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Nicotine-based ionic liquid: as a green catalyst for pyridine-catalyzed Huisgen reaction

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ABSTRACT

Nicotine-based ionic liquid has been used as a green catalyst for pyridine-catalyzed Huisgen reaction. It promoted addition of dimethylacetylenedicarboxylate to aldehydes or *N*-tosyl imines leading to efficient synthesis of 2-benzoylfumarates and 1-azadienes respectively under pyridine free odorless ionic liquid conditions. The improved results were obtained in terms of enhanced yields, with minimal work up.

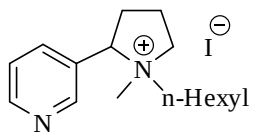
***Keywords**: Pyridine, Nicotine-based ionic liquid, Pyridine-catalyzed Huisgen cycloaddition.*

1. Introduction

The major applications of pyridine involve catalysis in esterification, acylation and Knoevenagel condensation reactions [1]. The more active pyridine derivatives like 4-dimethylamino pyridine (DMAP) and 4-(1-pyrrolidinyl) pyridine are used as an efficient nucleophillic catalyst for a variety of useful reactions like esterifications with anhydrides, Baylis-Hillman reaction, hydrosilylations, tritylation, Steglich rearrangement, Staudinger synthesis of *β*-lactams and many more. Chiral DMAP analogues are also used in kinetic resolution of secondary alcohols and amides [2].

Since pyridine is toxic, many alternative reagents and methods have been devised to circumvent its use. Nevertheless the use of pyridine, in certain experiments, seems to be unavoidable. The ionic liquids have emerged as efficient substitutes of ordinary solvents. They are replacing, wherever possible, the traditional toxic organic solvents and reagents due to their non volatility, non-flammability, thermal stability and ease of recyclability [3]. More importantly the task specific ionic liquids serve as ionic liquid versions of relevant organocatalysts. It is special class of ionic liquids that contain specific functionalities which are designed to promote a particular organic transformation. During our research studies on functional ionic liquids, we have discovered that a functional ionic liquid can be capable to accomplish more than one task and thus can be termed as "multipurpose". This case is in sharp contrast with other functional ionic liquids which are called "task specific" means they can perform one task. Thus we have the credit of introducing a novel concept of "multipurpose ionic liquids" which can promote many different types of reactions. In this regard, we have reported the synthesis and applications of novel *N*,*N*-dimethylformamide-like (DMF-like) multipurpose ionic liquid for promoting all DMF-dependent reactions.[4] Due to its ability to promote myriad type of reactions, this has become the first example of "multipurpose ionic liquids". We have reported some useful applications of "multipurpose" DMF-like ionic liquid as a solvent and as a solvent-cum-reagent. More remarkable application of our DMF-like ionic liquid is the preparation of ionic liquid version of Vilsmier reagent from it. The ionic liquid-based Vilsmier reagent has been used efficiently for various Vilsmier reagent catalyzed reactions. Such as direct iodination of alcohols [5], and some more applications have also been reported [6].

Handy *et al* have reported nicotine-based ionic liquid as a green and efficient alternative to pyridine (Scheme 1). He investigated its potential as a nucleophillic solvent for



Scheme 1. Nicotine based task specific ionic liquid.

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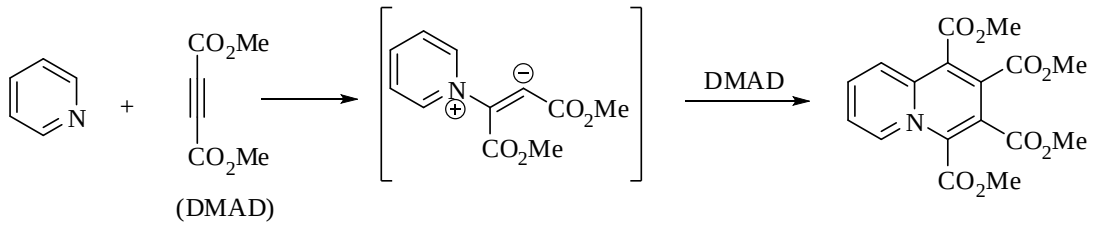


Scheme 2. Reaction of pyridine with dimethyl acetylenedicarboxylate to form 4H-quinolizine.

acylation of different types of alcohols with acetic anhydride [7]. It contains active pyridine unit with nucleophillic nitrogen which is non-volatile, stable and free from all hazardous effects of pyridine. In addition to this, the nicotine-based ionic liquid demonstrates the enhanced reactivity which leads to efficient results *i.e.* rapid reaction rates and enhanced product yields. This observation arises from marginal stabilization of transition states or reactive intermediates associated with reactions performed under ionic liquid conditions. The formation of polar transition states and charged reactive intermediates in ionic liquids is encouraged by the greater stabilization effect of ionic liquid arising from its highly polar and saline nature. Consequently the nicotine-based ionic liquid was proved to be an efficient substitute of ordinary pyridine as a green solvent as well as stable and recyclable organocatalyst for acetylation of alcohols with acetic anhydride.

The success of this reaction tempted us to believe that other pyridine-catalyzed reaction can also be carried out with nicotine based TSIL. In order to prove this nicotine-based ionic liquid another "multipurpose ionic liquid" for all pyridine catalyzed reactions, we carried out extensive literature survey to collect all related reactions. As a result we have already reported a successful use of nicotine-based task specific ionic liquid (TSIL) in achieving pyridine-dependent Baylis-Hilmann reaction with improved results and procedural convenience [8].

In continuation of our efforts to widen the scope of applications of nicotine-based ionic liquid and to prove it to be "multipurpose" in its function, we are reporting another pyridine-catalyzed reaction known as Huisgen cycloaddition reaction. This reaction involves the pyridine mediated cycloaddition reaction of dimethylacetylenedicarboxylate (DMAD) with dipolarophiles like aldehydes or *N*-tosylimines leading to the efficient synthesis of 2-benzoylfumarates and 1-azadienes respectively [9]. The process involves the nucleophillic attack of pyridine on DMAD to form highly reactive 1,3-dipolar intermediate that reacts with dipolarophiles like aldehydes or *N*-tosylimines to give 2-benzoylfumarates or highly substituted 1-azadienes respectively with in situ elimination of pyridine. Diels and Alder have already established the ability of pyridine to attack DMAD to form a 1,3-dipolar intermediate which reacts further with one more DMAD to form an adduct called 4H-quinolizine (Scheme 2) [10].

This reaction has been studied in detail by Acheson, who has provided more evidence of the existence of the 1,3-zwitterionic intermediate (Scheme 2) [11]. He showed that pyridine reacts feasibly with DMAD forming 1,3-dipolar zwitterion which can be trapped with suitable dipolarophiles to form corresponding adducts. Nair et al identified the potential of this reaction for construction of heterocyclic systems by trapping the 1,3-zwitterionic intermediates with carbonyl compounds [12]. He demonstrated that trapping the 1,3-dipole with aryl aldehydes afforded the corresponding aroyl fumarate. Similarly the same reaction with *N*-tosylimines as a dipolarophile produced 1-azadienes in quantitative amounts. In case of using arylmethylidenemalononitrile (*β*-dicyanostyrene) as dipolarophile afforded a highly substituted 1,3-butadiene with complete stereoselectivity [13].

Mechanistically, the reaction involves [2 + 2] cycloaddition of the 1,3-zwitterion generated from pyridine and DMAD to the carbonyl group of the aldehyde to give an unstable oxetene, which undergoes stereospecific ring opening to give the *Z*-isomer (Scheme 3).

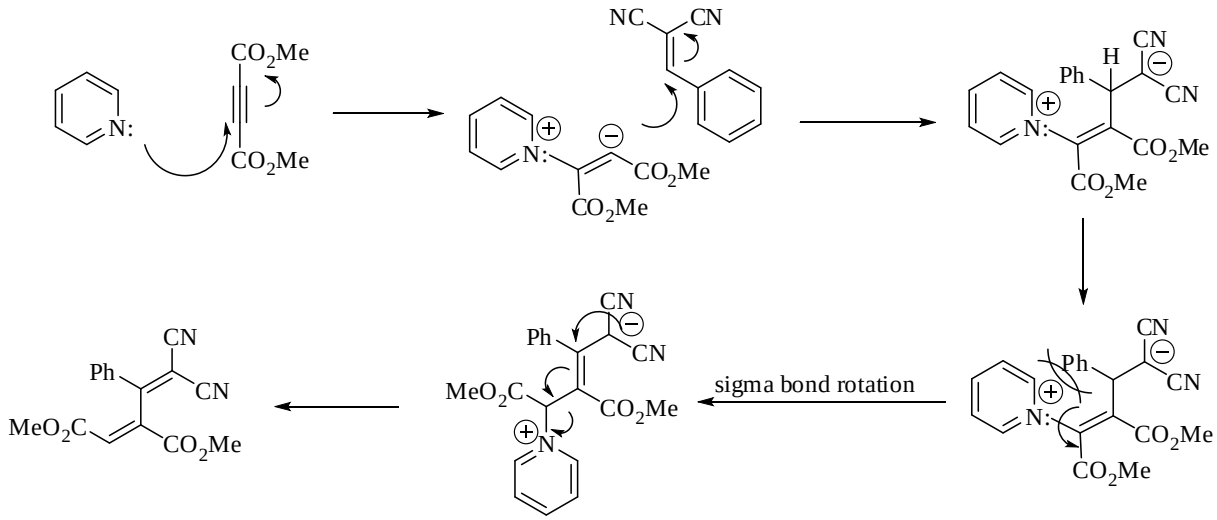
2. Experimental

2.1. Preparation of nicotine-based task specific ionic liquid

The nicotine-based task specific ionic liquid was prepared according to reported procedure [7].

2.2. General representative procedure

The nicotine-based ionic liquid (20 mol %) was added in dry acetonitrile (10 mL) in three-neck 50 ml round bottom flask and was stirred to mix at room temperature. Then the solution was cooled to 10 ˚C and dimethylacetylene-dicarboxylate (1 equiv.) was added to it dropwise through dropping funnel. The resulting mixture was stirred and temperature was allowed to reach room temperature. To this mixture, the aldehyde (1 equiv.) was added drop wise and the reaction mixture was stirred at room temperature until completion of reaction as evident from TLC. The solvent was then removed under vacuum, the product as extracted from ionic liquid by diethylether. Ether was removed under vacuo to get 2-oxo-3-benzylidenesuccinates. The nicotine-based TSIL was washed with distilled water then dried under *vacuo* and reused for next run.



Scheme 3. Proposed mechanism pyridine-catalyzed reaction of dimethylacetylene dicarboxylate and aldehydes.

3. Results and discussion

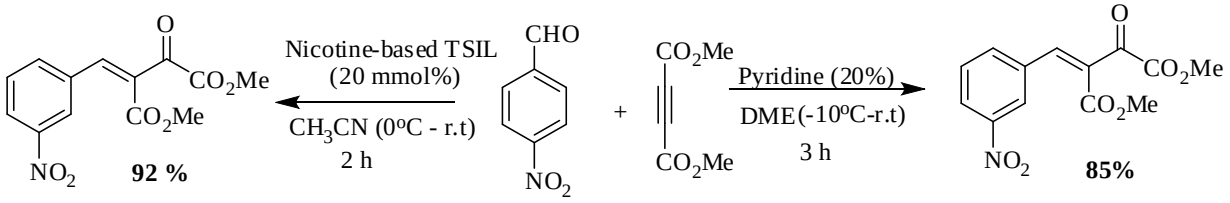
In this paper, we are reporting the outcome of the investigation of the potential of nicotine-based TSIL to catalyze the formation of 1,3-zwitterion intermediate from DMAD. The resulting intermediate was subsequently reacted with various active unsaturated compounds like carbonyls, N-tosylimines and arylmethylidenemalononitriles (β-dicyanostyrenes) to form corresponding adducts. nts had influence on the reaction time and yield. It was found that *ortho*-substituted benzaldehydes afforded the corresponding fused pyrimidinones in relatively lower yields (Table 2, entries 2, 12 and 18). Moreover, thiourea was successfully used to provide the corresponding products in good yields (Table 2, entries 15-18).

3.1. Nicotine based TSIL-catalyzed reaction of dimethylacetylenedicarboxylate with aldehydes

The Huisgen cycloaddition reaction of DMAD with 3-nitrobenzaldehyde in the presence of nicotine-based TSIL was selected as model reaction to set the standard conditions (Scheme 4). The 1 equivalent of DMAD was treated with nicotine-based TSIL (20 mol %) in acetonitrile at 0 °C and stirred for 30 minutes. Then 1 equivalent of 3-nitrobenzaldehyde was added to stirring mixture. After this, the reaction was allowed to stir initially at 0 ˚C for 1 hr and then temperature was gradually increased to room temperature. The progress of reaction was monitored by thin layer chromatography (TLC) analysis. The reaction was found to be completed after 6 h as indicated by TLC. After completion of reaction the acetonitrile was removed under vacuo and product was isolated from ionic liquid phase by extraction with diethyl ether. The removal of ether provided the required product 2-oxo-3-benzylidenesuccinate in 92% yield.

The excellent yield obtained in relatively lesser time indicates the worth of the reaction conditions employed. These conditions were used as standard conditions for further studies. Different structural variants of aldehydes were studied to check the scope of new procedure. The comparison of results obtained under ionic liquid conditions with those of normal reported procedure indicates the superiority of new methodology over the reported one. The remarkable aspects associated with current methodology include the rapid reaction rate, highest yeild of products and procedural convenience. The major reason for improved results obtained under ionic liquid conditions is the significant stabilization of 1,3-dipolar intermediate by higher solvating effects of ionic liquid.

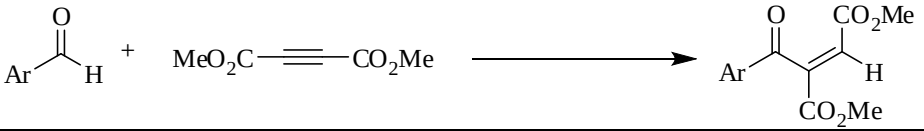
We tested the scope of nicotine-based task specific ionic liquid as a green recyaclable catalyst using same compounds

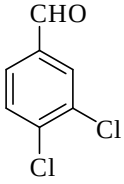
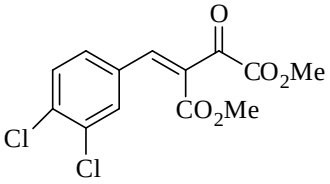
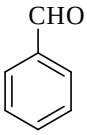
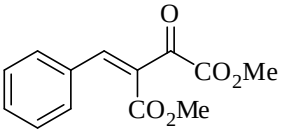
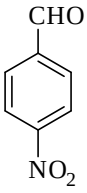
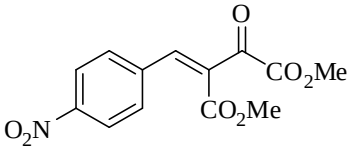
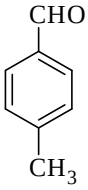
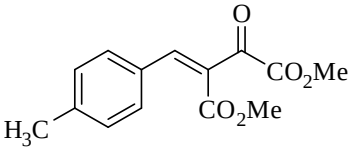
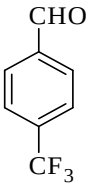
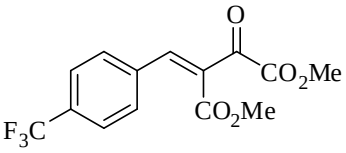
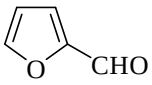
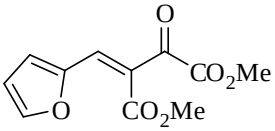
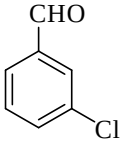
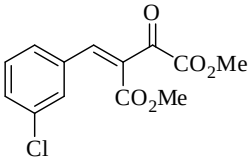
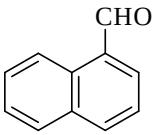
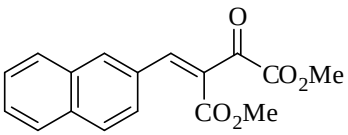


Scheme 4. Huisgen cycloaddition reaction of DMAD with 3-nitrobenzaldehyde in the presence of pyridine and pyridine-based TSIL.

as reported under normal proecdure for sake of comparision and to prove it as a better substitute of ordinary pyridine. The results obtained were consistantly excellent. Apart from other typical advantages associated with use of task specific ionic liquid procedure like operational convenience, green reaction conditions, rapid reaction rates, we got relatively enhanced yields of the products under new protocol as

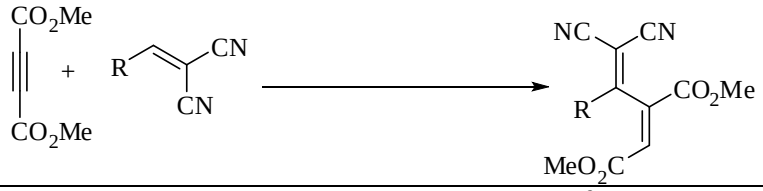
Table 1. Reaction of aldehydes with DMAD in the presence of a catalytic amount of and pyridine and Nicotine-based TSIL.



Entry	Aldehyde	Product	Yield (%)[a]	Yield (%)[b]
1			89	84
2			62	44
3			92	72
4			56	43
5			96	84
6			83	61
7			76	66
8			66	43

[a]Isolated product with TSIL.
[b]Isolated yield under normal method.

Table 2. Reaction of arylmethylidenemalononitriles with DMAD catalysed by pyridine and nicotine-based TSIL.



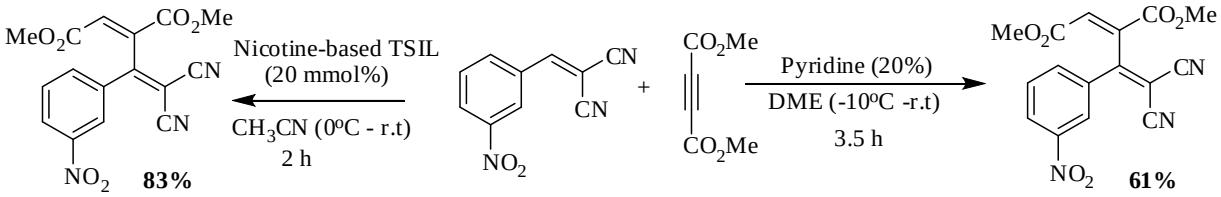
Entry	R =	Yield (%)[a]	Yield (%)[b]
1	4-Fluorophenyl,	93	82
2	3-Nitrophenyl,	85	71
3	4-Chlorophenyl,	97	87
4	1-Naphthyl,	98	92
5	3,4-Dichlorophenyl,	89	82
6	4-Methoxyphenyl,	84	78
7	*trans*-Cinnamyl,	64	45
8		54	43
9	3-Benzyloxyphenyl,	87	75

[a]Iisolated yield in TSIL.
[b]Isolated yield in normal conditions.

various derivatives of benzaldehyde were treated with DMAD in presence of nicotine-based TSIL. The pyridine ring present in nicotine moiety having active nucleophilic nitrogen was responsible for converting DMAD into zwitterion intermediate. The rapid reaction rate of each entry and higher yield of the product obtained under new protocol can be rationalized with fact that zwitterion being highly charged intermedate was stabilized by greater solvation effects of highly polar nature of ionic liquid. This factor promoted the formation of zwitterion intermediate thus enhancing the reaction rate and leading to higher yield of products. The benzaldehydes with electron withdrawing groups gave excellent yields (Table 1, entry 3, 5).

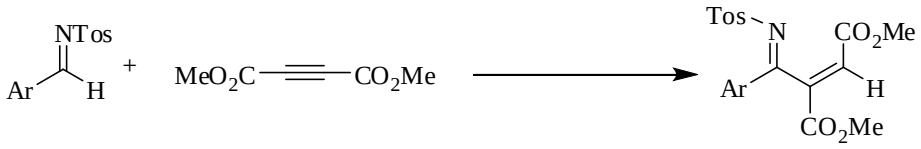
3.2. Nicotine based TSIL-catalyzed reaction of dimethylacetylenedicarboxylate with benzylidenemalono-nitrile

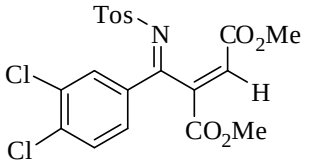
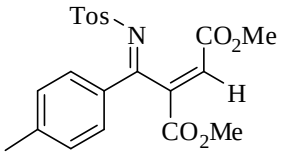
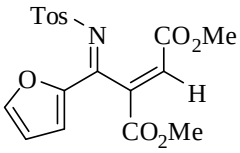
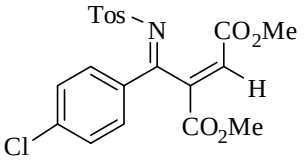
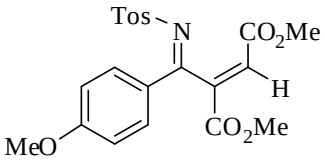
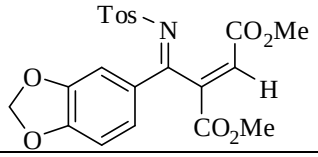
Other reactive alkenes which can react with DMAD were also investigated. In order to establish the optimum condition, one equivalent of 3-nitrobenzylidenemalono-nitrile was treated with one equivalent of DMAD in presence of nicotine-based TSIL (20 mol%) in acetonitrile as a solvent. The reaction mixture was stirred initially at 0˚C and then at room temperature. The reaction proceeded substituted butadiene derivative in 83% yield as compared to 61 % yield reported under normal procedure (Scheme 5). After having set the reaction conditions, a variety of dicyanostyrenes were tested for their potential react with DMAD intermediate. Every entry was found to participate in this reaction affording the corresponding 1,3-dienes in good to excellent yields. The results obtained are summarized in (Table 2). The values of the yields reported under normal conditions are just taken from the reported literature and no such reactions were performed. The better results obtained under present protocol, can be ascribed to same reasons as given above. The successful reaction of different reactive alkenes like arylmethylidenemalono-nitriles with same 1,3-dipolar intermediate reflects the power and capacity of nicotine-based TSIL to facilitate the various versions of a given type of reaction. Again the electron withdrawing effect of substituents on aromatic ring resulted in enhanced yields of corresponding products.



Scheme 5. Huisgen cycloadditions reaction of DMAD with 3-nitrobenzylidenemalononitrile in presence of pyridine and nicotine-based TSIL

Table 3. Reaction of tosylimines with DMAD catalyzed by pyridine and Nicotine-based TSIL.



Entry	Product	Yield (%)[a]	Yield (%)[b]
1		93	84
2		56	43
3		78	61
4		98	86
5		88	70
6		87	78

[a]Isolated yield in TSIL.
[b]Isolated yield in normal conditions.

3.3. The pyridine-catalyzed reaction of dimethylacetylene-dicarboxylate with N-tosylimines

In order to further explore the scope of nicotine-based TSIL, we investigated the N-tosylimines as third different type of dipolarophile to react with 1,3-dipolar intermediate resulting from reaction between DMAD nicotine-based TSIL. under similar optimum conditions, various tosylimines led to the efficient synthesis of corresponding 1-azadienes and N-substituted isatins. The results obtained under this new protocol were compared with those reported under normal conditions and are summarized in (Table 3).

The improved yields of products and reduced reaction time imply the relatively higher nucleophilicity of pyridine in nicotine-based ionic liquid. The greater stabilization of zwittorionic intermediates in ionic liquid conditions contributed to the efficiency of the reaction. The easy recovery of the product and recycling of the catalyst and replacement of toxic pyridine are additional advantages. The new protocol was equally beneficial for variety of structural variants of aldehydes.

The products were characterized by latest spectroscopic methods. The reported data of the Huisgen reactions performed under ordinary conditions were taken as it is. And it was compared with the data obtained from the replica of those experiments in proposed nicotine- based task specific ionic liquid. The data is compared in form of table which indicates the relatively enhanced yields of the isolated products as compared to that obtained using

Table 4. Recycling studies of nicotine-based ionic liquid.

Recycle times	1	2	3	4
Product yield (%)	92	88	84	81
Recovered ionic liquid (%)	98	97	97	95

original conventional methodology. Relative increase in product yields can be attributed to the highly polar nature of the reactive intermediates which are stabilized by the highly polar and saline nature of ionic liquid. The nicotine-based ionic liquid reacted efficiently with DMAD to form kinetically controlled 1,3-dipolar intermediate. It was treated with variety of dipolarophiles which reacted effectively with it form corresponding products. This observation indicates the wide scope of Huisgen cycloadditions when performed under ionic liquid conditions. In addition to this, the current study also provides another clue to the "multipurpose" nature of nicotine-based ionic liquid.

3.4. Recycling

The one of the important aspect of green reagents is their recyclability. We investigated the opportunity of recovering and recycling of nicotine-based TSIL for present reaction conditions. For this, we chose the cycloaddition reaction of 4-nitrobenzaldehyde with DMAD in presence of nicotine based TSIL. The results are summarized in (Table 4), which show that the product yields are quite consistent. The recovered ionic liquid maintains its catalytic efficiency up to four recycles.

4. Conclusion

The nicotine-based task specific ionic liquid was found to be very efficient facilitator of cycloaddition reactions of dimethylacetylenedicarboxylate (DMAD) with various dipolarophiles like aldehyde, benzylidenemalononitrile, and N-Tosylimines forming corresponding adducts with improved yields. The ionic liquid has been shown as a best substitute of toxic pyridine for pyridine promoted reactions. In addition it was recyclable and with appreciable retention of catalytic efficiency. The multipurpose nature of nicotine-based ionic liquid has been proved and further studies are underway.

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