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One-pot multicomponent synthesis of 2-amino-5,6,7,8-tetrahydro-4-phenylquinoline-3-Carbonitrile Derivatives

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Abstract

We report simple, efficient and one pot multicomponent protocol for the synthesis of the highly substituted 2-amino-5,6,7,8-tetrahydro-4-phenylquinoline-3-carbonitrile derivatives via the reaction of various aromatic aldehydes, malanonitrile, cyclic ketones and ammonium acetate in the presence of catalytic amount of cellulose based cerium (IV) as reusable catalyst at room temperature. For this transformation we used ethanol as green solvent and considering green chemistry approach. The synthesized compounds were characterized by FT- IR technique. The advantages of procedure include simplicity of operation, wide substrate scope, good yields, no chromatographic separation technique, and easy recovery & recyclability of the catalyst.

Keywords: Multicomponent reactions, Green chemistry, aromatic aldehydes, Ce(IV)CMC, Pyridines.

Introduction

In the recent years, all the chemist being focused on green chemistry by using environmentally benign reagent, prevent waste, design safer chemicals, no toxicity to human and environment. Particularly those reactions are performed by using green solvent, eco-friendly catalyst; maximize atom economy as well as reaction performs at room temperature, to increase energy efficiency[1]. Multicomponent reactions (MCRs) have becomes an important tool for the efficient synthesis of wide variety of organic molecule[2-3].

Nitrogen contains heterocyclic compounds and their derivatives have attracted the attention of chemist mainly because of broad spectrum biological and pharmacological[4].

A lot of pyridine derivatives possess a wide range of biological and pharmacological activities and are already used as dopamine transporter inhibitors, anti-inflammatory agent[5], and antimicrobial agent[6]. The 2-amino-3-cyano-pyridine derivatives have medicinal

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applications as such as analgesic and anti-pyretic properties[7]. Pyridine containing compounds have medicinal applications as anti-viral, anti-malarial and anti-cancer[8].

Due to their wide range of biological advancement, synthesis of title compounds are still of intrigue. The preparation of 2-amino-5,6,7,8-tetrahydro-4-phenylquinoline-3-carbonitrile derivatives has been reported in the literature via a reaction of four components under reflux condition[9]. However many of these methods suffer from drawbacks such as expensive catalyst, long reaction time, low ordinary yield and environment pollution.

There is no attention has been paid to using biopolymer and its derivatives as a carrier in the preparation of support catalyst for this synthesis. The biopolymer carboxymethylcellulose (CMC) supported Ce^{IV} metal particles provided good surface area, by cationic absorption of CMC makes it active catalyst[10]. Smaller particles are dispersed onto a high surface area refractory support. Nano-particles (NPs) of catalyst are dispersed on surface and make it more active[11].

Considering these facts, we report simple, efficient and one pot multicomponent protocol for the synthesis of the highly substituted 2-amino-5,6,7,8-tetrahydro-4-phenylquinoline-3-carbonitrile derivatives, via the reaction of various aldehydes, malanonitrile, cyclic ketones and ammonium acetate in the presence of catalytic amount of cellulose based cerium (IV) as biodegradable catalyst at room temperature. For this transformation we used ethanol as green solvent and considering green chemistry approach.

Materials and Methods

All reagents used were of laboratory grade. Melting points were determined in open capillaries. Progress of reaction was monitored by silica gel-G coated TLC plates in n-hexane: ethyl acetate system (9:1).The spot was visualized by exposing dry plate in UV chamber. IR spectra were recorded on Shimadzu FT-IR (Affinity Model) using KBr.

Preparation of Cu(II)carboxymethylcellulose (CMC−Ce^{IV}) Catalyst[12]

The Ce(IV)carboxymethylcellulose (CMC−Ce^{IV}) catalyst was prepared by metathesis reaction of cerric ammonium nitrate and Na-CMC. The yellow solid was precipitated which was left to equilibrate in a solution for overnight. The resulting yellow solid was separated from the solution and washed thoroughly with distilled water. The wet CMC− Ce^{IV} was dried at 60^0C in the oven till constant weight.

Synthesis of Polysubstituted pyridine by using CMC-Ce(IV) Catalyst

In 150 ml round bottom flask, a mixture of ketone (10 mmol), malononitrite(10 mmol) and

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ammonium acetate (15 mmol), as ammonia source, and CMC-Ce^{IV}(20mg) were added to 30ml ethanol solution of aromatic aldehyde (10 mmol) and stirred for appropriate times at room temperature (Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, catalyst was recovered simply by recrystallization of crude product in hot ethanol. Catalyst is insoluble in ethanol and by using this method catalyst was easily recovered and to get corresponding pure product.

Result and discussion:-

Optimized reaction conditions:

a) Effect of the Solvent

It is well known that the reaction medium plays an important role on the reaction rate. To optimize the reaction condition; we performed the model reaction of p-nitro bezaldehyde and cyclohexanone using various solvent and without solvent as shown in **table (1).**

Table 1: Effect of solvent

Entry No.	Solvent	Time(Min)	Yield (%)
1.	Solvent Free	150	71
2.	**Ethanol**	**120**	**93**
3.	Water	180	40
4.	CH_2Cl_2	180	53
5.	CH_3CN	180	68
6.	n-Hexane	180	62
7.	Toluene	180	55

From the above table it clear in pure ethanol get high yield of product & minimum time required for the completion of reaction.

b) Effect of catalyst:

Initially we performed reaction without catalyst the yield of product only about 60% and time required was also more to complete the reaction. To optimize the reaction condition; we performed the model reaction of p-nitro bezaldehyde and cyclohexanone with different amount of CMC− Ce^{IV} catalyst loaded as shown in **table-2.**

Table 2: Optimized amount of catalyst loaded

Entry	Catalyst (mg)	Time(Min)	Yield (%)
1.	0	150	60

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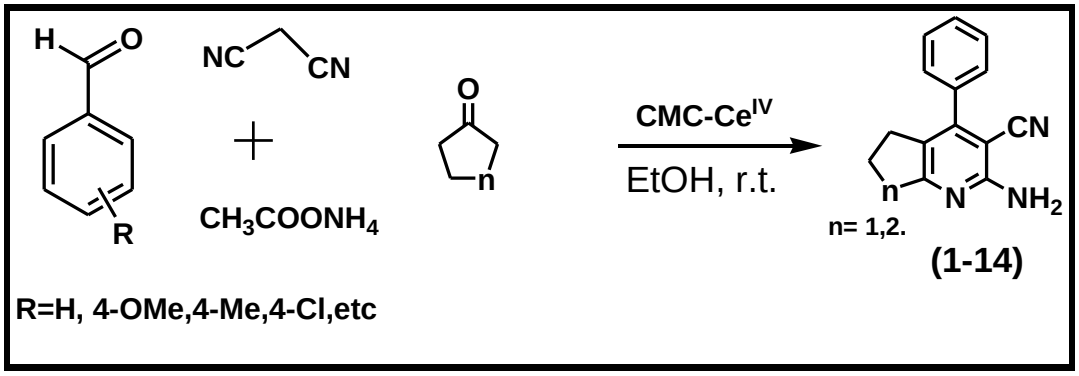
2.	5	80	71
3.	**10**	**60**	**93**
4.	15	60	93

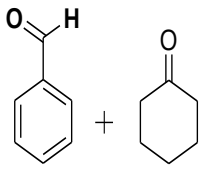
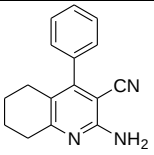
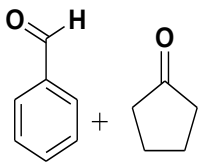
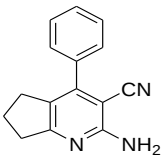
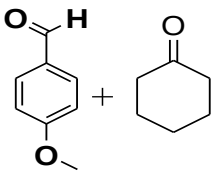
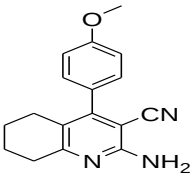
It was found that, the 10 mg catalyst is sufficient to push the reaction forward. Hence the reaction was perform with 10 mg catalyst by optimized the reaction condition.

After the study of above optimized reaction condition were explored for the synthesis of series of 2-amino-5,6,7,8-tetrahydro-4-phenylquinoline-3-carbonitrile derivatives polysubstituted pyridines derivatives(1-14) from various substituted benzaldehyde, ketone, malononitrite and ammonium acetate using CMC-Ce^{IV} as catalyst as shown in **scheme-1** and the results are summarized in **Table-3**.



Scheme 1: Synthesis of polysubstituted pyridines by using CMC-Ce^{IV} as catalyst

Table-3: Synthesis of polysubstituted pyridines derivatives(1-14)

Entry NO.	Starting compounds	Product	Time (min)	Yield (%)	Melting point(ºc)
1.			90	93	234
2.			80	88	218
3.			120	90	234

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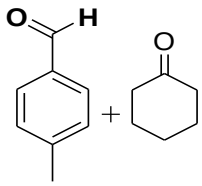
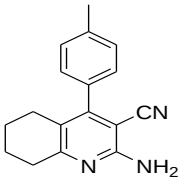
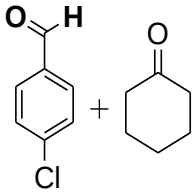
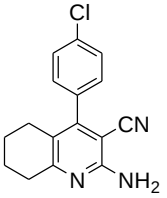
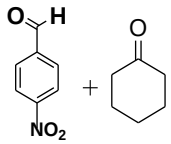
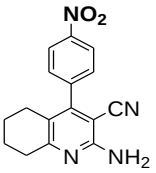
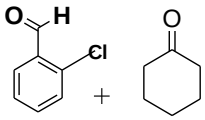
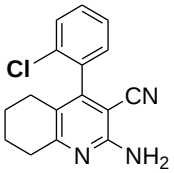
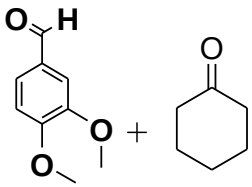
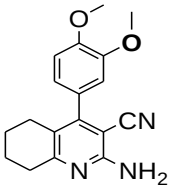
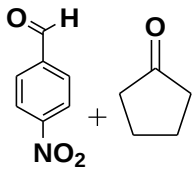
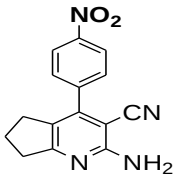
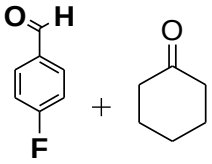
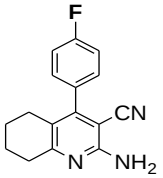
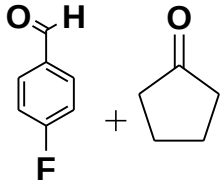
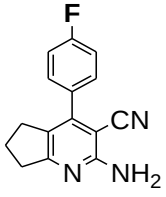
4.			80	92	246
5.			50	90	224
6.			60	93	232
7.			75	86	218
8.			80	92	214
9.			60	83	228
10.			80	88	256
11.			80	87	224

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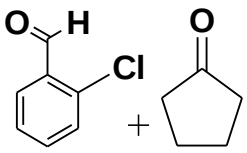
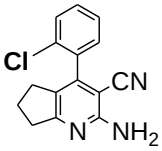
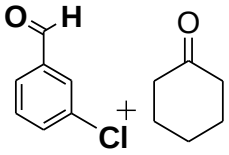
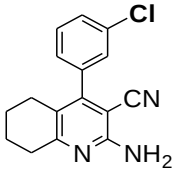
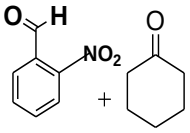
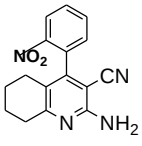
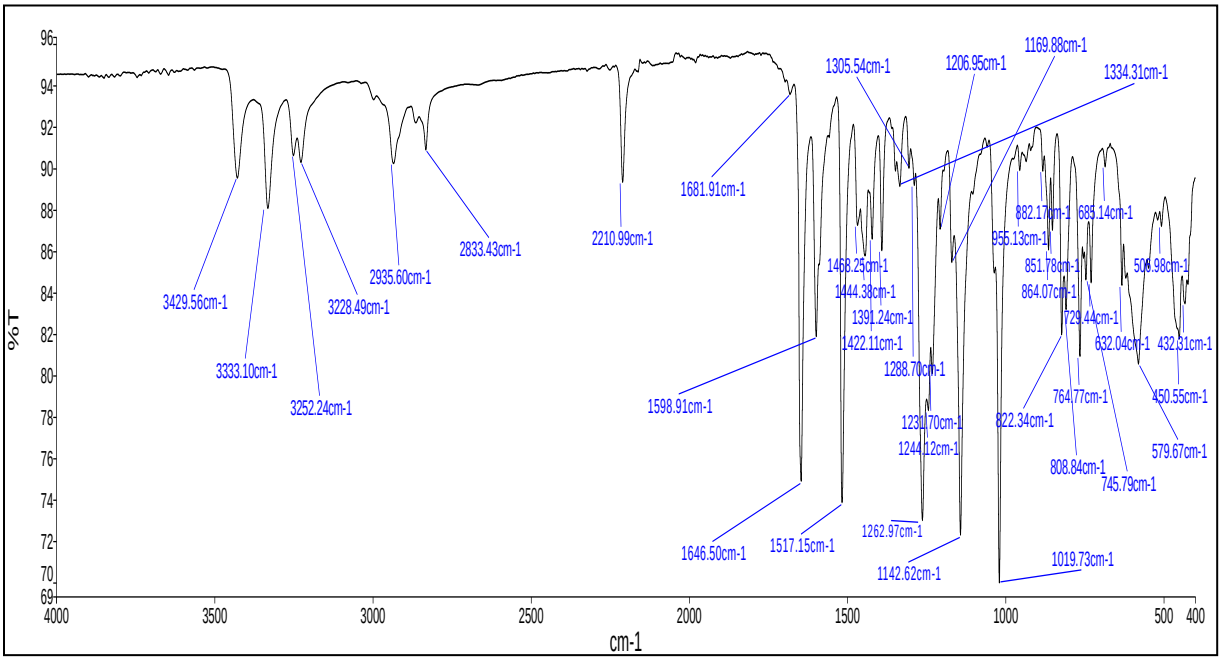
12.			80	84	214
13.			90	85	232
14.			75	92	246

IR Spectra of compounds (1&2)



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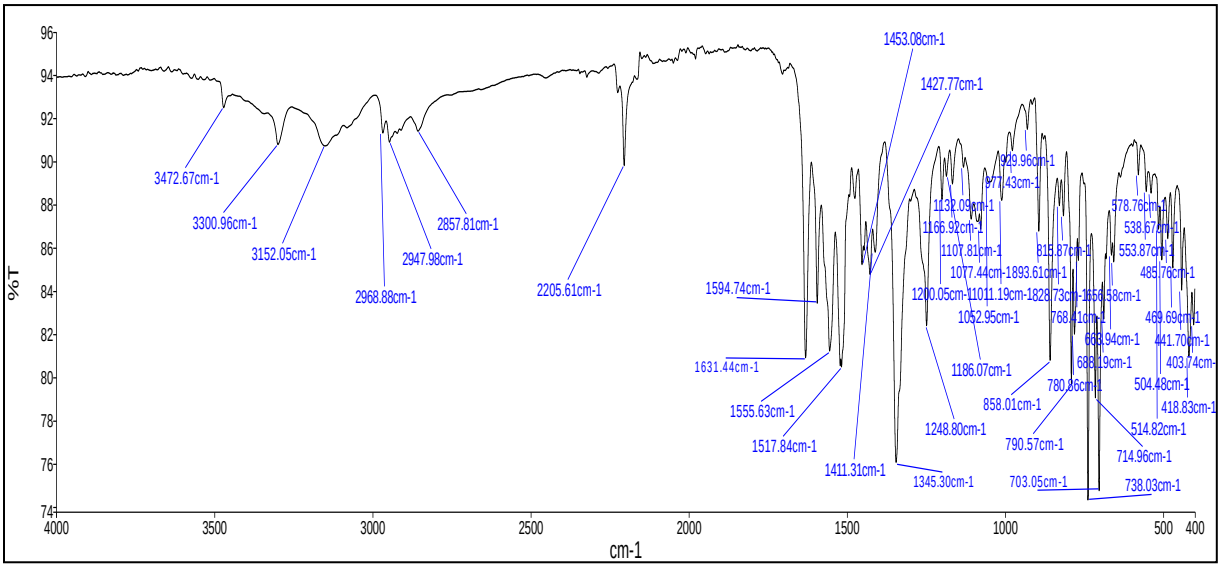

Data

1) Cream white IR (cm^{-1}): 3333.1(-N-H); 2210.9 (-CN), 1646.5(C=N), 1589.2(C=C), 1330 (C-N),

2) White solid, IR (cm^{-1}): 3300.9(-N-H); 2205.6(-CN), 1631(C=N), 1594.74(C=C), 1311 (C-N), 790.57(C-Cal)

3) White solid, IR (cm^{-1}): 3339.9(-N-H); 2235.99 (-CN), 1603.3(C=N), 1598.74(C=C), 1344 (C-N),

4) Brown solid, IR (cm^{-1}): 3349.0(-N-H); 2211.3(-CN), 1638(C=N), 1589.2(C=C), 1311 (C-N), 1346.86(NO_2)

5) Pale Yellow solid, IR (cm^{-1}): 3338.0(-N-H); 2227.(-CN), 1661(C=N), 1589.2(C=C), 1311 (C-N),

6) White solid, IR (cm^{-1}): 32909.9(-N-H); 2205.99 (-CN), 1623.3(C=N), 1578.74(C=C), 1304 (C-N),

Conflict of Interest

There is no conflict of interest for given article

Conclusion

The CMC-Ce^{IV} NPs were prepared by the ion exchange reaction. The inclusion phenomenon of sodium carboxymethyl cellulose with cerric ammonium nitrate was successfully characterized by FT-IR techniques. We have developed a simple and efficient protocol for one-pot synthesis of the highly substituted 2-amino-5, 6, 7, 8-tetrahydro-4-phenylquinoline-3-carbonitrile derivatives via the reaction of various

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aldehydes, malanonitrile, cyclic ketones and ammonium acetate in the presence of catalytic amount of cellulose based cerium(IV) as reusable catalyst at room temperature. For this transformation we used ethanol as green solvent and considering green chemistry approach. The high catalytic activity of CMC-Ce^{IV} was accounted due its Lewis acid sites. The advantages of procedure include simplicity of operation, wide substrate scope, good yields, no chromatographic separation technique and an easy recovery of the catalyst and recyclability of catalyst.

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