiently catalyse processes in both aqueous and non-aqueous conditions. The observation of lipase enzymes in bulk enzymes and their high production value. The lipases enzyme has numerous uses in the chemical, pharmaceutical, fine chemical, food, agrochemical, and paper industries. It is also used in biosensors, cosmetics, and bioremediation processes. Lipase is mostly used to biocatalyst to chemical reactions (Alhamdani 2016).

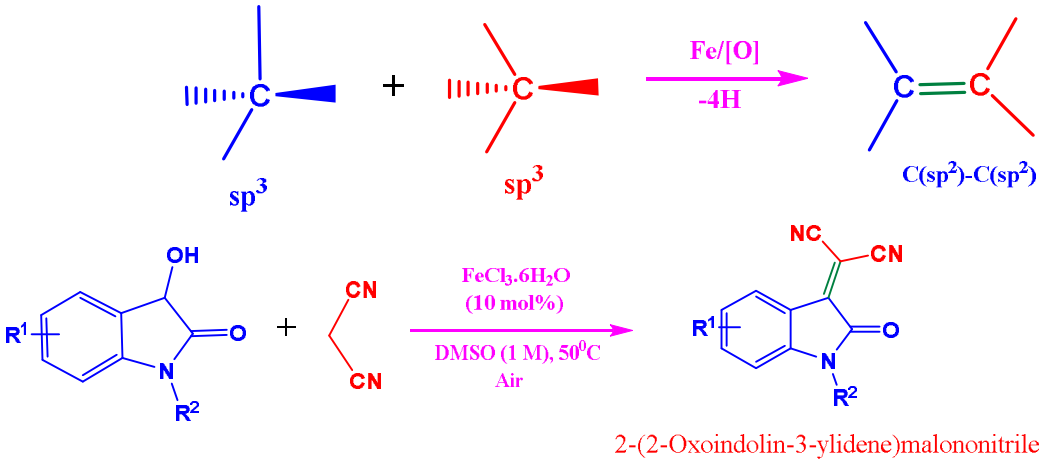
The versatile enzymes known as lipases can be utilised in a wide range of biocatalyzed processes. They can frequently fascinating than traditional chemical catalysts because of their selectivity and their moderate reaction conditions. Other lipase-catalyzed reactions have found these enzymes to be very appealing in addition to their use in oil and fat processes. Among the many different types of enzymes, it is one that has the special ability to catalyse both synthetic and hydrolytic reactions in non-aqueous and microenvironmental environments (Kishore 2011, Verma 2014).

We are reporting a new method for the synthesis of 3-methylene-indoline-2-one and their derivatives from Isatin and active methylene molecules using Lipase as a biocatalyst. For the synthesis, Isatin (1mmol), Lipase (1mol %), and EtOH with water were taken in a 10 mL round bottom flask and carried out for eight hours. After this, the active methylene compound (malononitrile, dimedone or ethylcyano acetate) was added to the reaction mixture. The precipitate was obtained and washed after filtration with EtOH. The biologically active methylene product was obtained in excellent yields after recrystallization. Initially, we tested isatin with malanonitrile using lipase as biocatalyst but we reported a few amount of desire product (1a). So Lipase have crucial role that can function as biocatalysts in this reaction here lipase bound with the lone pair of oxygen of carbonyl group and increase the reactivity of isatin (increase the electrophilicity). So excellent yield of final product (1a) was obtained. After that we tried this same with dimedone so there is also good yield was obtained.

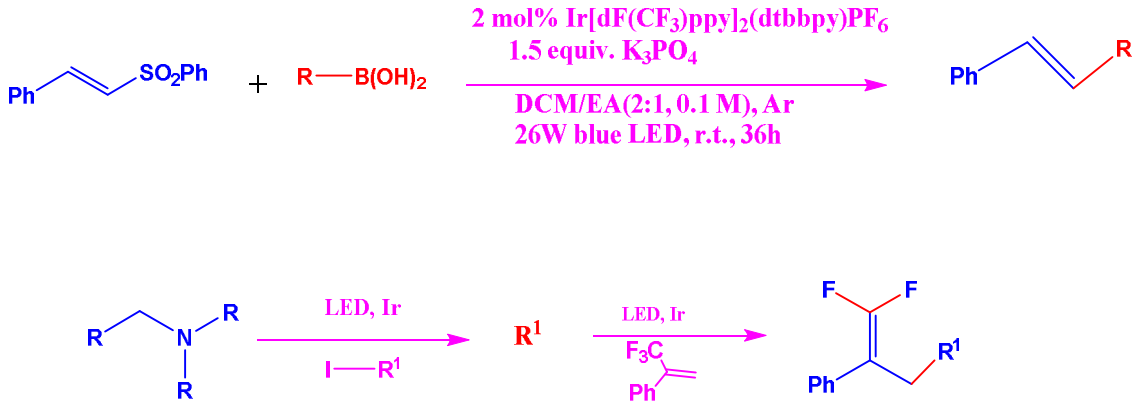
MATERIALS AND METHODS

There have only been a few methods, including conventional (Zhi-Yu Tan, et. al. 2020 & Huang, Lu-Shan, et al. 2019) and visible light-initiated (Yue, et. al. 2021) procedures that have been documented to be effective in forming carbon-carbon double bonds.

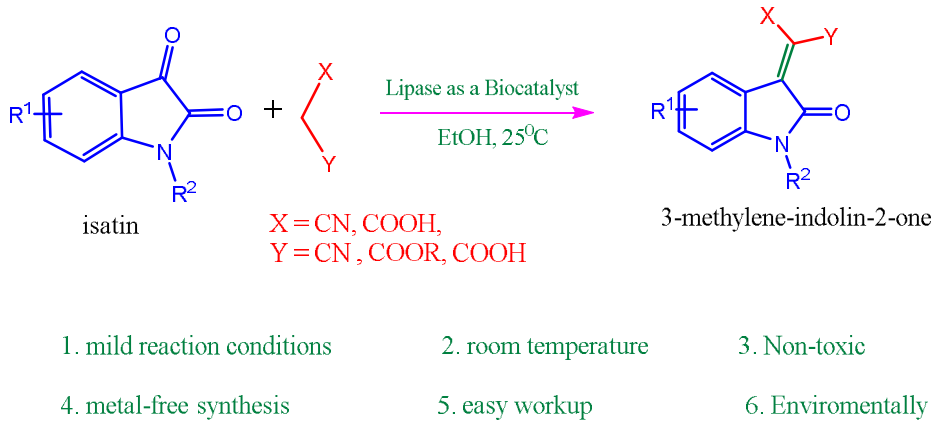
Conventional method:



Visible light-initiated method:



Also, as far as we know, there are couple of reaction to synthesis of 3-methylene-indoline-2-one and their derivatives. Therefore, there is a need to develop low-cost, environmentally friendly and alternatives to metal catalysts, which have a harmful impact on the environment. We report a green and benign method for the synthesis of 3-methylene-indoline-2-one and their derivatives using Lipase as a green catalyst. Which is easily available, benign, and ecofriendly.



Scheme 1

Isatin (1mmol), Lipase (1mol %), and EtOH: H_2O (4:1) were taken in a 10 mL round bottom flask and mixture was stirred for 8 h. After that malononitrile(1mmol) was added into RB. The reaction was screening via TLC After the reaction completed, the precipitate was filtered and rinsed with ethanol. After recrystallization, the product 2-(2-Oxoindolin-3-ylidene malononitrile was obtained in excellent yields.

Characterization: Yield -88%, Colour-Brick Red Crystal, Melting Point-196°C

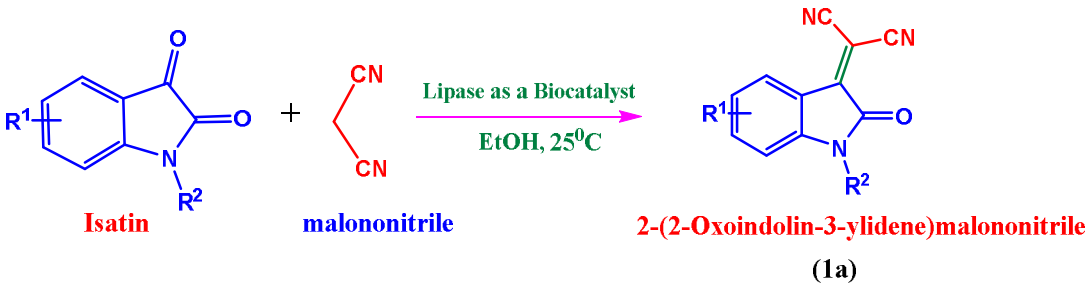


Figure 1: 2-(2-Oxoindolin-3-ylidene) malononitrile

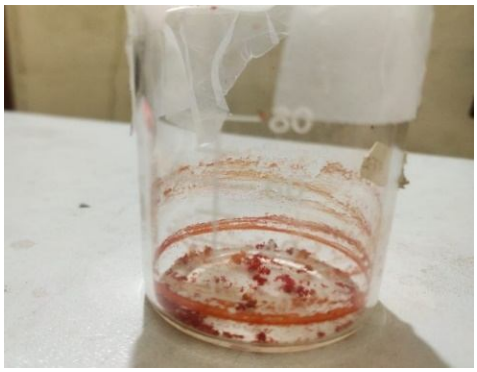
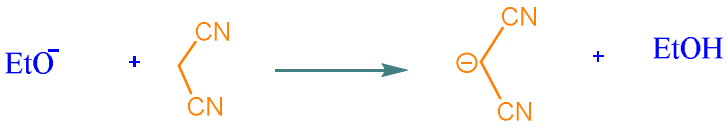


Figure 2: 2-(2-Oxoindolin-3-ylidene) dimedone

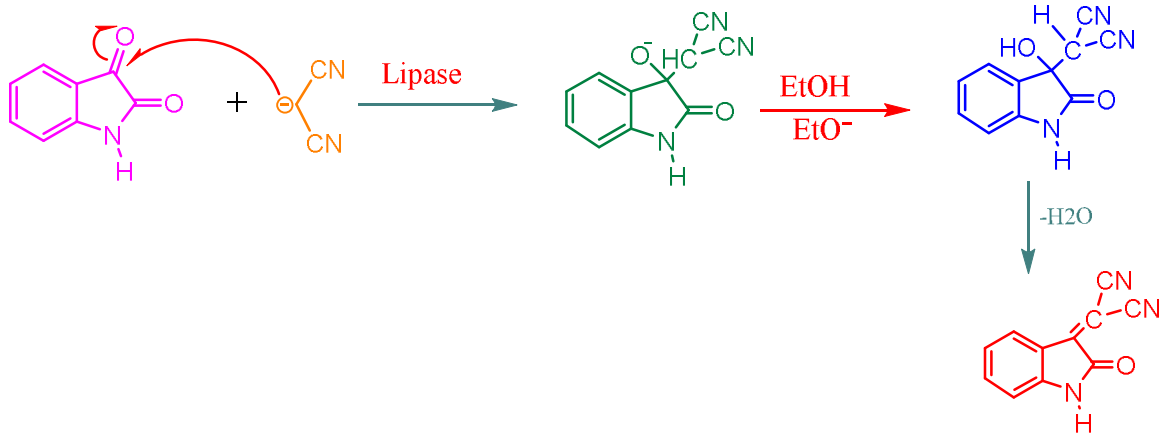
Mechanism

Step 1

Step 2



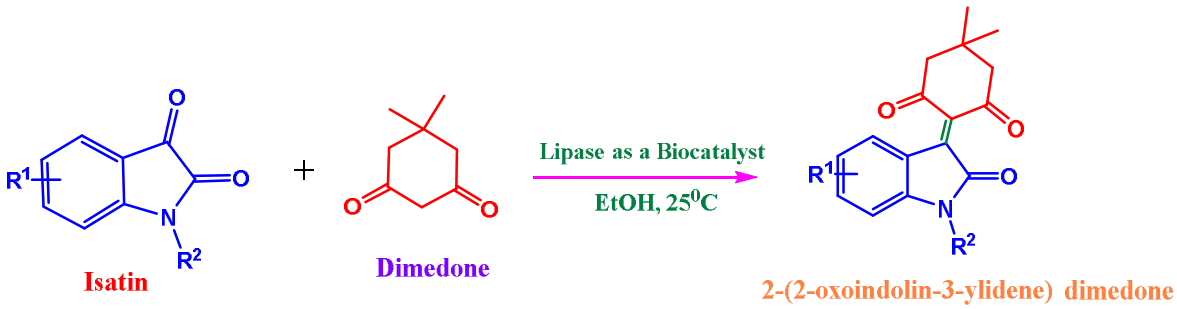
Step 3



Scheme 2

Isatin (1mmol), Lipase (1mol %), and EtOH: H_2O (4:1) were taken in a 10 mL round bottom flask and mixture was stirred for 8 h. After that dimedone (1mmol) was added into RB. The reaction was screening via TLC. After the reaction completed, the precipitate was filtered and rinsed with ethanol. After recrystallization, the product 2-(2-Oxoindolin-3-ylidene) dimedone was obtained in high yields.

Characterization: Yield-84%, Colour -Light Orange Crystal, Melting Point-265^{o}C



(2a)

RESULT AND DISCUSSION

Initially, we tested some catalysts role like Rhodamine B, Rose Bangle, Xanthone, EosinY, and Lipase for the reaction of Isatin with Malononitrile using DMF solvent. But we reported less yield of product of the first 4 catalysts and a 14% yield with Lipase as a biocatalyst. After that, we optimized solvents like acetonitrile, DMSO, DCE and Ethanol. But no one could provide 1a in a high yield except Ethanol. We optimized various molar ratio of EtOH / H_2O (1:1, 1:2, 2:1, 3:1, and 4:1).

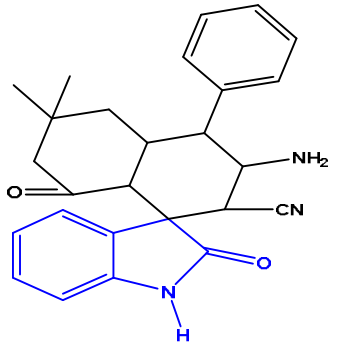
Table 1: Yield of various molar ratio of EtOH/H_2O

No.	Catalyst	Solvent	Water	Yield (%)
1	Rhodamine B	DMF	none	6
2	Rose Bengal	DMF	none	4
3	Xanthone	DMF	none	3
4	Eosin Y	DMF	none	14
5	Lipase	DMF	none	15
6	Lipase	DMSO	none	NA
7	Lipase	DCM	none	NA
8	Lipase	MeCN	none	NA
9	Lipase	DCE	none	NA
10	Lipase	EtOH / H_20	(1:1)	41
11	Lipase	EtOH / H_20	(1:2)	37
12	Lipase	EtOH / H_20	(2:1)	46
13	Lipase	EtOH / H_20	(3:1)	62
14	Lipase	EtOH / H_20	(4:1)	88
Reaction conditions: indole (1 mmol), malononitrile (1 mmol), AND catalyst (1 mol%), 24 h.				

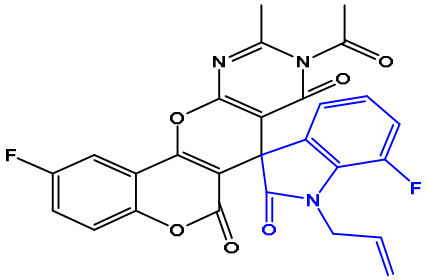
Medical Approach

The biological activity of 3-methylene-indoline-2-one and its derivatives, which include carbon-carbon unsaturated bonds, include those of anti-HIV, antiviral, anticonvulsants and anticancer agents. It is necessary to use 3-alkylideneoxindoles for producing a variety of heterocyclic compounds. Such substances are potential drug for pharmaceutical development, including chiral spirooxindole derivative with anticancer, spiro [indole-3,4′-quinolines] with antibacterial, and derivatives of cyclic spiro-2-oxindoles with some biologically activity. These substances also have anti-angiogenic and apoptotic properties.

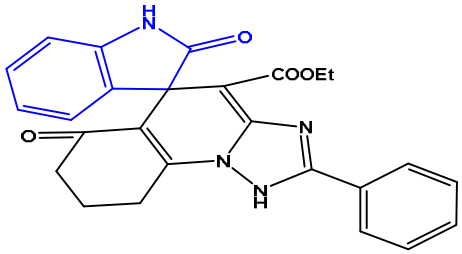
Numerous biologically significant heterocycles have been prepared using 3-methylene-indoline-2-one and its derivatives as synthons. In addition, indoles derivatives are present in significant synthetic therapeutic compounds with intriguing pharmacological characteristics, such as SARS coronavirus 3CL protease inhibitors, anti-HIV activity, antituberculosis activity, anticonvulsant, and HIV-TB coinfection, as well as anti-cancer. A number of 3-substituted indole derivatives have been discovered to possess significant anti-cancer capabilities, including the ability to suppress the growth of human ovarian cancer (SK-OV-3) and human colon carcinoma (HT-29) cell lines. Significantly, when compared to conventional medications, and have demonstrated good anticancer efficacy against MCF-7 breast cancer cell lines (Lakhdar 2006, Sharma 2010).



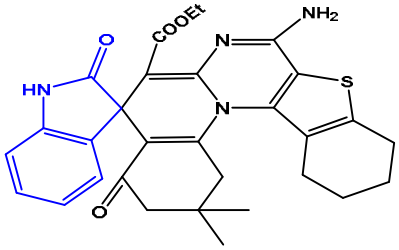
Antibacterial Activity



Anticancer Activity



Antimalarial antifungal



Apoptotic and Anti-Angiogenic

CONCLUSION

In conclusion, a unique, sustainable, and green method for producing 3-methylene-indoline-2-one and its derivatives has been established. Lipase was used as the catalyst. The reaction proceeds efficiently under milder condition with a substantially assessable yield of the coupling products. It can be attributed to several additional characteristics including a reaction without metal, a high product yield, the absence of side products, and the effective use of renewable energy sources. Greener procedures with less negative environmental impact and lower drug costs are made possible by green solvents, nanocatalysts, and biocatalysts. We anticipate that this chapter, along with the others, will provide a quick overview of the significance of green chemistry. With the benefits of green chemistry, the industry should change traditional approaches. On the other hand, we have previously seen that pharmaceutical corporations looked for green manufacturing practices when they are manufacturing medicines. Accordingly, the majority of pharmaceutical companies are working harder than ever to cut back on waste, stop air pollution, and use environmentally friendly processes.

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