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GREEN PROTOCOLS FOR AMIDATION REACTIONS

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Abstract: Amide functionality is gaining importance day by day because of wide use in synthetic organic chemistry as well as biological, medicinal and pharmaceutical field. Classical amidations are carried out using homogenous metal catalyst but several drawbacks have come infront. New generation research demands more advanced catalytic approach for amidation where green chemistry takes its entry. This paper provides an overview of metal free and photocatalytic amidation of aldehydes and alcohols. It also covers enzyme catalyzed amidation reactions of both established and newer methods and compares the efficiency along with which will be very helpful for new generation researchers with a sensible and educated choice of catalyst. Remaining challenges in this process are also carefully analyzed.

Key words: Amidation reactions, Aldehydes, Amides, Green chemistry, Enzyme catalyzed

1. Introduction:

Amide bond is the one of the most abundant functional groups in natural product, polymer and phermaceuticals. One of the most demanding functional groups of medicinal chemists is amide since more than 25 % of known drug contain carboxymide group according to medicinal chemistry database.[1] It is definite because carboxymides are neutral, stable and having both hydrogen bond donating and accepting properties. Protein synthesis in nature involves the sequential peptide coupling reaction which is actually amide bond formation among two alpha amino acids.[2] Apixaban (Fig 1) is one of the most top marketed drug that is used to prevent strokes in people who have a condition in which the heart beats irregularly, increasing the chance of clots forming in the body and possibly causing strokes, having several amide connectivity.[3]

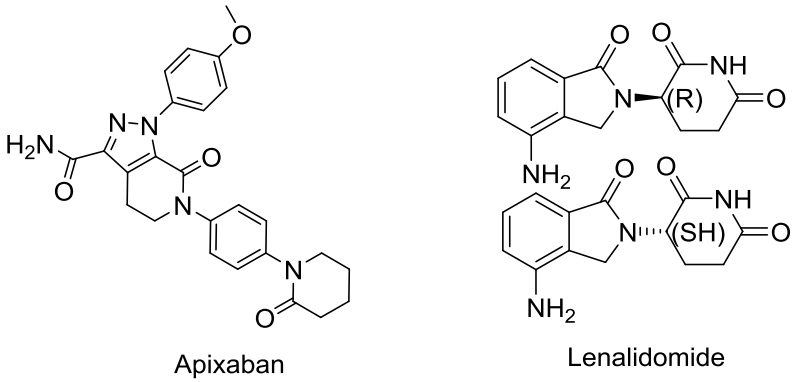

Fig 1. Structure of Apixaban and Lenalidomide

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Like this Lenalidomide (Fig 1) (used to treat multiple myeloma which basically a cancer of plasma cell)[4], Rivaroxaban (Fig 2) (an anticoagulant medication that is used to treat and prevent blood clots)[5], Ledipasvir (Fig 2) (is an important medication used to treat hepatitis C) have a number of amide functionality.[6]

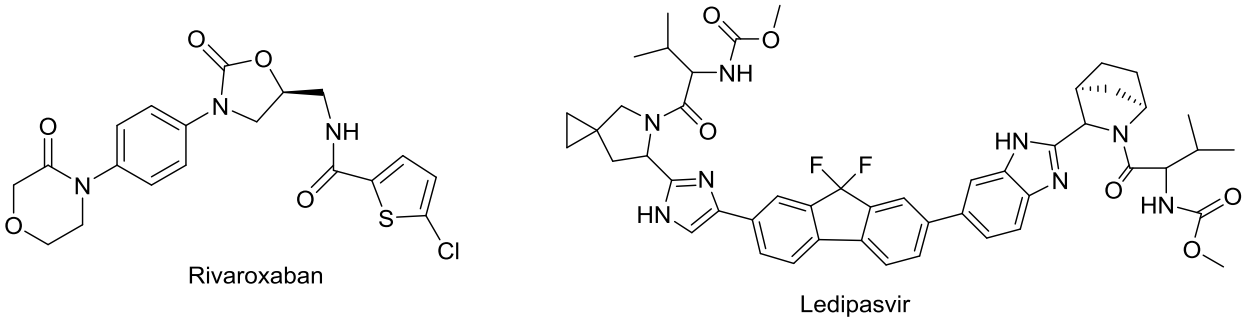
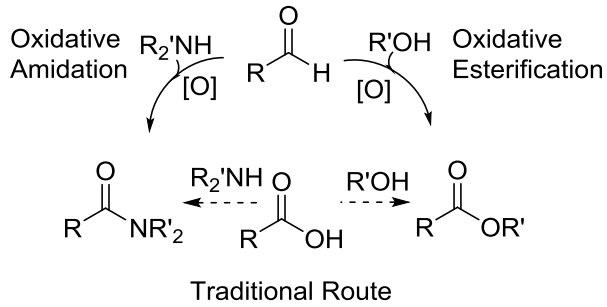


Fig 2. Structure of Rivaroxaban and Ledipasvir

Amides are routinely prepared from free carboxylic acids and amine via condensation reaction. This occurs very fast because it is the mixing of acid and base to form a salt but the point is it require high temp (160-180^{o}C) that may be functional gr intolerance. The amide formation step has to fight against adverse thermodynamics since equilibrium lies towards salt stage rather than amide stage. (Scheme 1)[7] Other strategy that include activation of carboxylic group to an acylating agent followed by aminolysis. It involves two separate steps – activation and C-N bond formation.



Scheme 1: Amidation strategies

The second approach has become economically attractive since it avoids the isolation of carboxylic acid derivatives which particularly important for natural product synthesis when there is incompatible functional group or protecting groups present. Hereby we report an overview of metal free and photocatalytic amidation of aldehydes and alcohols along with enzyme catalyzed amidation reactions.

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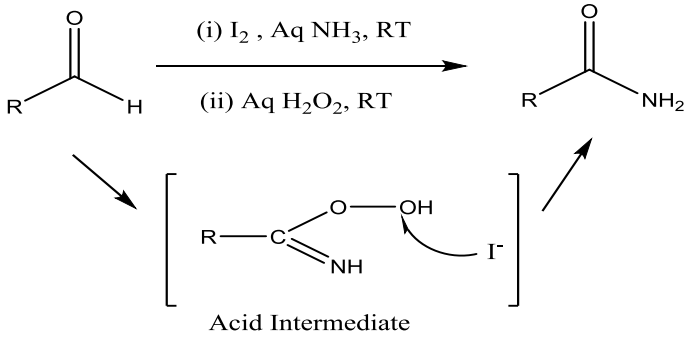
Metal free green Amidation reactions:

1. **Amidation in aqueous medium**

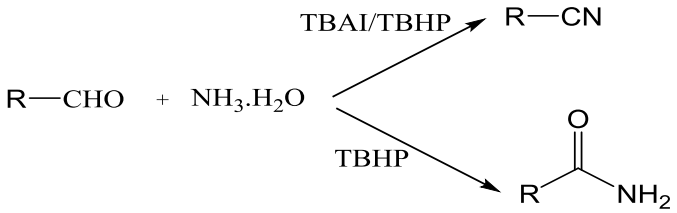
When compared to certain flammable and toxic organic solvents, water emerges as a superior and safer alternative for use in organic reactions. Its affordability contributes to greater cost-effectiveness in chemical processes. Additionally, water often allows for recycling, addressing solvent disposal concerns. Moreover, employing water as a solvent presents benefits such as straightforward operation and heightened efficiency, particularly in organic reactions involving water-soluble substrates and reagents.[8]

Over two decades ago, J-M Fang *et al* proposed amidation reactions in aqueous medium.[9] Different aldehydes underwent a reaction with iodine in ammonia water at room temperature, resulting in nitrile intermediates. These intermediates were captured by the addition of hydrogen peroxide, sodium azide, or dicyandiamide, yielding their respective amides, tetrazoles, and 1,3,5-triazines in moderate to high yields. (Scheme 2)



Scheme 2: Amidation reactions in aqueous medium

L. Wang and colleagues have devised a straightforward and selective method to convert aldehydes into their respective nitriles and primary amides in an aqueous ammonia environment.[10] The aldehydes were effectively transformed into the corresponding nitriles with moderate to excellent yields by employing tetrabutylammonium iodide (TBAI) and tert-butyl hydroperoxide (TBHP) as co-oxidants. However, the synthesis of primary amides was achievable only in the presence of *tert*-butyl hydroperoxide, showcasing selective synthesis under these conditions (Scheme 3). Their current approach circumvents the need for costly metal catalysts, harmful solvents, and severe conditions. Its excellent yield, exceptional selectivity, and adherence to atom economy render our methods more environmentally friendly and widely accepted.



Scheme 3: Synthesis of nitriles and primary amides

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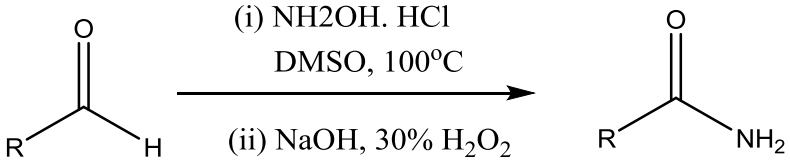
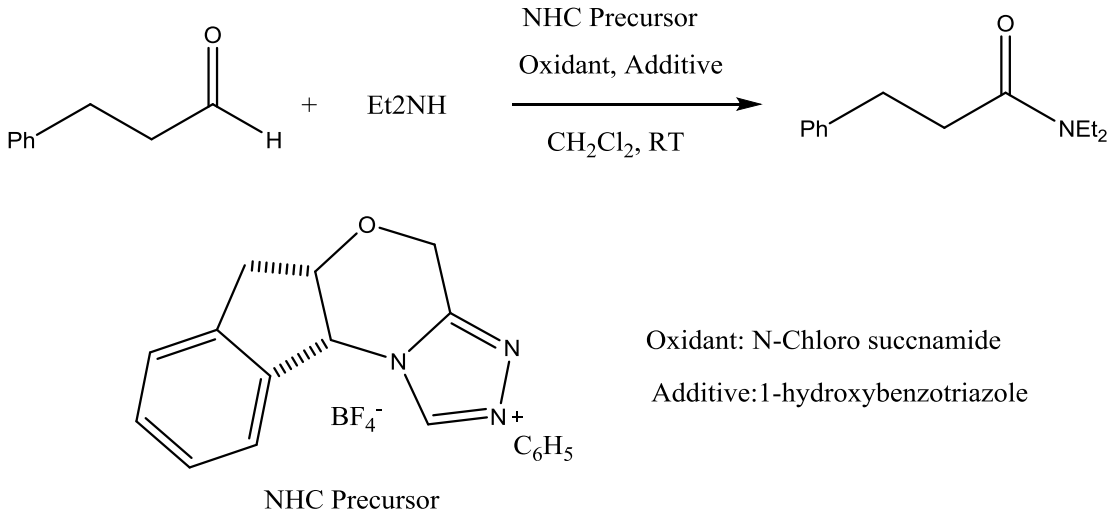
Over a decade ago *R.C Mebane et al* showcased a straightforward one-step method for synthesizing amides from aldehydes.[11] This sequential process starts with creating a nitrile intermediate by reacting an aldehyde with hydroxylamine hydrochloride in dimethylsulfoxide at 100°C, followed by treating the nitrile with basic hydrogen peroxide (Scheme 4). This consecutive one-step process doesn't require costly or risky substances, presenting an appealing alternative to recent methods for transforming aldehydes into amides.



Scheme 4: Facile one pot metal free amidation reaction

2. N-heterocyclic carbene catalyzed amidation reactions

N-heterocyclic carbenes (NHCs) serve as organocatalysts in diverse transformations. *K. Yamada et al*. demonstrated the direct conversion of aldehydes to esters or amides using NHC-catalysis, specifically noting success with aromatic and unsaturated aldehydes in the reported direct amidation.[12](Scheme 5) The selective conversion of unbranched aldehydes and the avoidance of isolating unstable α-chloroaldehyde intermediates offer significant advantages. The observed selectivity of nucleophiles, dependent on NHC, indicates that the choice of NHC catalyst can effectively control chemoselectivity.



Scheme 5: NHC catalyzed amidation reaction

C.D. Brown and colleagues have outlined a flow method for the anodic oxidative amidation of aldehydes mediated by N-Heterocyclic Carbenes (NHCs). This approach employs an electrolysis cell to oxidize enaminol intermediate. Following electrochemical oxidation, the reaction between the cationic intermediate and primary amines was accomplished by passing it *via* a warmer cell, achieving excellent conversion at once (Scheme 6)[13]. Amidation of electron-rich aromatic and heteroaromatic aldehydes resulted in excellent isolated yields. Additionally, primary amines with

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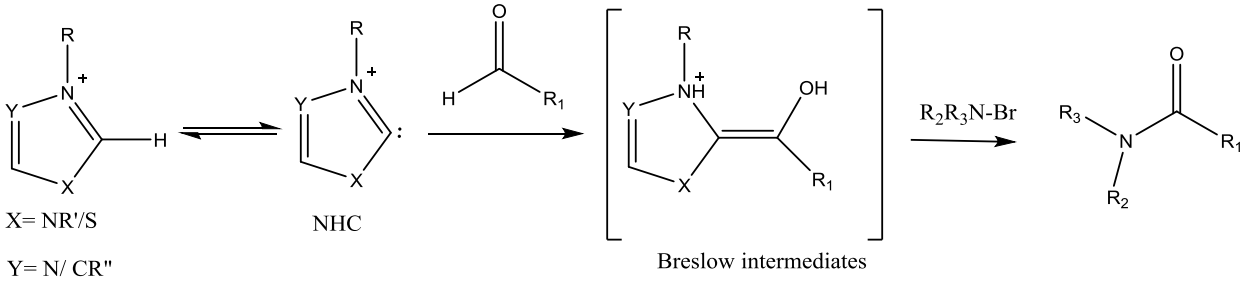
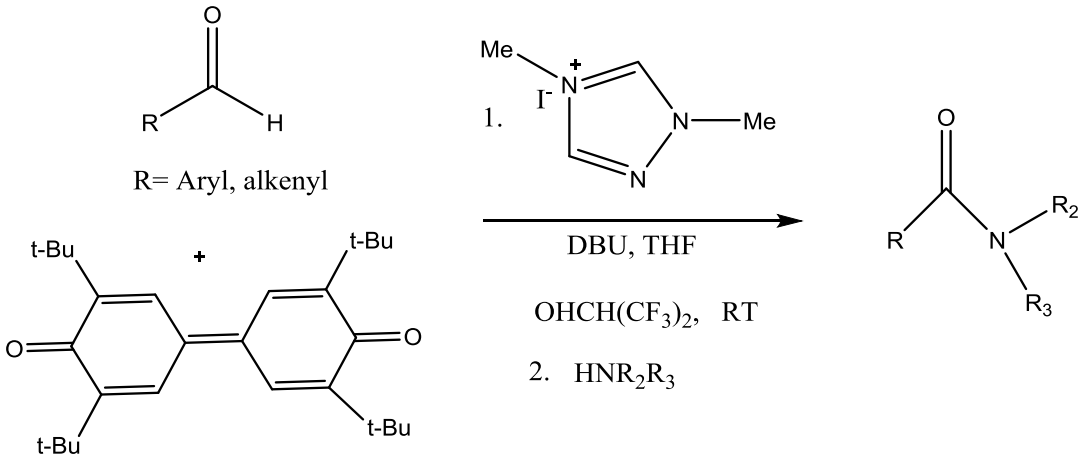
electron-rich, electrochemically oxidizable functionalities like indole, furan, and phenol groups produced amides in yields ranging from 71% to 86%. An unbranched aliphatic aldehyde yielded the N-benzylamide in a 71% yield. They have achieved high yields of (71-99%) and productivities (up to 2.6 g h-1), and current efficiencies (65-91%) on scales up to 20 g.



Scheme 6: NHC mediated amides from aldehydes

The oxidative amidation of aromatic and *α, β*-unsaturated aldehydes were catalyzed by a NHC type of intermediate, as outlined in the findings by A. Studer *et al*. Significantly, the reactions exhibit efficacy with a minimal catalyst loading (Scheme 7). Notably, the study highlights the utility of hexafluoroisopropyl esters as active intermediates for amide bond formation. The hexafluoroisopropanol produced as a byproduct during the amidation process can be easily eliminated from the reaction mixture through straightforward evaporation.[14]



Scheme 7: Oxidative amidation by NHC

3. Biomass catalyzed amidation

L. Ma et al. introduce a straightforward and effective method utilizing triphosgene to enable a one-pot conversion of aldehydes and ketones into nitriles and amides.[15] Recent attention in research has focused on converting biomass platform compounds into valuable chemicals and pharmaceutical intermediates. Directly transforming these compounds into nitriles and amides is poised to significantly guide the utilization of biomass resources. The outlined protocol ensures a seamless process without the necessity of organic bases or metal catalysts. Leveraging biomass-

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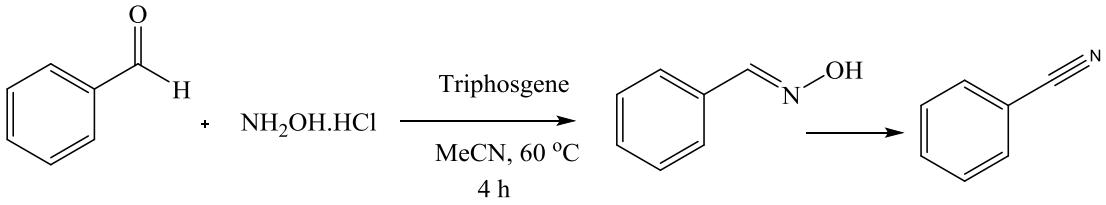
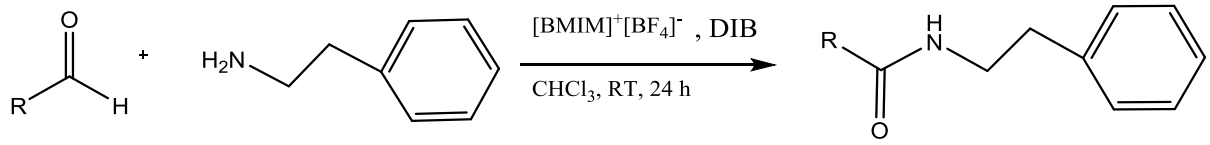
derived platform compounds, a range of functionalized aromatic, aliphatic and allylic aldehydes and ketones were successfully converted into nitriles and amides, yielding excellent results (see Scheme 8). In contrast to sequential reactions, this tandem approach offers multiple-step transformations within a single vessel, featuring gentle reaction conditions and generating fewer by-products.



Scheme 8: Transformation of benzaldehyde to benzonitrile

4. Ionic liquid catalyzed amidation

Over the past few years, environmentally friendly reaction media for carbohydrate synthesis have shown promise with the emergence of room temperature ionic liquids (RTILs). These liquids are potent catalysts for multicomponent one-pot reactions involving carbonyl entities.[16] Ionic liquids shows their performance for oxidative amidation reaction as carried out by *Tiwari et al* along with diacetoxyiodobenzene (DIB) as catalyst (Scheme 9).[17] The protocol described herein, offers a straightforward, and effective pathway to form novel carboxamides derived from aldehydes. Consequently, it constitutes a formal oxidative amidation of aldehydes. This recent inclusion in the expanding array of instances showcasing the notably oxidation potential of DIB is, the first report for a single step amidation of aldehydes into amides having mild reaction conditions utilizing ionic liquids. Given its ability to circumvent the employment of costly and hazardous metals while accommodating the involvement of different groups, this chemistry could be acknowledged as an environmentally friendly alternative to existing synthetic methods.



Scheme 9: Diverse Carboxamides from aldehydes

5. Photocatalytic amidation reactions

The next approach involves a photo organocatalytic reaction between aldehydes and diisopropyl azodicarboxylate, resulting in an intermediate carbonyl imide. This intermediate can subsequently engage with various amines, leading to the synthesis of amides. The methodology put forth by *G. Kokotos et al*. allows for a mild, one-pot, and environmentally friendly synthesis of amides from aldehydes and aminesd using di-isopropyl azodicarboxylate (DIAD) in petroleum ether as the photocatalyst (Scheme 10).[18]

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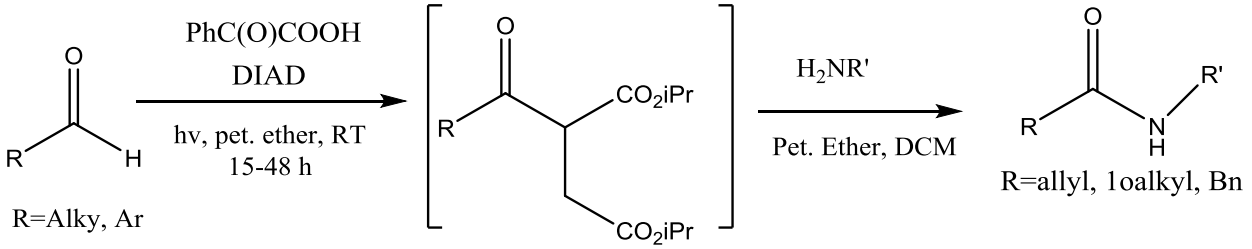
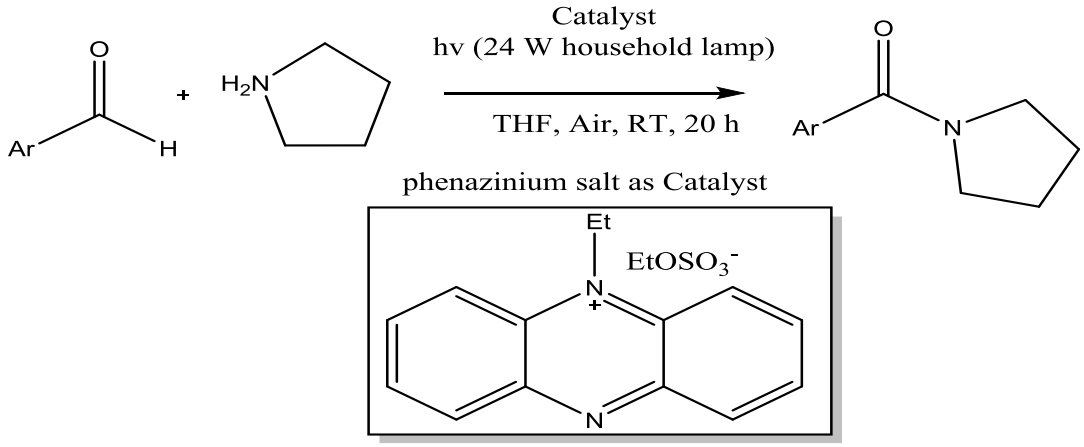
In the initial step, a photo organocatalytic reaction involving aldehydes and diisopropyl azodicarboxylate results in the formation of an intermediate carbonyl imide. This intermediate can undergo subsequent reactions with a diverse range of amines, yielding the desired amides. The initial activation, mediated by visible light, is typically rapid for various monosubstituted or disubstituted aldehydes, taking only a few hours. Subsequent to the photocatalytic reaction, introducing the primary amine at room temperature or the secondary amine at elevated temperatures facilitates the production of the corresponding amides with yields ranging from moderate to excellent, all achieved without epimerization.[18]



Scheme 10: Photo organocatalytic amidation reactions

Dasheng Leow has reported an oxidative amidation process for aromatic aldehydes, utilizing low quantities of phenazine ethosulfate as an affordable, metal-free visible light photocatalyst. This procedure operates at ambient temperature and relies solely on air as the oxidant (Scheme 11).[19]The presented method focuses on the phenazinium salt-catalyzed aerobic oxidative amidation of aromatic aldehyde derivatives with a minimal catalytic loading. Notably, the protocol eliminates the requirement for costly reagents by utilizing air as the oxidant. Under visible light irradiation, the phenazinium cation is proposed to undergo a two-electron reduction to hydrophenazine. The operationally straightforward procedure offers an economical, environmentally friendly, and gentle alternative for the synthesis of amide bonds.



Scheme 11: Oxidative amidation by phenazinium salt

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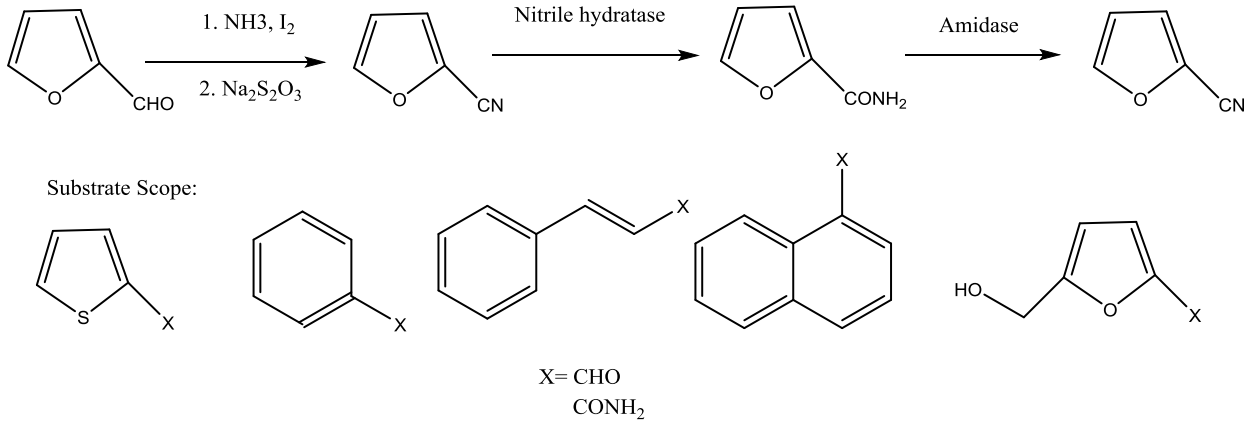
Enzyme catalyzed Amidation reactions

Enzymatic conversions offer a significant advantage: they can occur under gentle conditions, like neutral pH and room temperature. Consequently, there has been substantial focus on boosting the catalytic efficiency of these enzymes for various synthetic substrates in organic functional group alterations.[20]

T Sugai et al. established a single-step chemo-enzymatic process to convert aldehydes into amides. They investigated the efficacy of nitrile hydratase and amidase in whole cells harvested from Rhodococcusrhodochrous IFO 15564.[21] Amidase exhibited superior heat resistance compared to nitrile hydratase, exclusively functioning at 45°C. The addition of DMSO facilitated the preferential action of nitrile hydratase. However, with more than a 30% (v/v) addition of DMF, nitrile hydratase lost all activity, leaving only amidase functional. One pot conversion of aldehydes to amides were studied in DMSO in the presence of Aq NH_3 and I_2 as additives at room temperature. (Scheme 12)



Scheme 12: Chemo-enzymatic one pot amination

In the instance of R. rhodochrous IFO 15564, the proximity of the genes encoding two enzymes has posed a challenge,[22]hindering the isolation of enzyme proteins and the independent overexpression of their cloned genes. Leveraging the ready availability of cultured and harvested microorganism cells, the specific "preferential action" of either nitrile hydratase or amidase within the whole cell holds immense significance for selective functional group transformations in synthetic organic chemistry.[23,24]

A highly effective single-step biocatalytic process combining amine transaminase and acyl transferase has been developed by *P. Bergland et al*.[25]This cascade efficiently forms amides from aldehydes and ketones in aqueous solutions. (Scheme: 13) The enzyme acyl transferase from Mycobacterium smegmatis (MsAcT) demonstrates proficiency in executing trans-acylations within aqueous solutions. Over recent decades, amine transaminases have undergone thorough examination for their capability to conduct asymmetric methods, producing both varieties of primary amines (chiral and achiral) from the respective ketones or aldehydes bearing

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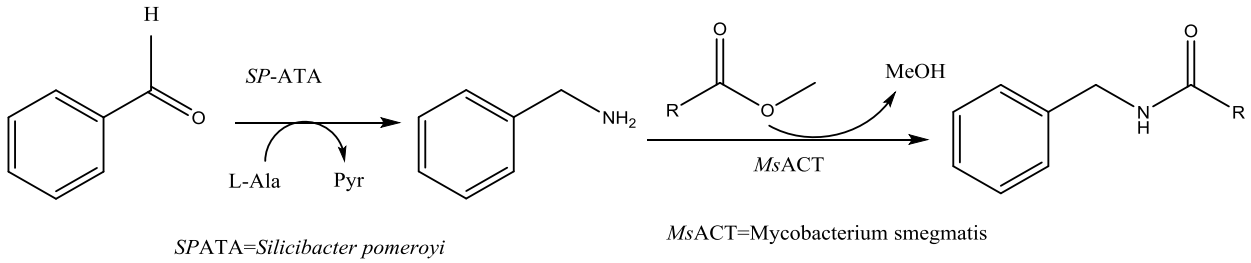
pro-chiral centers. This process consistently yields excellent results in both yield and enantiomeric purity.[26,27]



Scheme 13: Biocatalytic amidation process

They have also demonstrated a synthesis of *N*-benzyl-2-methoxyacetamide at a higher scale (> 95 mg). The reaction had produced 92% of acetamide conversion with a good yield under optimized conditions.

Conclusion:

Amide bonds are indeed crucial in organic chemistry due to their prevalence in various compounds like pharmaceuticals, polymers, and natural products. The direct amination of aldehydes has gained significant interest because it offers more efficient ways to create amide bonds. These methods utilize easily accessible starting materials, making the synthesis process more atom-efficient and reducing the number of steps required to produce amides. This not only benefits organic synthesis in laboratories but also holds potential implications for industrial-scale production of important compounds.

This paper provides a metal-free and photocatalytic amidation of aldehydes and alcohols alongside enzyme-catalyzed amidation reactions offers a broad view of various methodologies for amide bond formation. Comparing their efficiencies can guide researchers in making informed decisions about which catalyst to choose for their specific synthesis goals. This kind of overview is invaluable for new researchers entering the field, providing a clear understanding of the available options and helping them select the most suitable catalyst for their desired reactions. It's great to see research that consolidates and compares different methodologies to aid the scientific community.

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