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First Report of Application of Simple Molecular Complexes as Organo-Catalyst for Knoevenagel Condensation
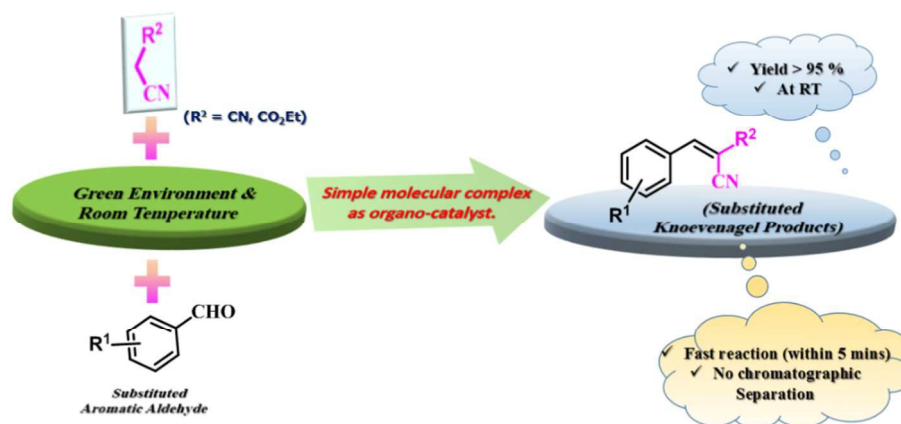
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Graphical Abstract

Abstract

10 A series of molecular complex have been designed, synthesized and used as organo-catalyst for the first time for very efficient Knoevenagel condensation. Molecular complexes are thermally stable, low cost for preparation, easily recyclable. Role of acidic proton in molecular complexes towards Knoevenagel condensation has been identified as the key factor and helps us to provide useful information of reaction path way. The acidic proton of catalyst enhances the electrophilicity of the aldehyde and accelerates dehydration process of reaction at room temperature (RT). Eco-friendly, green synthetic protocol for Knoevenagel condensation is used to synthesize
15 a series of important cyano group containing synthetic precursor for synthesis of biologically active molecules at RT using minimum amount of catalyst (~5 mol %) without chromatographic separation technique. Detailed mechanistic studies and substituents effect of aromatic aldehyde on reaction have been investigated. In addition biologically active 2-Amino-4*H*-Chromene derivatives have also been synthesized by Knoevenagel condensation of salicylic aldehydes with active methylene compounds, followed by intramolecular cyclization (via Michael addition) delivering higher yield within shortest reaction time at RT without any need of chromatographic
20 separation.

Introduction

Synthetic organic chemist has focused on converting a difficult synthetic protocol to an easier and greener one with simple organic synthone to produce entirely new organic molecules.[1]
25 The useful synthetic techniques is expected to contain one-pot single step using environmentally benign non-hazardous catalyst and solvent-free condition.[2] Performing an organic reaction in environmentally suitable mode is still a challenge to the chemist even today. One of the important objectives in organic synthesis,
30 especially in the synthesis of fine chemical products such as pharmaceuticals, is the facile synthesis of new carbon-carbon bonds etc. The Knoevenagel reaction is a well-known carbon-carbon bond-forming reaction, discovered by E. Knoevenagel in 1896, is also widely used both in the chemical, pharmaceutical
35 and perfume industries.[3] The reaction is also well known for the synthesis of a large variety of intermediates useful in the manufacture of top selling drugs (such as Atorvastatin, Pioglitazone, AMG 837, Pregabalin, Lumefantrine, Entacapone) in the world.[4]

40 Traditionally, Knoevenagel condensation is carried out under homogeneous conditions in the presence of catalysts such as organic bases[5] solid bases,[6] ionic liquids,[7] amino acids,[8] Lewis acids,[9] organometallic catalysts,[10] metal complexes immobilized on a solid support such as oxide and zeolite deteriorates,[11] oxides
45 modified by salts,[12] and amine-functionalized materials affording variable yields with different reaction time.[13] Recently, synthesis of 2-Amino-4*H*-chromenes derivatives has attracted great interest to their biological and pharmacological activities.[14] 2-Amino-4*H*-chromenes constitute a major class of naturally occurring
50 compounds, and interest in their chemistry continues because of their utility as biologically active agents.[15] They occur widely in plants, including edible vegetables and fruits.[16] Synthetic chromene analogues have been developed over the years, and some of them have been employed in pharmaceuticals,[17] which
55 includes antifungal[18] and antimicrobial agents.[19] 2-Amino-4*H*-chromenes are employed as pigments,[20] cosmetics, agrochemicals[21] and are major constituents of biologically active many natural products (such as HA 14-1, Inhibitor of MK-2,
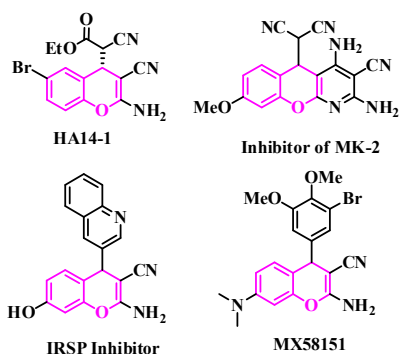
IRSP Inhibitor and MX58151) as shown in Fig 1.[22]

Figure 1: Example of Biologically Active 2-Amino-4*H*-Chromene

Recently Li et.al. have used task specific ionic liquid as catalyst for Knoevenagel condensation at room temperature (RT) with catalyst loading is as high as 15 mol%.[23] Vakili et.al. have reported L-histidine and L-arginine catalysed Knoevenagel condensation reaction though the protocol is not superior in terms of reaction condition, reaction time and yield.[24] Further Mase et.al. have also reported eco-friendly organo-catalysed Knoevenagel condensation but preparation, stability and recyclability of organo-catalyst are still challenging factors. [25] In our continuation of work with various kind of molecular complexes, we are reporting for the first time the use of simple molecular complexes (**chart 1**) based on weak acid and tertiary amine as organo-catalyst for the popular Knoevenagel condensation reaction. The mechanistic aspects of Knoevenagel condensation using these molecular complexes has been investigated and presented in our present work. Further our synthetic protocol is used to synthesize a biologically active 2-amino-4*H*-chromene derivative.

Chart 1: Structural Formula and Abbreviations for the Components of Molecular Complexes

Results and Discussions

A well-known simple condensation reaction, Knoevenagel condensation is preferred as model reaction for studies of our newly synthesised molecular complexes as organo-catalyst. As depicted in Scheme **1**, 1 mmol of benzaldehyde (**1a**) and 1.01 mmol of malononitrile (**2a**) are taken in different solvent system and different amount of catalyst loading (range 0.02 to 0.1 mmol) at RT. Several set of reactions are performed to optimize the reaction in terms of yield, reaction time, solvent condition, and amount of catalyst. It was observed that reaction does not proceed in absence of catalyst (molecular complex) either in ethanol or in neat condition at room temperature (Table 1, entry 1). But when reaction is carried out using 0.02 mmol of catalyst (MP(DNP)) in ethanol, yield of the desire product (**3aa**) is found to be 85 % at

RT (Table 1, entry 2). Further, when the catalyst loading is increased to 0.05 mmol in the same condition, yield of **3aa** (desired product) is increased to 98 % (Table 1, entry 3). However, no change of yield is observed when higher mole % of catalyst is used (Table 1, entry 8).
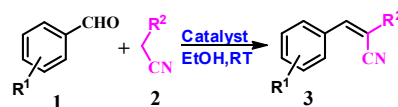
R^1= H (**1a**), 2-NO_2 (**1b**), 4-CN (**1c**), 4-NO_2 (**1d**), 4-Cl (**1d**), 4-Me (**1e**), 4-OMe (**1f**) 4-OH (**1g**), 4-NMe_2 (**1H**), etc.

R^2 = CN (**2a**), CO_2Et (**2b**)

Scheme 1: Synthesis of Knoevenagal Condensation

Therefore, the optimized reaction condition is found to be 0.05 mmole (5 mole %) catalyst in ethanol with reaction time of 3 min at RT. We have also carried the reaction in solvent-free condition using 0.05 mmole (5 mol %) catalyst at RT. We found that 98 % of desire product (**3aa**) is obtained within 3 min in neat condition for making the reaction even more environment friendly. We have also examined the yield of the reaction in different solvents. When the reaction is carried out in H_2O, 92 % desired product is obtained using 0.05 mmole (5 mol %) of catalyst, 3 min at RT (Table 1, entry 5). Slight decrease in yield in DCM (88 %) is observed using 0.05 mmole (5 mol %) of catalyst, 120 min reaction time at RT (Table 1, entry 6). Similarly, decrease of yield is also observed when reaction is carried out in an aprotic polar solvent like acetonitrile (ACN) at RT (Table 1, entry 7).

Table 1: Reaction Optimization Conditions[a]

Sl.	Catalyst (mmol)	Solvent	Time (min)	Yield[b]
1	-	EtOH	90	-[c]
2	MP(DNP) (0.02)	EtOH	3	85
3	MP(DNP) (0.05)	EtOH	3	98
4	MP(DNP) (0.05)	Neat	3	98
5	MP(DNP) (0.05)	H_2O	5	92
6	MP(DNP) (0.05)	DCM	120	88
7	MP(DNP) (0.05)	ACN	45	90
8	MP(DNP) (0.1)	EtOH	3	98
9	MP(DNP) (0.05)	Neat	3	98
10	MP(0.05)	EtOH	180	80
11	DNP(0.05)	EtOH	360	-[c]
12	DNP(0.05)+ MP(0.05)	EtOH	5	98
13	MP(NP)$_2$ (0.05)	EtOH	20	85
14	MP(TNP) (0.05)	EtOH	15	84

[a]Reaction condition: benzaldehyde (1 mmol) and malononitrile (1 mmol) was stirring with different amount of catalyst in ethanol or neat (solvent-free) condition, [b]Isolated pure yield. [c]No reaction.

Role of individual counter parts of the catalyst (MP(DNP)) towards product formation has been investigated with an aim to understand the detailed reaction mechanism. Therefore, MP and DNP, two components of this organo-catalyst have been used separately as a probable catalyst at otherwise optimized reaction condition. Interestingly, when MP is used as a catalyst at RT, reaction takes place but with very long time (~3h) with drastically low yield (Table 1, entry 10). On the other hand, no reaction is observed even after 6h when DNP is used alone (Table 1, entry 11). For finding out the combining effect of MP and DNP in reaction, same molar ratio MP is added to reaction mixture containing DNP. Interestingly, reaction is completed within 5 minutes of time at RT. It is clearly indicating that DNP component actively participates to enhance the reaction rate and

to complete the reaction in short time (Table 1, entry 4, 12). Above experimental result indicates that the *in-situ* generated molecular complex shows very similar catalytic activity as externally added molecular complex (MP(DNP)). *This fact is very important considering the reduction of effort of preparing the molecular complex separately for usage as catalyst.* Other molecular complexes, (such as MP(NP)$_2$ and MP(TNP)) have also been studied. It is observed that MP(NP)$_2$ and MP(TNP) take longer reaction time with lower percentage of yield compared to MP(DNP) (Table 1, entry 13, 14). The higher efficiency of DNP containing molecular complex compared with other two is due to the relative stability of nitrophenolate ion in molecular complex and can be explained considering the the pK$_a$ values of nitrophenols. pK$_a$ values of NP, DNP and TNP are 7.16, 4.11 and 0.38 respectively.[26] The intermediate value for DNP suggests that it can efficiently acts as both proton donor and acceptor depending on situation. Since, Scheme 3 and 4 indicates that catalyst should preferably have both proton donor and accepting efficiencies depending on reaction steps, DNP containing catalyst therefore works best. Further, it is evident that a very weak acid additive such as nitrophenol derivatives and/or its salts (molecular complex: tertiary amine) enhances the electrophilicity of the aldehyde accelerating the dehydration process shown in Scheme 3. As a result, Knoevenagel condensation reported here is found to take place at much lower temperature with higher yield than reported till date. Substituent effect on yield is also investigated. It is found that excellent yield in all most all cases is observed except the aldehyde with electron donating group at *para* position (Table 2, entry 6 and 18).

Table 2: Synthesized Knoevenagel Condensation products at optimized reaction condition in terms of time taken (min) and yield (%).

This is due to the increase of electron density at carbonyl centre and reducing the formation of stable intermediate as depicted in intermediate **3a′** (Scheme **3**). Using the method and optimized reaction conditions that are described in this report, a large number of derivatives have been synthesized and are depicted in Table 2. As a further application of the catalyst (MP(DNP)) and synthone from Knoevenagel condensation, 2-Amino-4*H*-Chromene derivatives have been synthesised via Knoevenagel condensation of salicylic aldehydes with active methylene compounds, followed by intramolecular cyclization (via Michael addition). Scheme 2 shows the reaction in ethanol at RT. Yield of desired reaction product, 2-Amino-4*H*-Chromene (**5aa**) is quite high (~97 %) using 0.05 mmol (5 mol %) of MP(DNP) as catalyst in ethanol which completes within 7 minutes at RT (Table 3, entry **5aa**). The Michael addition becomes faster and thereby favouring the formation of 2-Amino-4*H*-Chromene at room temperature (scheme 4).
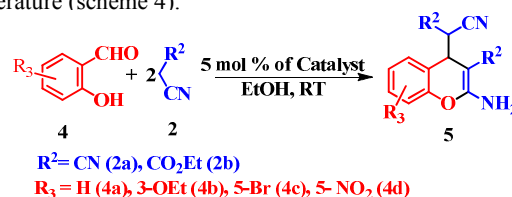

Scheme 2: Synthesis of 2-Amono-4*H*-Chromene derivatives.

Based on the experimental results, a conceivable mechanism for Knoevenagel condensation is proposed in Scheme **3**. Initially tertiary amine component (MP, BN,) of the catalyst acts as a Lewis base and makes **2a′** as the nucleophile from substrate **2a** (pK$_a$ ~ 11.1). The **2a′** further takes part in the condensation reaction with substrate **1a** to provide intermediate **3a′**. The intermediate **3a′** is then dehydrated in presence of acidic part (HA, DNP) of the catalyst to give us the desire product (**3a**).

**Table 3**: Synthesized 2-Amino-4*H*-Chromene Derivatives
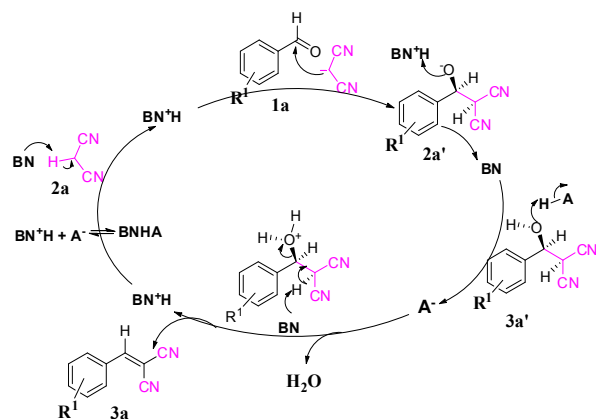
Scheme 3: Plausible reaction mechanism of Knoevenagel Condensation. Here, BN represents proton acceptor (i.e., MP) and HA represents proton donor (i.e., NP, DNP and TNP).

Formation of **2a′**, enhancement electrophilicity of the aldehyde and dehydration process lead the reaction faster. Further, creation of **2a′** is controlled by base (MP), enhancement electrophilicity of the aldehyde whereas the dehydration process is controlled by acidic proton of catalyst. The synergetic effect is found to be the key factor faster reaction rate.

Separation of desired product and recovery of catalyst from reaction mixture are also important part of any catalysed reaction. In this case, the crude reaction mixture is filtered and washed several times with ethanol (3x10 mL each time) until the catalyst is completely removed. The solid residue is then collected and dried under vacuum. It is found to provide pure desired product. Therefore, no column chromatographic separation is necessary. The collected ethanol is evaporated to obtain pure catalyst back. Finally, the product is crystallized from ethanol. Reusability of the catalyst is tested by carrying out repeated runs of the reaction at standard reaction condition. After each cycle of usage, the catalyst is collected in ethanol and evaporated the solvent. It was then washed with diethyl ether several times (at least three times) to get pure catalyst for another set of reaction. We have tested for five times to recycle and observed that there is no loss of its activity and selectivity (Figure 2).
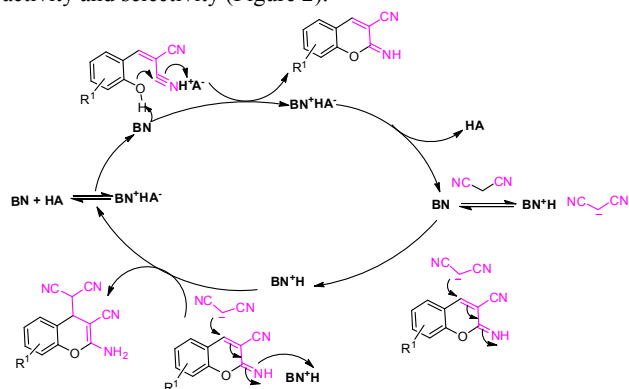
Scheme 4: Probable reaction mechanism of 2-Amino-4*H*-Chromene. Here, BN represents proton acceptor (i.e., MP) and HA represents proton donor (i.e., NP, DNP and TNP).
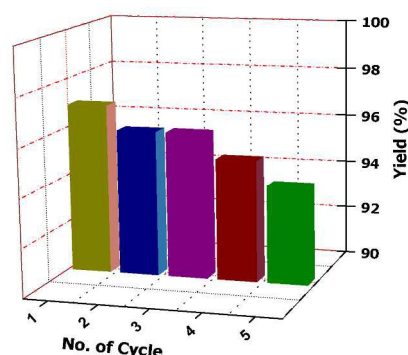

Figure 2: Recyclability chart (recyclability of the catalyst was tested on the reaction at standard reaction condition)
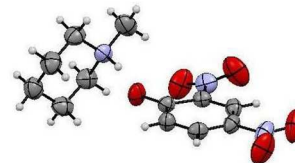

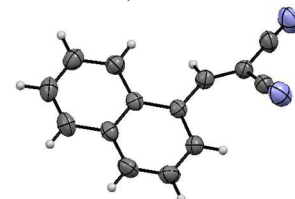**Figure 3**: ORTEP diagram of Catalyst (MP(DNP)) (50 % ellipsoid probability) (CCDC No.: 873550)

Figure 4: ORTEP diagram of 2-(naphthalen-1-ylmethylene)malononitrile (3aj) (CCDC No. 937875)
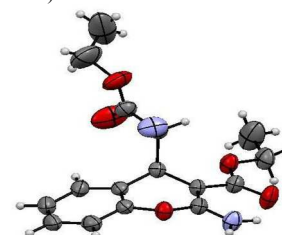

Figure 5: ORTEP diagram of ethyl 2-amino-4-(1-cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (5ba) (CCDC No 946632)

The structure of catalyst is mainly confirmed beyond doubt by measuring the single crystal X-ray diffraction (SCXRD) as depicted in Figure 3. In case of condensation products, the confirmations are made by the detailed analysis of ^{1}H, ^{13}C-NMR, FT-IR and ESI-MS. In some cases, the desired products (as in **3aj** or **5ba**) are further confirmed by SCXRD measurements. The ORTEP diagram obtained from these SCXRD measurements are presented in Figure 4 and 5. Further hexahydroquinolines synthetic protocol has been chosen to test the wider applicability of our molecular complex as efficient catalyst.[27] We have successfully obtained the desired product (Table 2, entry 4N-HHQ) with this molecular complexes at high yield (80%) within 15 mins at room temperature (ESI)

Conclusion

In conclusion, we have reported here some simple molecular complex which can be used as remarkable organo-catalyst for

Knoevenagel condensation and Michael addition reactions. Even the *insitu* generation of these molecular complexes works as efficiently as in case of separately preparing and adding in the condensation step. Among all the catalysts, MP(DNP) is found to be the most efficient catalyst. Moderate and easily available of acidic proton of molecular complexes is the key for highly efficient and remarkable catalytic activity in Knoevenegal condensation. Further, detailed mechanistic studies reveal that the electrophilicity of the aldehyde and dehydration process are enhanced in presence of acidic proton of catalyst to make the reaction feasible at RT. Therefore, a eco-friendly, green (in addition to low cost) synthetic protocol has been developed for synthesizing important organic precursors via the Knoevenagal condensation suing this highly stable catalyst having higher yield and shortest reaction time at room temperature using minimum amount of catalyst (~ 5 mol%) without the need of chromatographic separation. The catalytic activity is not significantly lost significantly after use of several times. Further application purpose of above procedure, 2-Amino-4*H*-Chromene derivatives have been synthesized by Knoevenagel condensation of salicylic aldehydes with active methylene compounds, followed by intramolecular cyclization (via Michael addition) delivering higher yield within shortest reaction time at RT without any need of chromatographic separation.

Synthesis and Characterization of Catalyst

N-methylpiperidine (1.01 mmol) was taken in 50 ml round bottom flask containing 5 ml CHCl$_3$ and nitrophenol derivative (1 mmole) was added. Immediate yellowish coloured liquid was obtained. Resulting yellowish solution was stirred for 1-3 h at room temperature and was kept in refrigerator. Finally yellow colour crystal was separated out from solvent.[28] (ESI)

General Procedure for Synthesis of Knoevenegal Product

Substituted aromatic aldehyde **1** (1 mmol) and active methelene **2** (1.01 mmol), 0.05 mmol, of catalyst (MP(DNP)) were taken in a round bottom flask stirred at room temperature for the stipulated period of time (Table **2**) till the completion of the reaction (monitored by TLC). After completion of the reaction, solid precipitated separated out, filtered and washed with water (3x10 mL) followed by ethanol (3x10 mL), dried in high vacuum to afford NMR pure product.

General Procedure for Synthesis of 2-Amino-4*H*-Chromene derivative

Substituted salisaldehyde (1 mmol, **4**), malononitrile (2.01 mmol, **2**) and 0.05 mmol of catalyst (MP(DNP)) were taken in ethanol solvent at room temperature for stipulated period of time (Table 3) till the completion of the reaction (monitored by TLC). After completion of the reaction solid precipitated was separated out which was filtered and washed with water (3 x 10 mL) followed by ethanol (3 x 10 mL) and dried in high vacuum to afford NMR pure product.

Note: In case the final product does not separate from the reaction mixture, cold water need to be added after the completion of the reaction with vigorous shaking. Solid precipitated then filtered and washed with cold water several time (3 x 10 mL) followed by ethanol (3 x 10 mL) and dried in high vacuum to afford NMR pure product.

General Procedure for Synthesis of hexahydroquinolines

The mixture of the aldehydes (**1** mmol), dimedone (**1** mmol), ethyl acetoacetate (**1** mmol), ammonium acetate (**2.5** mmol) and MP(DNP) containing (**5** mol%) as catalyst were stirred at room temperature for the 15 minute in ethanol. After completion of the reaction (monitored by TLC), the ethanol is evaporated and 3 mL of water was added to the mixture. Solid product is obtained and washed several times with water (at least four times). For recycling the catalysts, after washing the solid products with water completely, the water containing the molecular complex (MP(DNP)) was evaporated under reduced pressure and molecular complex (catalyst, MP(DNP)) was recovered and reused after washing with diethylether (~three times). The solid product was purified by recrystallization from ethanol.

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† Electronic Supplementary Information (ESI) available: Electronic Supplementary Information (ESI) available: Detailed experimental procedure, separation techniques, electronic spectra, NMR spectra of all compounds.

‡ Crystallographic data in CIF and CCDC reference number: 871913 (**3aj**), and 946632(**5ba**).

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