Review Article: Applications of Alum ($KAl(SO_4)_2.12H_2O$) in Organic Synthesis and as Catalysis: A Quinquennial Update (2017-2022)

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ABSTRACT

Recently, synthetic scientists have become interested in potassium alum ($KAl(SO_4)_2.12H_2O$), also referred to as "alum," as an effective, safe, and environmentally friendly acid catalyst for carrying out various organic transformations. The current mini-review piece provides an overview of the representative catalytic uses of this easily accessible and inexpensive inorganic sulphate salt in organic reactions that have been reported from mid-2017 to the present.

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Vijay Kotra: He completed his Ph.D Degree in Pharmaceutical Chemistry from Andhra University, Visakhaparnam, Andhra Pradesh, India in 2010. He worked as assistant professor in University College of Pharmacy, Acharya Nagarjuna University, Guntur, India during 2010-2018. Next, he moved to Faculty of Pharmacy, Quest International University, Ipoh, Malaysia with the designation of Associate Professor, from 2018 till date. He has published around 75 research articles, 2 book chapters, and a patent to his credit.

Content

1. Introduction

Potassium alum ($KAl(SO_4)_2.12H_2O$), one of the many types of commercially accessible alums, is widely used for both domestic and medical purposes [1-3]. Potassium alum, more commonly known as "alum," is used in everyday living as an inexpensive, non-toxic water purifier, and antiseptic agent (**Figure 1**).

Figure 1. Potash Alum in crystalline form

As E number E522, potassium alum is frequently used in baking flour, leather tanning, dyeing, and water purification. In addition, it can be used cosmetically as a deodorant, an aftershave, and a styptic for small shaving-related bleeding. Potassium alum has been used to stop bleeding in instances of hemorrhagic cystitis because it has antibacterial and antiperspirant properties [4, 5]. Since the 1920s, hydrated potassium aluminium sulphate has been the main adjuvant used to boost the effectiveness of immunizations. It is frequently found as $KAl(SO_4)_2.12H_2O$, a dodecahydrate. With a space group of P a 3 and a lattice value of 12.18, it crystallizes in an octahedral structure in a neutral solution and a cubic structure in an alkali solution. The substance, which is frequently referred to as just "alum", is the most significant member of the general family of substances known as alums.

The literature review shows that it is an effective acid catalyst for carrying out a wide range of organic transformations [6-17]. Alum has recently captured the interest of synthetic chemists who are investigating its use in organic transformations because of its innate catalytic proficiency, low cost, non-toxicity, and environmental friendliness. Up until the middle of 2017, Bramhachari *et al.* provided a comprehensive report on potash alum [18]. Keeping in view of continued process in updating emerging areas in catalysis and organic synthesis [19-26], herewith, we have discussed the most representative instances of alum-catalyzed organic transformations from the middle of 2017 to the present in this mini overview.

2. Applications of Alum as Catalyst in Organic Transformations

2.1. Heterocyclic ring formations

Heterocycles of nitrogen and oxygen have numerous uses in biology and medicine. Several bioactive natural compounds contain the pyrrole-2-one moiety [27]. Another such molecule found in nature is furan-2(5*H*)-one (butenolide). This core fragment also exhibits a wide range of biological actions [28].

To create polysubstituted pyrrol-2-ones and furan-2-ones (**4** and **5**), Singh *et al.* [29] reported a practical, one-pot, and multicomponent condensation of various aldehydes (**3**) and amines (**2**) with dialkyl acetylenedicarboxylates (**1**) (**Figure 2**).

One of the key advantages of this technique is the utilization of potash alum as a solid catalyst that is affordable, recyclable, and environmentally friendly. Low-cost reagents, benign reaction conditions, convenience of operation, fast reaction durations, no requirement for chromatographic purification, and excellent yields are further aspects of disclosed methodology. The necessary pyrrol-2-one derivatives (**4**) were regularly synthesized with excellent yields (**Scheme 1**).

These findings showed that electron-withdrawing benzaldehydes interacted with aniline more favourably than electron-donating benzaldehydes. Using one equal of each amine, DEAD, and aldehyde, the authors expanded it to the preparation of furan-2(5*H*)-ones (**5**) in good to excellent yields (**Scheme 2**). The synthesis of pyrrol-2-ones and furan-2-ones was suggested using possible methods (**Schemes 3** and **4**, respectively). When producing pyrrole-2-one, the first amine molecule **2** (1 mmol) was combined with dialkyl acetylenedicarboxylate **1**

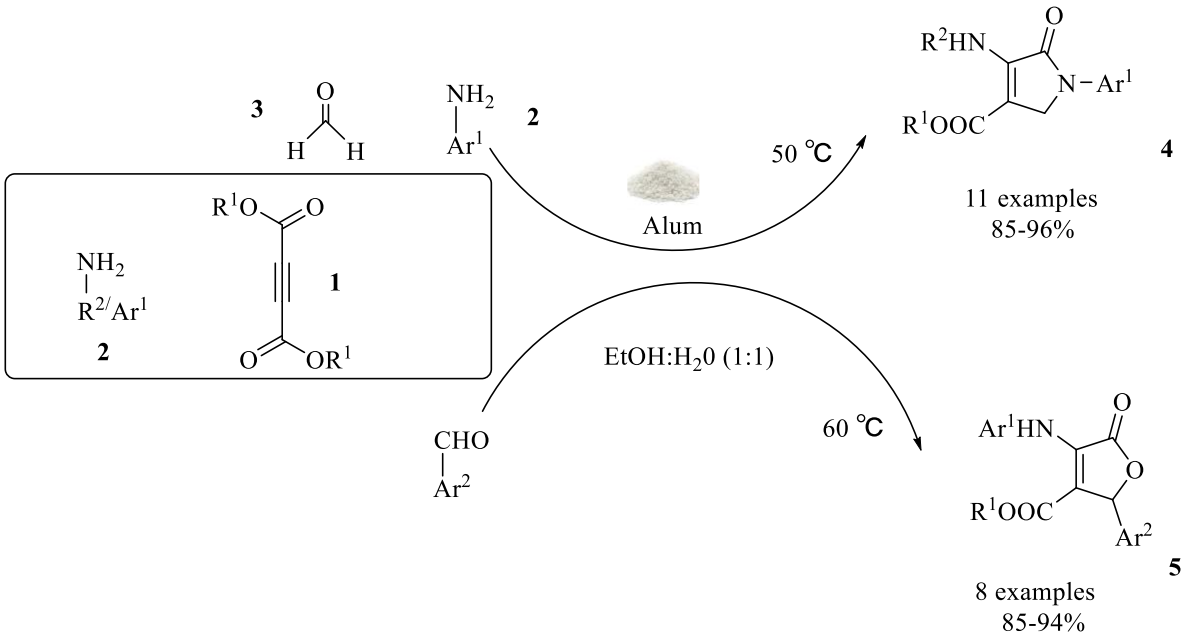
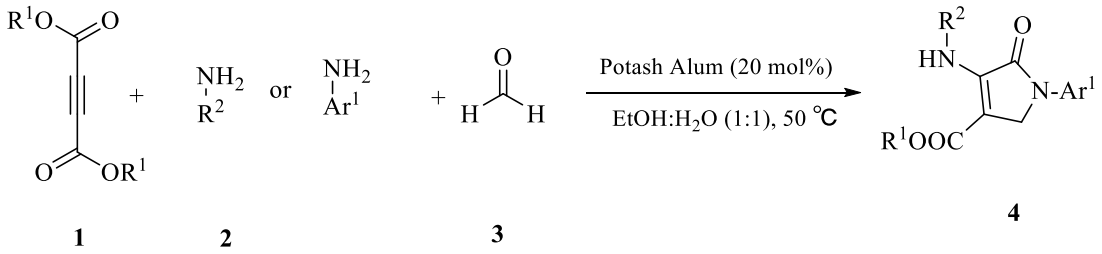
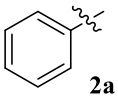
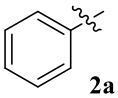
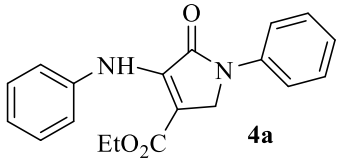
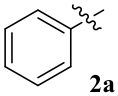
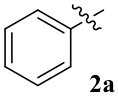
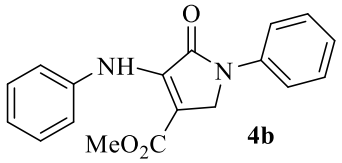
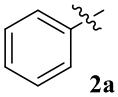
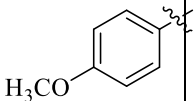
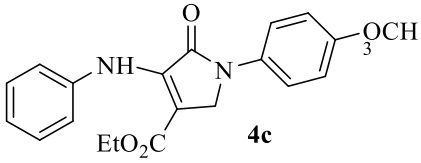
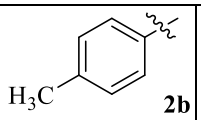
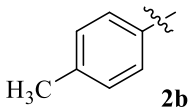
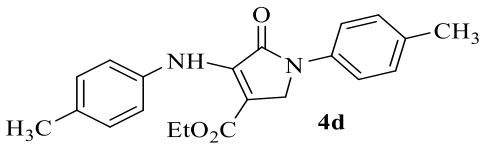
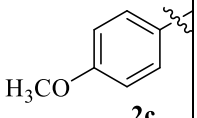
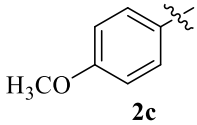
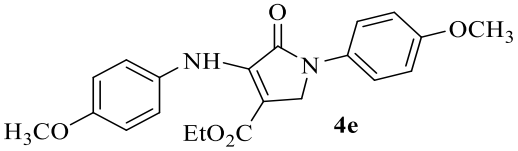
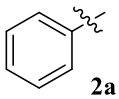
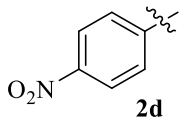
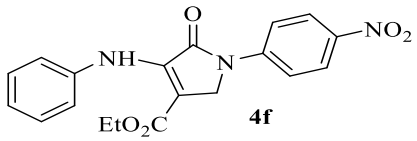


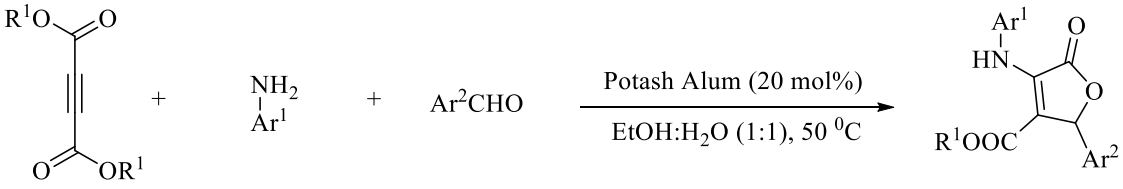
Figure 2. Preparation of pyrrol-2-ones and furan-2-ones



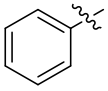
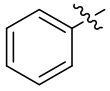
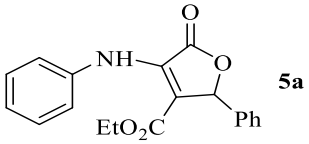
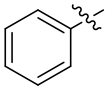
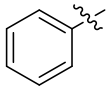
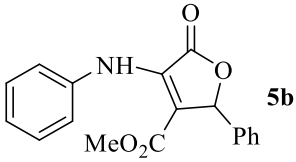
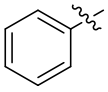
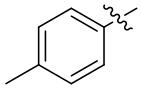
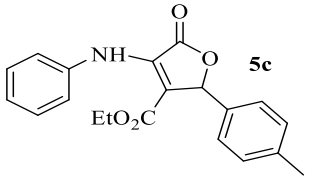
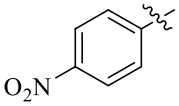
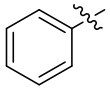
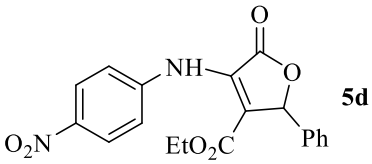
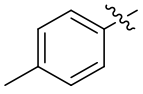
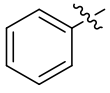
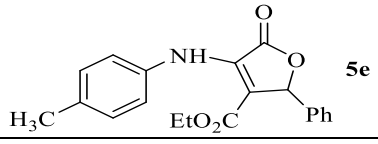
Entry	R1 for 1a-b	R^2	Ar^1	Time (min) Yield (%)	Product (4)
1	Et **1a**	 **2a**	 **2a**	96/45	 **4a**
2	Me **1b**	 **2a**	 **2a**	94/50	 **4b**
3	Me **1b**	 **2a**	 **2c**	85/80	 **4c**

4	Et **1a**	 **2b**	 **2b**	89/50	 **4d**
5	Et **1a**	 **2c**	 **2c**	87/90	 **4e**
6	Me **1b**	 **2a**	 **2d**	88/45	 **4f**

Scheme 1. Substrate scope in the synthesis of pyrrol-2-ones [selected examples]



1 **2** **3** **5**

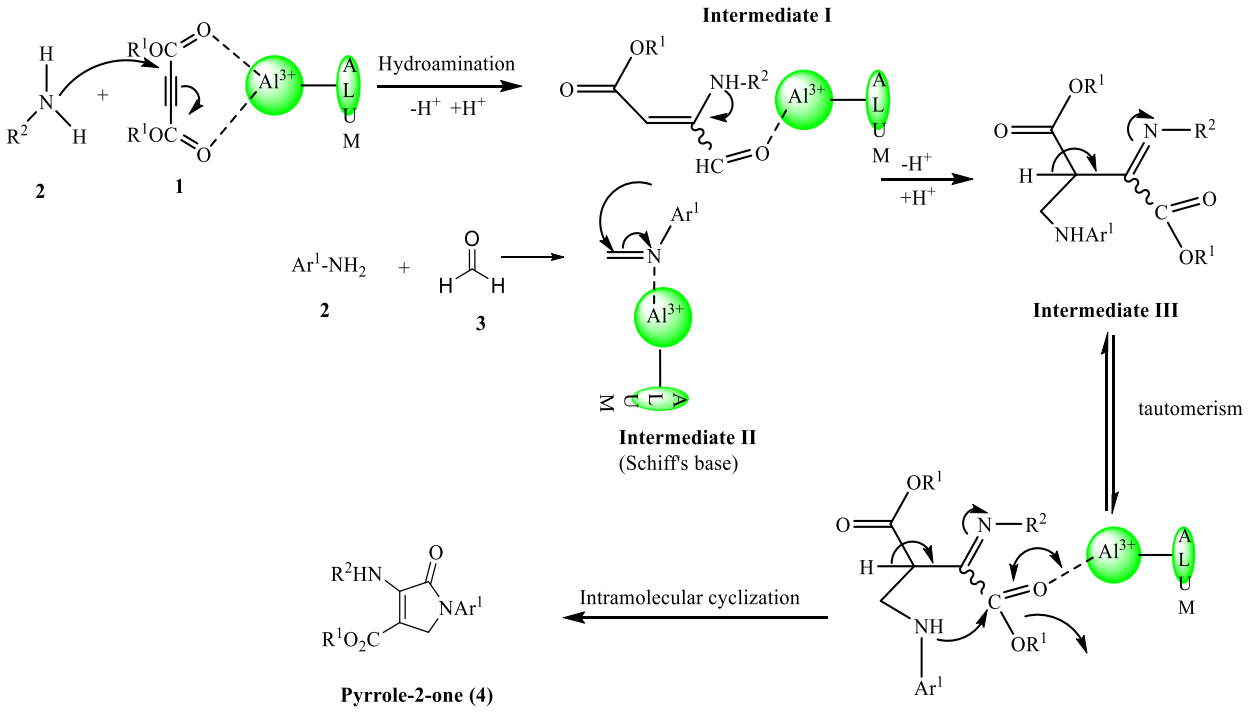
Entry	R^1	Ar^1	Ar^2	Time (min) Yield (%)	Product (5)
1	Et **1a**			94/50	 **5a**
2	Me **1b**			90/50	 **5b**
3	Me **1b**			92/50	 **5c**
4	Me **1b**			90/50	 **5d**
5	Et **1a**			88/90	 **5e**

Scheme 2. Preparation of furan-2-ones [selected examples]

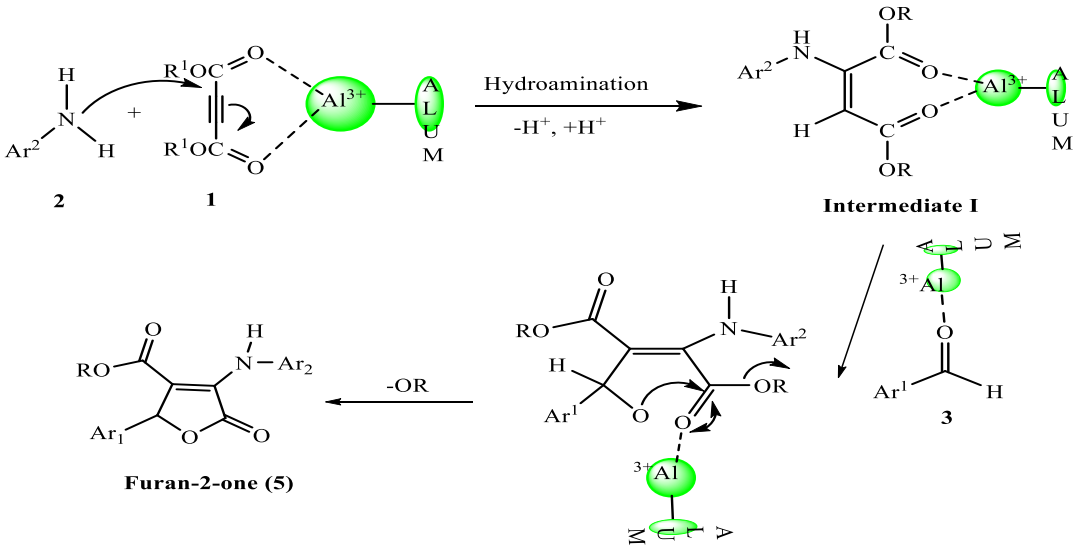
(DEAD, 1 equiv.) in the presence of potash alum (20 mol%) to produce intermediate **I** (TLC control), to which a second amine molecule **2** (1 mmol) was then added.

Now, instead of combining with the intermediate I, the second molecule decided to do so with the aldehyde (**3**), resulting in the synthesis of Schiff base (Intermediate **II**). The target pyrrole-2-one (**4**) was created as a consequence of the tautomerization of intermediate III and subsequent intramolecular cyclization, as depicted in **Scheme 3**, and then the intermediate I and intermediate II came together to create the intermediate **III**.

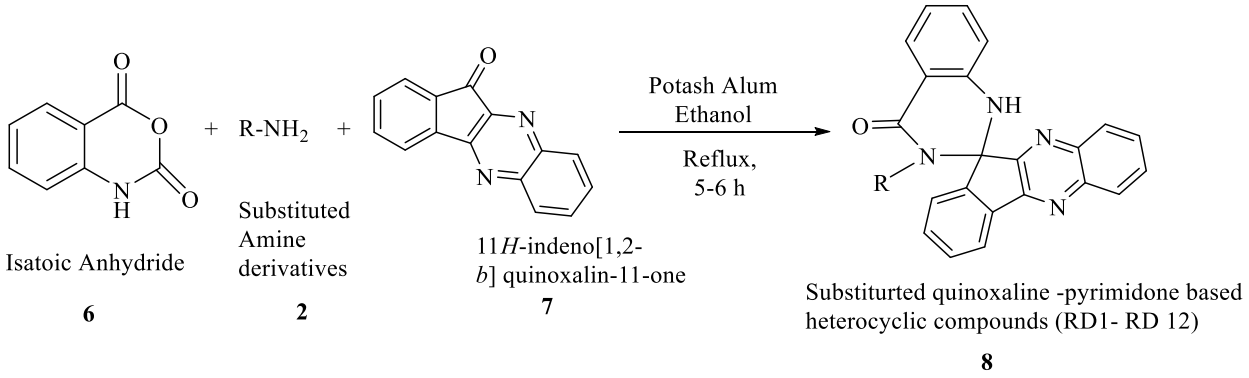
But when the purpose of the synthesis was to create furan-2-one (**5**), the process needed to start with the addition of amine 2 and DEAD 1, then the aldehyde (**3**), as illustrated in **Scheme 4**.



Scheme 3. Plausible mechanism for the synthesis of pyrrol-2-ones



Scheme 4. Proposed mechanism for the synthesis of furan-2-ones

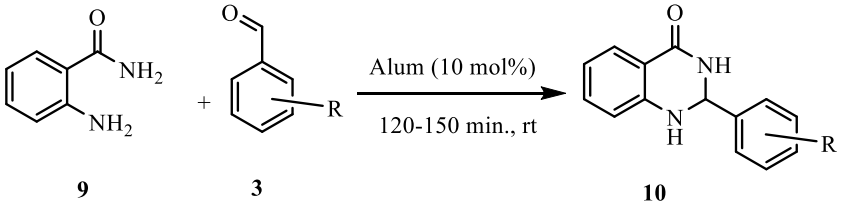


Scheme 5. Preparation of spiro quinoxaline-pyrimidone based derivatives

Antimalarial, antiviral, anti-inflammatory, anti-oxidant, antidiabetic, antipsychotic, antimicrobial, and anticancer actionare all displayed by the pyrimididone moiety [30]. The quinoline molecule is a bioisostere of benzothiophene, benzimidazole, naphthalene, and quinoline. Numerous biological actions, including bactericidal, fungal, antitubercular, antimalarial, antioxidant, anti-inflammatory, and anticancer activity, are demonstrated by the quinoxaline nucleus [31]. Both of spiro rings surrounding the common atom in spiro compounds are perpendicular to one another, which may enhance their affinity for DNA and potentially boost their anticancer properties. Bhatt *et al.* [32] attempted to combine the quinoxaline and pyrimidone moiety in the spiro form and created spiro quinoxaline-pyrimidone based derivatives (**8**) using green catalyst potash alum (**Scheme 5**).

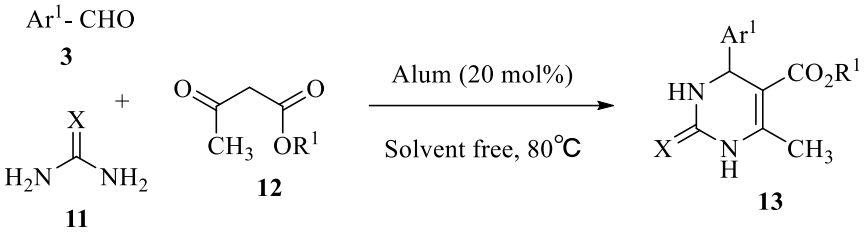
Due to its astoundingly diverse range of pharmaceutical characteristics, quinazoline has taken a special place in heterocycles containing nitrogen. Such a broad spectrum of quinazoline highly necessitates potential derivatization to explore additional pharmaceutical opportunities [33]. To prepare 2,3-dihydroquinazoline-4(1*H*)-ones (**10**) from equimolar 2-aminobenzamide (**9**) and substituted aromatic aldehydes (**3**) in the presence of 10% aqueous potash alum, Chavan and *et al.* [34] described an environmentally benign process using H_2O as green solvent (**Scheme 6**). The advantages of the current methodology include a good to outstanding product yield, a straightforward working method, and simple purification.

It was found that the type of substitute that is present on aromatic aldehydes affects the reaction's output. By taking into account the final yield, as depicted in **Scheme 6**, this correlation was highlighted. Product output is increased by electron-donating functionality while it is decreased by electron-withdrawing functionality.



Sr.No	-R	Time (min)	Yield (%)
1	-H	120	77
2	*p*-OMe	120	88
3	*p*-OH	140	69
4	*p*-Me	120	88
5	*p*-Br	120	90
6	*p*-Cl	150	72
7	*p*-NO_2	150	55
8	*p*-$N(Me)_2$	140	80
9	*m*-OMe	120	90
10	*m*-OH	120	67
11	*o*-Me	120	75

Scheme 6. Synthesis of 2,3-dihydroquinazoline-4(1*H*)-ones

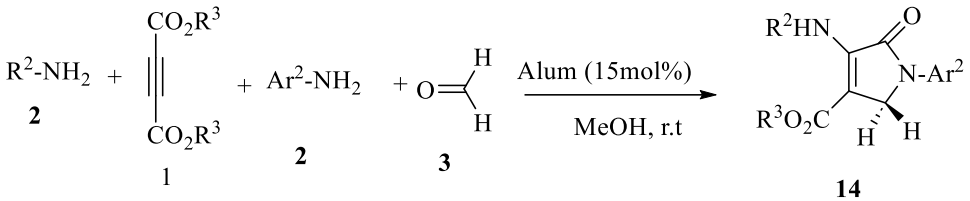


Scheme 7. Preparation of 2-oxo(thio)-1,2,3,4-tetrahydropyrimidines

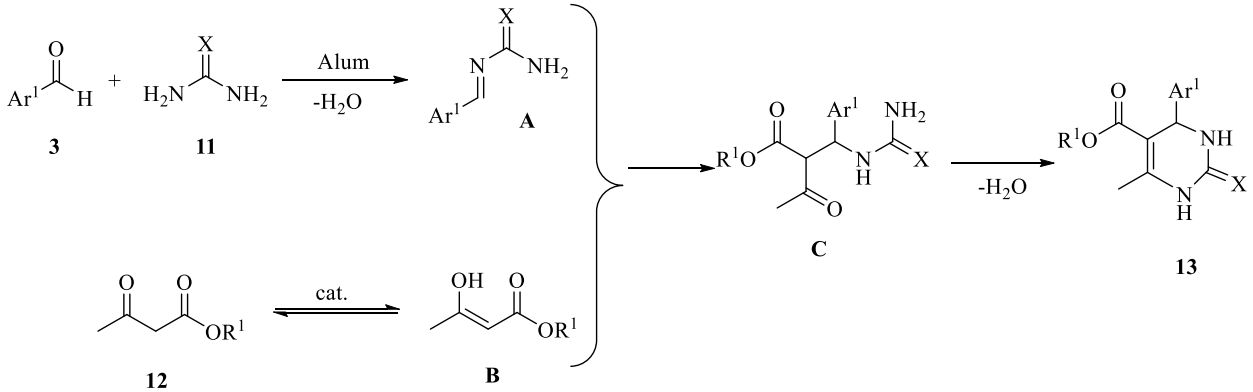
2-Oxo(thio)-1,2,3,4-tetrahydropyrimidines [35] and *N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates [36] due to their beneficial biological and pharmaceutical properties, are two types of the most significant heterocyclic compounds.

Mohamadpour [37] developed a one-pot, multi-component method for producing physiologically active 2-oxo(thio)-1,2,3,4-tetrahydropyrimidines (**13**) and *N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates (**14**) (**Scheme 7**). Some major benefits of the synthetic process included gentle reaction conditions, an inexpensive, affordable, non-toxic mineral catalyst, one-pot manufacture, environmental friendliness, and a decent to high yield of biologically active compounds. The compound synthesized during this procedure was easily crystallized, filtered, and purified. Using potassium alum (20 mol%), aldehyde derivatives (**3**), urea or thiourea (**11**), and ethyl/methyl acetoacetate (**12**) under optimal conditions, the scope of this reaction was investigated. Numerous compounds containing derivatives of electron-donating and electron-withdrawing aldehydes, including substituted benzaldehydes with Cl, NO_2, OH, and OMe were synthesized by the author.

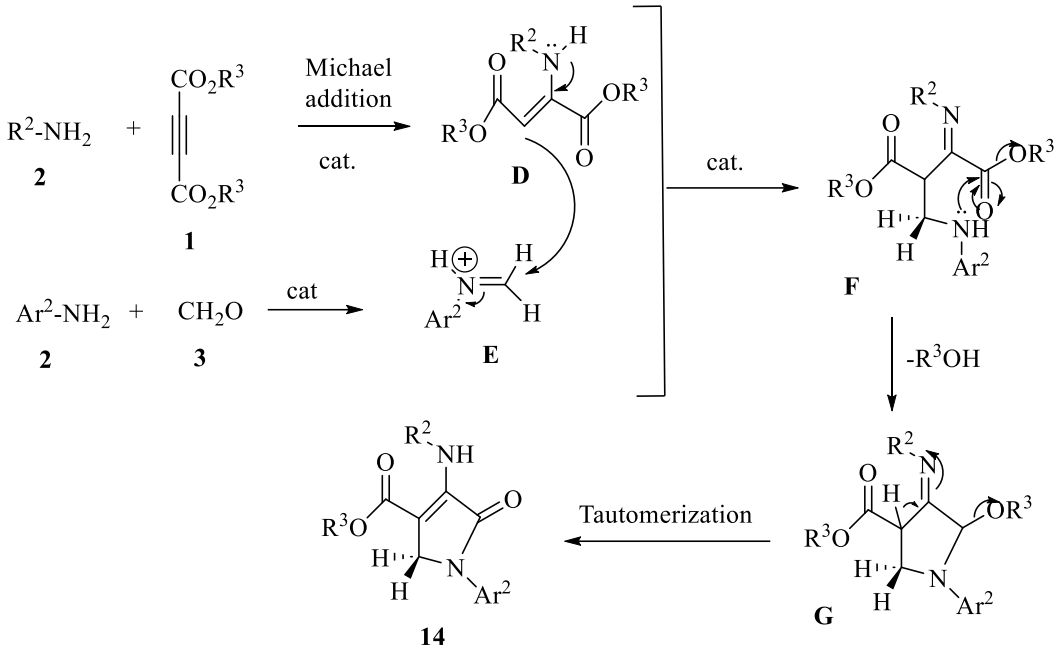
The authors then concentrated on the preparation of *N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates utilizing a one-pot four-component domino reaction via amines (2 equiv.) and dialkyl acetylenedicarboxylate (1.0 mmol). Excellent yields were achieved by these reactions, and **Scheme 8** shows the outcomes. In **Schemes 9** and **10**, the proposed strategies for producing target compounds (**13** and **14**) are depicted.



Scheme 8. Preparation of *N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates



Scheme 9. Plausible mechanism route for the preparation of **13**



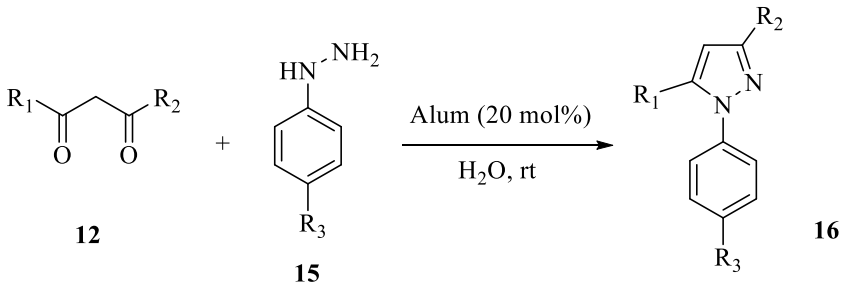
Scheme 10. Plausible mechanism for the preparation of **14**

Pyrazoles have a wide variety of biological activities and are useful synthons and building blocks for many heterocyclic products. They can also serve as a binucleophile. Herbicides, pesticides, and medications like lonazolac, fipronil, Viagra, celecoxib, and many others have all been made using pyrazole nucleus [38]. Devkate *et al.* reported a one-pot and alum-catalyzed method for producing *N*-phenyl pyrazoles (**16**) by cyclocondensing 1,3-dicarbonyl (**12**) with phenyl hydrazines (**15**) in water at ambient temperature (**Scheme 11**) [39]. The products produced with a straightforward work-up process in good to outstanding yields.

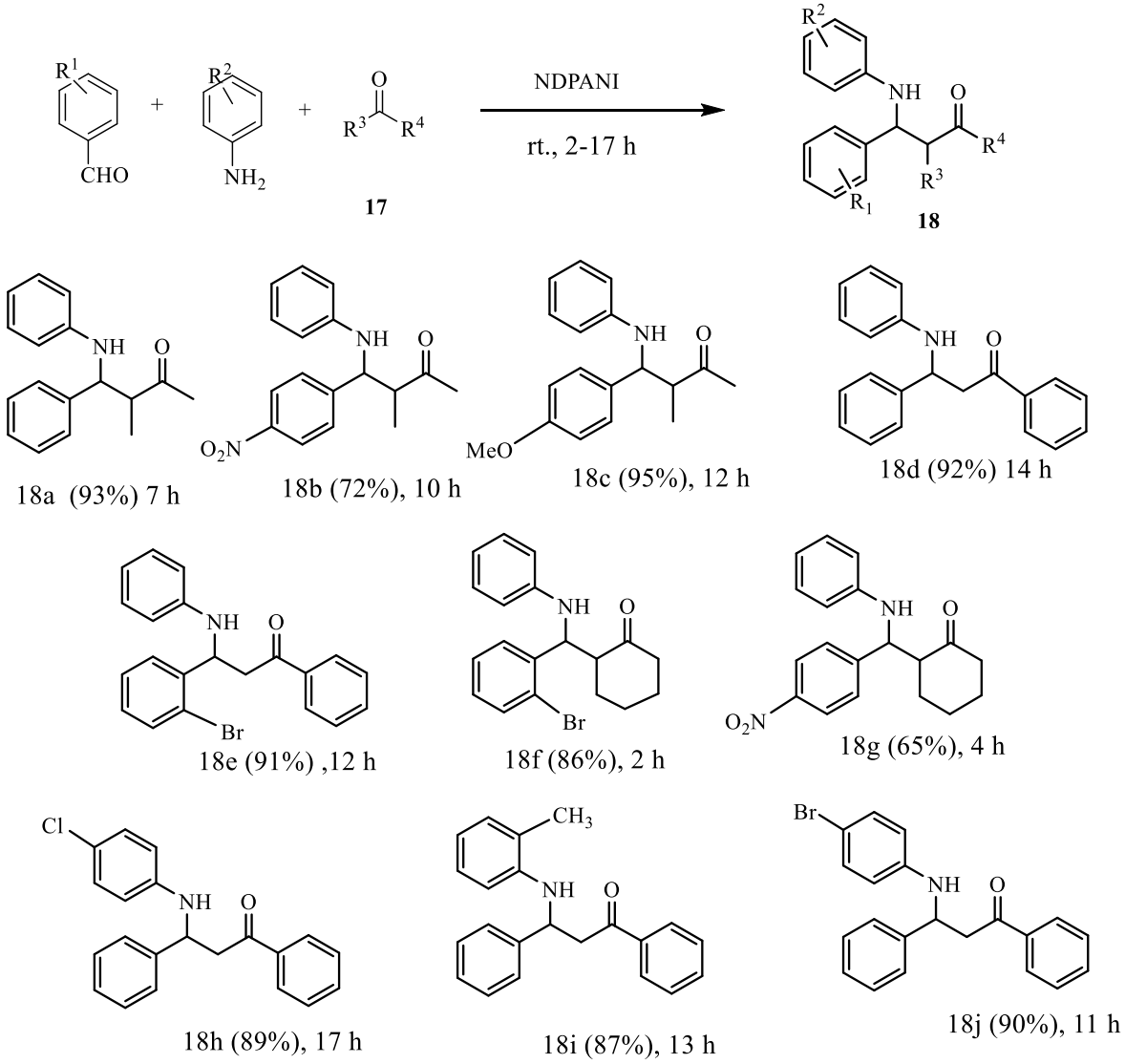
2.2. C-C and C-H functionalization

One of the effective methods for creating carbon-carbon bonds is the Mannich reaction, which is used to synthesise β-amino carbonyl molecules [40]. The β-amino carbonyl derivatives are widely used as crucial synthetic intermediates in the production of pharmaceuticals, drugs, and other biologically active substances.

Patra and Behera [41] have created alum doped nanopolyaniline (NDPANI), an effective and reusable green catalyst for the synthesis of *β*-amino carbonyl compounds (**18**). The desired *β*-amino carbonyl compounds were produced with good yield using a Mannich type reaction of different amines (**2**), aldehydes (**3**), and ketones (**17**) in a solvent-free environment. This catalyst's benefits include low cost, reusability, ease of work-up, and stability.



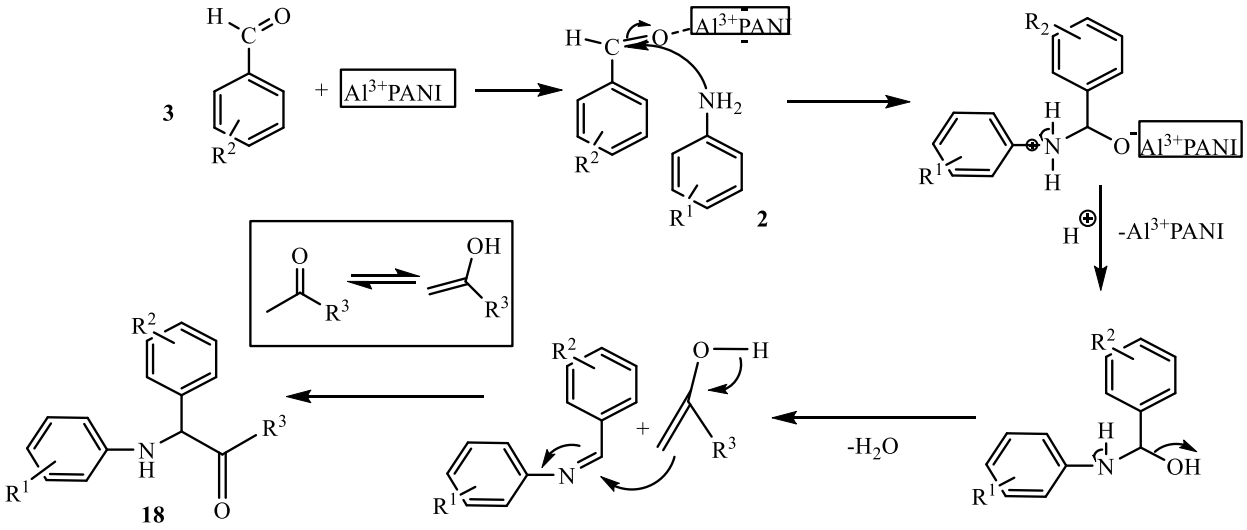
Scheme 11. Synthesis of substituted *N*-phenyl pyrazoles



Scheme 12. NDPANI catalyzed synthesis of β-Amino carbonyl compounds

The scope of the reaction was broadened to include a number of aldehydes, amines, and ketones derivatives using this improved protocol (**Scheme 12**). It was very interesting that increasing the yield by adding an electron-donating group to the benzaldehyde moiety's *para* location (**18c**). Similarly, adding an electron-withdrawing group to the benzaldehyde's *para* position reduced output (**18b**). Furthermore, when cyclohexanone was used as one of the precursors, a superb degree of diastereoselectivity was seen. To the authors' pleasure, 18f and 18g (*syn/anti* = 99:1 and 98:2, respectively) are the predominant produced *syn* isomers. When compared to an amine with an electron withdrawing group, 2-methyl aniline, which has an electron donating group, produces a less equivalent product. This table shows that a large yield (95%, **18c**) of -amino carbonyl compounds could be produced at room temperature. Although a higher temperature might speed up the reaction and cut down on the reaction time, the aldamine's volatility makes side reactions more likely. This procedure used a small excess of ketones along with stoichiometric amounts of aldehydes and amines. Moreover, this procedure did not use any solvent.

By reacting benzaldehyde (**3**), acetone (**17**), and aniline (**2**) for 7 hours at 30 °C with 3 mol% of the NDPANI catalyst, the catalyst's



Scheme 13. Plausible mechanism of Mannich reaction

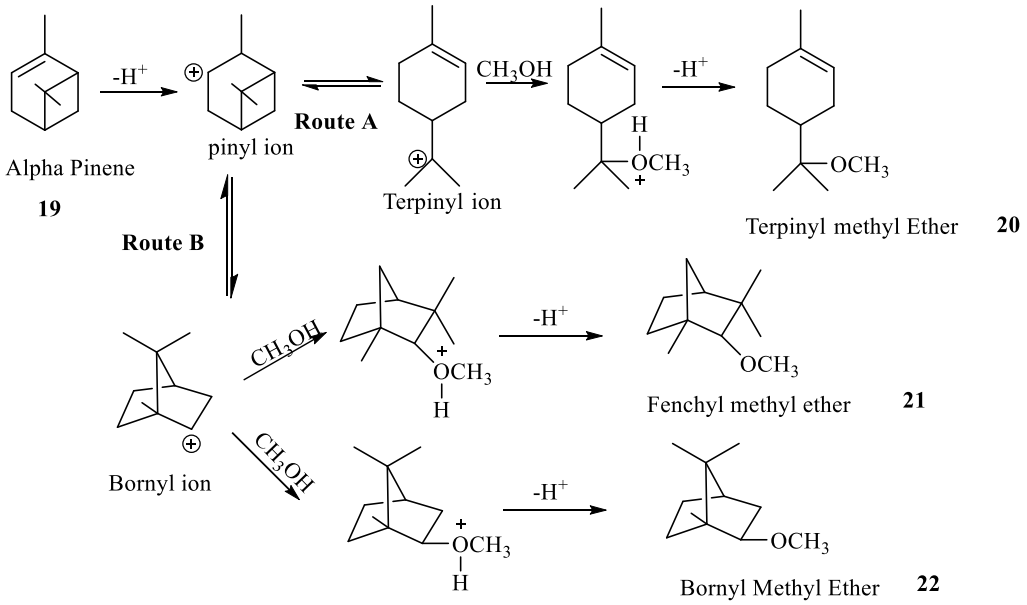
reusability was examined. The findings showed that the current catalyst could be used after five rounds without losing its catalytic activity. In **Scheme 13**, a reasonable mechanism was suggested and displayed. In addition to act as an activator to create an electrophilic centre and aiding the nucleophilic attack of the free amine to create an aldimine, the aluminium centre of NDPANI coordinates to the carbonyl group of aldehyde, and then the aldimine and enol forms of the ketone combine to produce an amino carbonyl molecule (**18**).

α-Pinene (**19**), which is obtained from pine trees by creating cuts in the wood's trunk openings, is the primary component of turpentine, an essential oil made from pine gum (a procedure similar to that used to obtain latex from *Hevea brasiliensis* for rubber). Turpentine is a valuable and renewable natural resource that is frequently used in food, flavor, scent, and cosmetics production as well as in the synthesis of chemical intermediates. These procedures, which also include hydration, pinene oxide isomerization, epoxidation, esterification, and etherification, among others, can be used to produce a range of products with additional value [42].

Methoxylation is an important technical procedure used in the creation of diverse functionalized α-pinene derivatives. The methoxylation of α-pinene using potassium alum as a catalyst was the subject of the study by Wijayati *et al.* [43]. The optimal conditions of 1 g of catalyst loading, a volume ratio of 1:10, a reaction temperature of 65 °C, and incubation times of 6 h led to the greatest selectivity of potash alum in the methoxylation of α-pinene.

The values for methoxylated products from the 98.2% conversion of α-pinene were determined by GC-MS to be 59.6%, 8.9%, and 7.1% for α-terpinyl methyl ether (**20**, TME), fenchyl methyl ether (**21**, FME), and bornyl methyl ether (**22**, BME), respectively. It became clear that the methoxylation reaction was more cost-effective with smaller alum loading (0.5-1.5 g).

The reaction process for the methoxylation of α-pinene using potassium alum as a catalyst is shown in **Scheme 14**. According to a literature study, potassium alum produces acid through two different pathways, A and B, obtained by the terpinyl and bornyl ions, respectively. The protonation of the α-pinene double bond to form the pinyl ion started the alkoxylation process. Due to the bicyclic and monocyclic types of product rearrangement, this reaction was carried out along two parallel paths. The chemical mixture's bornyl and terpinyl ions, and then interact with the methanol to produce the ethers TME, BME, and FME through deprotonation.



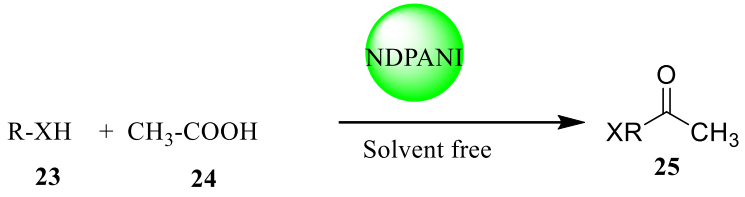
Scheme 14. Proposed route for α-pinene methoxylation

A helpful and simple method for protecting amino and hydroxyl groups in multistep organic transformations is acylation. When it comes to functional groups in chemistry, the ester and amide moieties stand out because they are essential to life and present in a wide variety of medicinal and synthetic structures. In the absence of an acid or base catalyst, AcCl or Ac_2O are typically exploited as acylating agents. However, its use is constrained by both the chemicals' corrosive and lacrimatory properties. According to reports, acetic acid can be used in place of other regulators to acylate alcohol [44]. Acetic acid is economically and environmentally preferable to acetic anhydride or acetyl chloride because it adheres to the atom economy and minimizes waste, both of which are highly desirable in industrial applications.

The unique physical and chemical characteristics of polyaniline, such as its affordability, ease of synthesis, and environmental stability, have attracted a lot of interest in the last few years. In a solvent-free environment, Patra and Behera [45] reported acylation of alcohols and amines (**23**) using acetic acid (**24**) as an acylating substance and alum doped nanopolyaniline (NDPANI) as a catalyst.

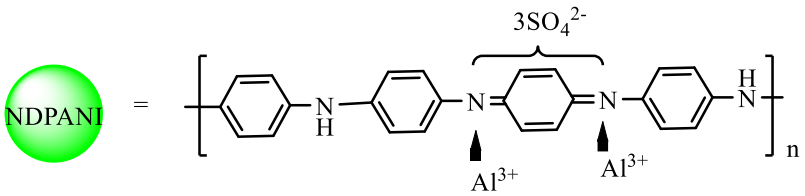
In addition, potassium alum rather than corrosive acids was used to dope polyanilines. The reaction conditions are an improvement over the conventional methods because they do not require any expensive catalysts or solvents and drastically cut down on reaction time. This catalyst's benefits include being non-hazardous, affordable, recyclable, and simple to prepare and handle. A range of alcohols are included in the acylation application. The corresponding ester (**25**) can be produced in good to outstanding yields (86-95%) by substituting benzyl alcohols with either electron withdrawing or electron donating groups.

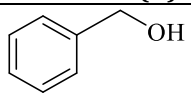
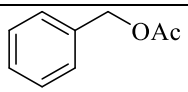
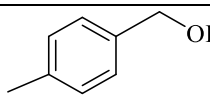
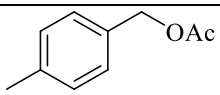
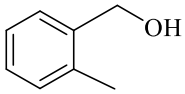
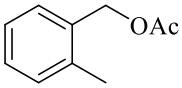
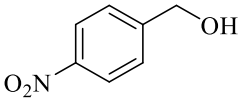
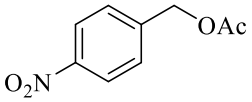
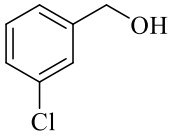
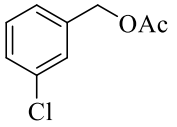
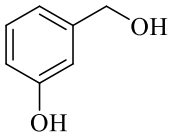
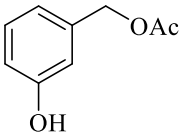
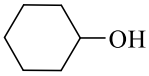
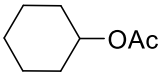
It should be emphasized that by simply removing the catalyst through filtration and solvent evaporation, the products can be directly separated with excellent purity. After successfully acylating alcohol, writers concentrated on diverse amine, phenol, and cyclohexanol functionalities in a solvent-free environment. **Scheme 15** provides a summary of the findings. It is surprising to observe that acylation of phenol occurs more slowly than acylation of amine. It was found that the acylation of secondary amine was slower and took longer than that of primary aromatic amine and aniline among the various amines investigated. Compared with aromatic amines



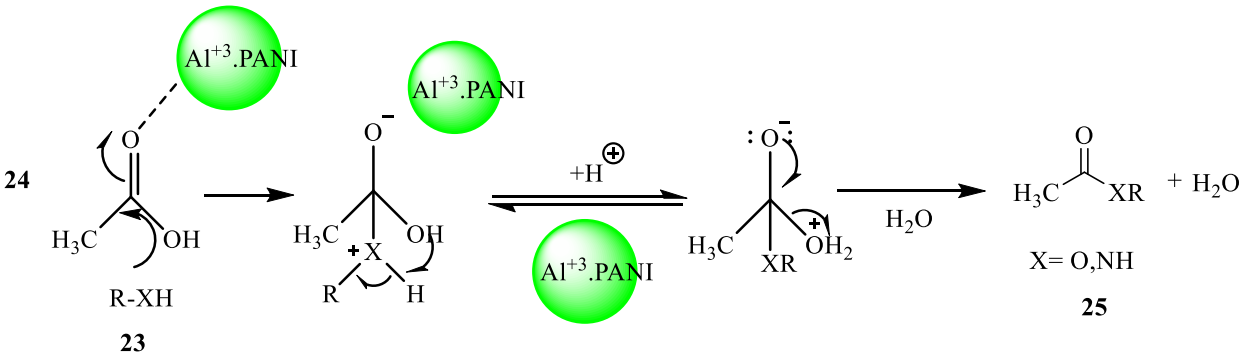
R = Alkyl, Aryl Alcohols

X = O or NH

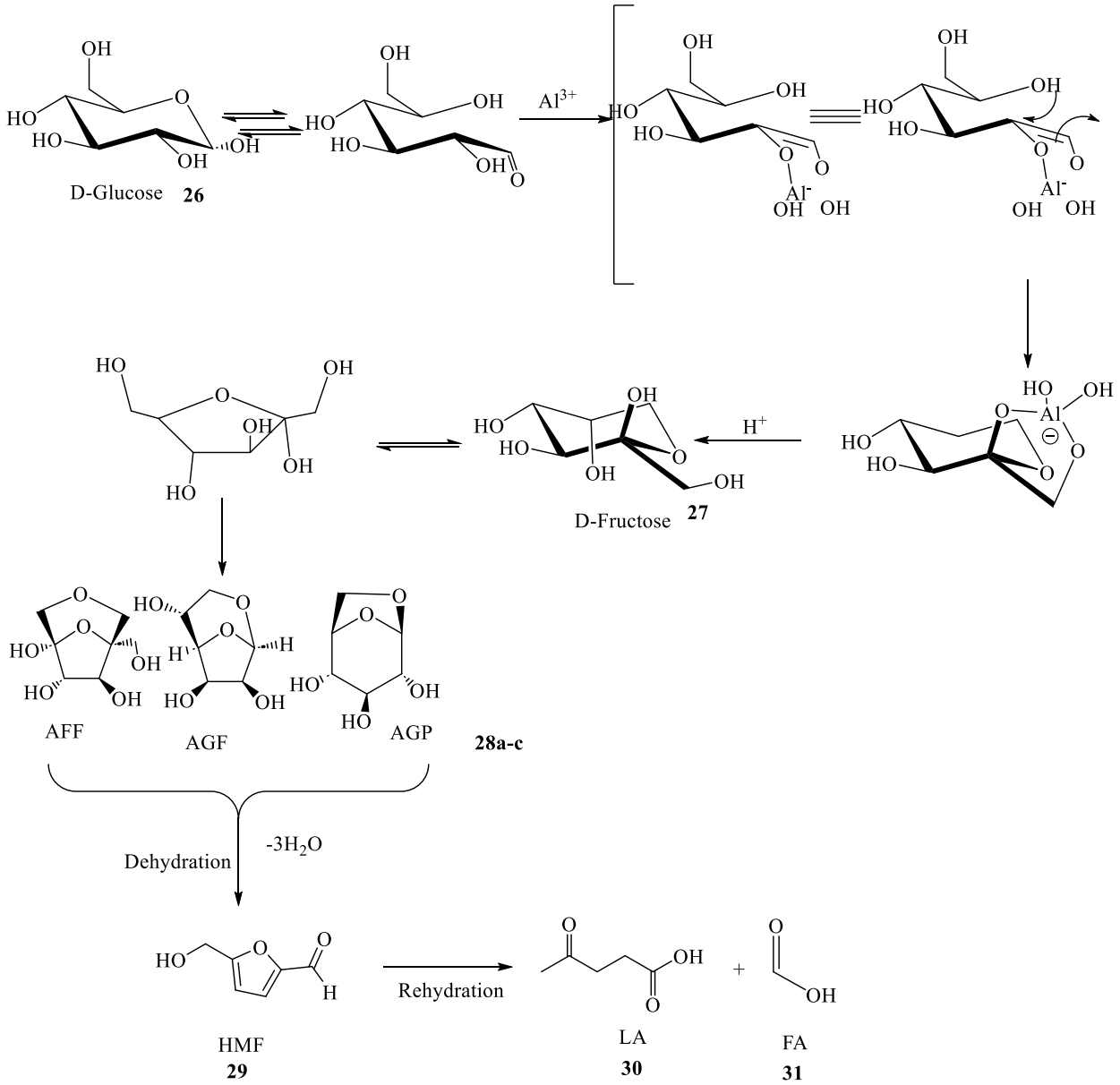


Entry	Substrate (R)	Product	25	Time(h)	Yield(%)
1			**25a**	3	94
2			**25b**	2	95
3			**25c**	3	91
4			**25d**	8	86
5			**25e**	7	89
6			**25f**	5	90
7	C_2H_5OH	C_2H_5OAc	**25g**	4	77
8			**25h**	2	92

Scheme 15. Acylation of alcohols/amines with AcOH catalyzed by NDPANI [selected examples]



Scheme 16. Proposed route of acylation of alcohols and amines catalyzed by NDPANI



Scheme 17. Proposed route for catalytic conversion of glucose into HMF & LA

with electron-giving groups (*p*-bromoaniline), those with electron-withdrawing groups (*p*-nitroaniline) showed slower reactions.

The solvent-free acylation of alcohols and amines (**23**) with acetic acid (**24**) in the presence of an alum-doped nanopolyaniline (NDPANI) catalyst is represented in **Scheme 16** as a possible process. According to theory, when aluminium from NDPANI interacts with the oxygen in the carbonyl group, the carbon atom becomes more sensitive to nucleophilic attack from oxygen, nitrogen from alcohol, and amines, respectively. The ester and amide bond is eventually stabilized by dehydration (**25**).

Recent socio-economic changes around the globe have been significantly influenced by the impending energy crisis caused by the rapid depletion of conventional fossil fuel resources. Excessive use of conventional fuels has increased greenhouse gas and toxic gas emissions, posing a permanent risk to both human health and the ecosystem. So far, efforts have been focused on developing renewable sources as alternatives to traditional fossil

fuels. Biomass has emerged as a potential bio-renewable resource in this respect, able to produce fuel and value-added chemicals in a closed carbon loop, eradicating the issue of greenhouse gases [46].

The research groups of Saha and Pant [47] examined potash alum (PA) as an effective and environmentally friendly catalyst for the synthesis of high value platform chemicals such as 5-hydroxymethylfurfural (HMF) furfural S from bio-renewable feedstocks in a biphasic reaction medium in this work. The maximum fructose and glucose dehydration outputs of 64% and 49% HMF, respectively, were attained after 6 h of reaction time at 140 ℃. Similarly, a 6 hour interval at 190 ℃ produced a 55% yield of furfural from xylose. This was the first study to highlight a method for using potash alum, which is safe and inexpensive, as a catalyst to turn glucose (**26**), fructose (**27**), and xylose (**28**) into their corresponding furans (**29**) (**Scheme 17**).

By cyclic or acyclic routes, glucose and fructose are initially dehydrated into HMF (**29**). In total, there are two stages involved in the direct conversion of glucose into HMF: Isomerizing glucose (glucopyranose) into fructose (fructofuranose), and dehydrating fructofuranose (losing 3 mol of water) to HMF. While Bronsted acidity aids in the dehydration of isomerized intermediates to HMF, followed by HMF rehydration into LA (**30**) and FA (**31**), Lewis acidity of PA is responsible for the longer reaction period isomerization of glucose to fructose.

3. Conclusion and Future Perspective

The current review provides the most recent information on the catalytic uses of potassium alum ($KAl(SO_4)_2.12H_2O$), also known as "alum," a cheap, non-toxic and environmentally benign catalyst in organic transformations involving heterocyclic ring formations and carbon-carbon/carbon heteroatom bonds. These experimental findings are in favour of additional investigation into the safeness and affordability of the catalytic capabilities to create more environmentally friendly and long-lasting protocols for compounds of potential interest. This information was reported from mid-2017 to the present and the upcoming researchers can create efficient methodologies for the development of biologically relevant heterocycles and catalysis. We sincerely expect that this article will encourage further progress in this direction.

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