Heterocyclic Letters
Vol. 9| No.4|437-445|Aug –Oct |2019
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

ANEFFICIENT AND GREEN SYNTHESIS OF SUBSTITUTED PIPERIDINE DERIVATIVES USING CERIUM CHLORIDE HEPTAHYDRATE AS CATALYST

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Abstract

A number of substitutedpiperidine derivatives were synthesized using a five component reaction in ethanol, with cerium chloride heptahydrate ($CeCl_3.7H_2O$), as a catalyst. This protocol provides a clean, safe, quick and efficient single pot route for the synthesis of the target molecules in good yields. The method uses a green solvent, an inexpensive and reusable catalyst and yields products in much less times than previously reported in literature.

Keywords

Piperidines, cerium chloride heptahydrate, Lewis acid, multicomponent reaction, green chemistry.

Introduction

Piperidine derivatives are abundantly found in nature. Organic fine chemicals[i,ii],therapeutic agents[iii,iv]and many physiologically active molecules have the piperidine skeleton in them.A large number of useful compounds are synthesized using piperidine derivatives as the starting materials. Piperidine derivatives are known to have anti-hypertensive[v], anti-bacterial[vi], anti-convulsant, anti-inflammatory[vii]and antimalarialaction[viii]. They contribute significantly in the treatment of influenza[ix],diabetes[x], viral infections including AIDS[xi] and cancer metastasis[xii].Many commercial drugs[xiii] such as Donepezil (Alzheimer's disease), Risperidone (schizophrenia), Naratriptan (migraine) and Sertindole[xiv]have piperidine backbone. Some of these derivatives show inhibitory activity against farnesyl transferase[xv] and dihydroorateDehydrogenase[xvi].(**Fig.1**)

Many general methods are developed for the synthesis of piperidine derivatives due to their uses in medicine. Significant among them are imino-Diels-Alder reactions[xvii],aza-Prins-

cyclizations[xviii], intramolecular Michael reactions[xix] and intramolecular Mannichreaction[xx]. Tsukamoto and Kondo reported a Pd (0) catalysed condensation of alkynyl or alkenyl amine with formaldehyde and boronic acid derivatives for the synthesis of 1,4-disubstituted 1,2,3,6-tetrahydropridines[xxi]. Other methods include the reaction of N-(p-methoxyphenyl) aldimines with tetrahydro-2*H*-pyran-2,6-diol[xxii], organocatalysed domino process involving aza-Morita-Baylis-Hillmannreaction[xxiii], radical cyclisation of Baylis-Hillman adducts[xxiv] etc.

Multicomponent reactions (MCRs) can be used as an alternative for the synthesis of piperidine analogues. In recent times, MCRs have been exploited in organic synthesis to produce molecules having complex structures and diverse skeletons[xxv]. These reactions are green as they are economic in terms of atom, pot and step and they avoid costly protection-deprotection steps and purification processes[xxvi]. Synthesis of highly substituted tetrahydropiperidines using a MCR of β-keto esters, amine and aldehyde and several catalysts has been reported. **(Scheme 1)** This strategy involves a five component condensation reaction.

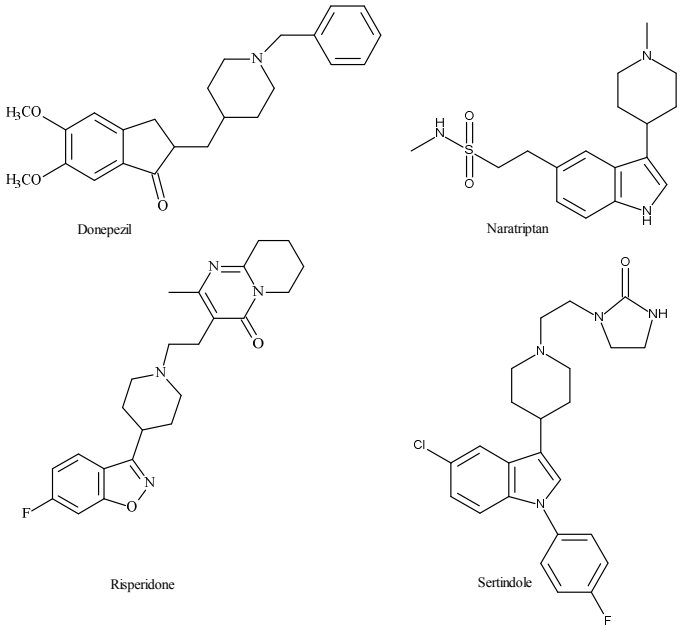
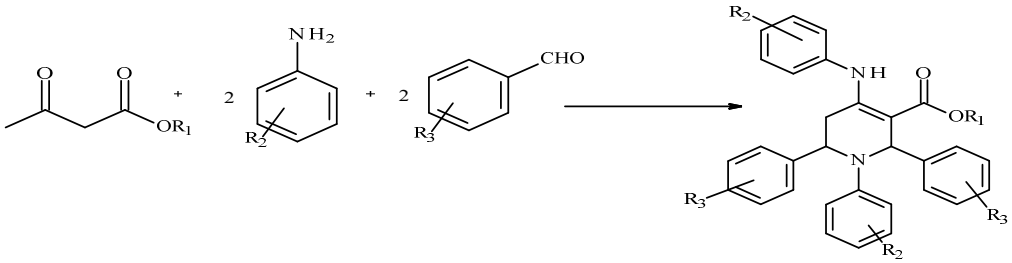


Fig. 1 Commercial drugs with piperidine scaffold



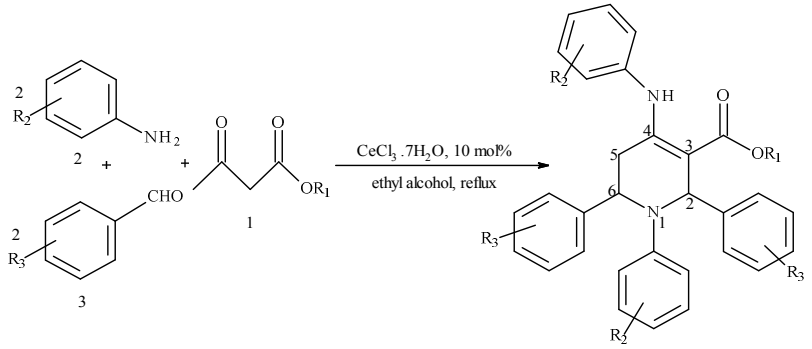
Scheme 1: Five component synthesis of piperidine derivatives

Some of the catalysts used for this reaction include $InCl_3$[xxvi],bromodimethylsulfoniumbromide[xxvii], L- proline/TFA[viii], tetrabutylammonium tribromide (TBATB)[xxviii], iodine[xxix], ceric ammonium nitrate (CAN)[xxx], $ZrOCl_2.8H_2O$[xxxi], picric acid[xxxii], $Bi(NO_3)_3$, $5H_2O$[xxxiii], $Bi(OTf)_3$[xxxiv], sulfamic acid[xxxv], tartaric

acid[xxxvi],$Ni(ClO_4)_2.6H_2O$[xxxvii], citric acid[xxxviii], $BiBr_3$[xxxix], acetic acid[xl], VCl_3[xli], $ZrCl_4$[xlii], 2,6-dicarboxylic acid[xliii]etc. However, there is still a need for a green method, which is simple, high yielding and applicable to a broad range of substrates.

Presently our work revolves on the use of Cerium chloride heptahydrate ($CeCl_3.7H_2O$) as aninexpensive, efficient and superior catalyst in the green synthesis of heterocyclic compounds. Over the years, a number of reactions promoted by cerium chloride have been reported[xliv]. As part of our work, we have shown the utility of $CeCl_3.7H_2O$ catalyst in imine synthesis[xlv] and reductive amination[xlvi]. In addition, 3-methyl isoxazolonederivatives[xlvii]and 2-pyrazolines[xlviii] in ethyl lactate (70%) and tetrahydrobenzopyrans and pyranopyrimidinediones in water as solvents respectively[xlix] have been synthesised in presence of $CeCl_3.7H_2O$. We have demonstrated the use of melt mixtures of urea, sugars and $CeCl_3.7H_2O$ as useful solvents for the synthesis of 1,4 -DHPs (dihydropyridines)[l].

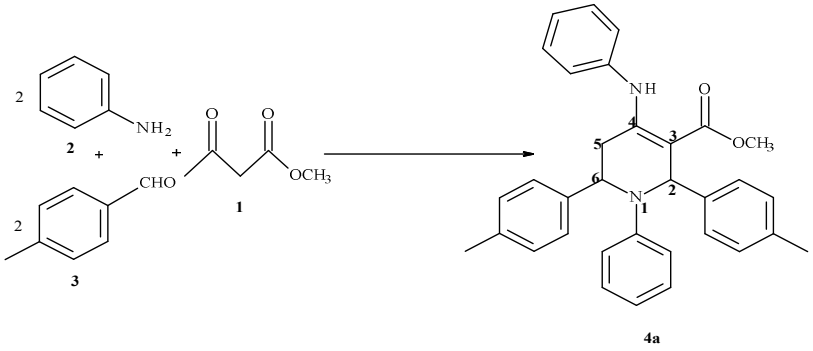
Highly substituted piperidine derivatives are interesting scaffolds and in this work, wedemonstrate a direct and simple approach for the synthesis of a number of them via a single pot five component reaction between β-ketoesters, aromatic aldehydes, and substituted anilines using $CeCl_3.7H_2O$ as catalyst in refluxing ethanol**(Scheme 2).** After intensive literature searches, we are able to affirm that the synthesis of these derivatives under the conditions used by ushas not been published in literature.



Scheme 2: Single pot reaction for the synthesis of highly substituted piperidine derivatives

Results and Discussion

The reaction conditions was optimised with respect to temperature, solvent and catalyst concentration by performing various trials with methyl acetoacetate (β-ketoester, **1**, 1mmol), 4-methylbenzaldehyde (**3**, 2mmol) and aniline (**2**, 2 mmol). **(Scheme 3)** The yields of **4a** obtained in the different trials are summarized in **Table 1.**



Scheme 3: Model reaction for single pot synthesis of highly substituted piperidine derivatives

Table 1 Optimization of reaction conditions for the single pot synthesis of 4a[a]

Entry	Solvent	$CeCl_3.7H_2O$ (mol %)	Temperature	Time (hrs)	Yield (%)
1.	Water	-	RT	10.0	trace
2.	Water	10	RT	10.0	trace
3.	Water	10	reflux	10.0	40
4.	70% Ethyl lactate	-	reflux	10.0	trace
5.	70% Ethyl lactate	10	reflux	10.0	45
6.	Ethanol	-	RT	10.0	trace
7.	Ethanol	-	reflux	10.0	30
8.	Ethanol	5	reflux	6.5	52
9.	Ethanol	10	reflux	5.0	82
10.	Ethanol	15	reflux	5.0	65
11.	50%Ethanol	-	reflux	10.0	40
12.	50%Ethanol	10	reflux	8.0	45
13.	Neat	-	RT	10.0	Trace
14.	Neat	-	reflux	10.0	Trace
15.	Neat	10	reflux	10.0	42

[a] Reaction conditions- methyl acetoacetate (1mmol), aniline (2 mmol) and 4-methylbenzaldehyde (2mmol)

It was found that 10 mol% of $CeCl_3.7H_2O$ gave the best yields in refluxing ethanol. (**Table 1**, entry 9) The yield did not increase even when the concentration of the catalyst was increased. (**Table 1**, entry 10) Only trace quantities of the product were formed in the absence of the catalyst in neat conditions as well as when using solvents. (**Table 1,** entries 1, 4, 6, 13, 14) The same was true when the reaction was carried out at ambient conditions. (**Table 1**, entries 1, 2, 6, 13) When the reaction was conducted under reflux in presence of water, 70% ethyl lactate and 50% ethanol, only moderate yields resulted. (**Table 1**, entries 3, 5, 7, 8, 11, 12, 15) Thus the optimal conditions for this reaction was established to be 10 mol% of $CeCl_3.7H_2O$ in refluxing ethanol.

Using the above optimum conditions, we investigated the reaction with other substituted aryl amines and aldehydes. **(Scheme 2)**Good yields of the products were obtained and the nature of the substituents on the aromatic nucleus did not affect the reaction. Changing the β-keto esterdid not significantly alter the yields of the reaction. The times required and the yields obtained in these trials are summarized in**Table 2**.

Table 2 Synthesis of highly substituted piperidine derivatives[a]

Entry	R_1	R_2	R_3	Time (hrs)	Melting point (◦C)		Yield (%)
					Found	Reported	
4a	$-CH_3$	-H	4-CH_3	5.0	213-214	215-216[xxix]	82
4b	$-CH_2CH_3$	-H	4-CH_3	5.5	227-228	228-231[xxix]	79
4c	$-CH_3$	-H	-H	4.0	182-183	185-186[xxix]	86
4d	$-CH_3$	-H	4-OCH_3	4.5	184-185	186-188[xxix]	75
4e	$-CH_3$	-H	4-Cl	5.0	225-226	225-227[xxix]	80

4f	$-CH_3$	-H	4-F	5.5	191-192	193-195 [xxix]	82
4g	$-CH_3$	-H	3-NO_2	3.5	179-180	182-183 [xxix]	84
4h	$-CH_3$	-H	4-NO_2	4.0	238-239	239-241 [xxix]	83
4i	$-CH_3$	4-CH_3	4-CH_3	5.5	204-205	206-208 [xxix]	78
4j	$-CH_3$	4-OCH_3	4-CH_3	5.0	228-229	230-231 [xxix]	82
4k	$-CH_3$	4-Br	4-CH_3	5.0	230-231	230-232 [xxix]	74
4l	$-CH_3$	4-NO_2	4-CH_3	5.0	251-252	253-255 [xxix]	79
4m	$-CH_2CH_3$	4-CH_3	4-NO_2	4.5	209-210	211-213 [xxxv]	84
4n	$-CH_2CH_3$	4-Cl	4-Cl	5.5	206-207	207-209 [xxxv]	74
4o	$-CH_2CH_3$	4-CH_3	4-Cl	5.0	229-230	232-235 [xxxv]	77

[a] Reaction conditions-β-ketoester (1mmol), aryl amine (2 mmol) and aryl aldehyde (2mmol),10 mol% $CeCl_3.7H_2O$, ethanol, reflux

Fig.2 shows the general structure of the substituted piperidine derivatives. The melting pointsand spectral characteristics of all the products were compared with that available in literature. Peaks were obtained in the following regions viz 1590-1595 cm^{-1}(C=C of aromatic ring), 1640-1660 cm^{-1}(C=O of ester) and 3340-3450 cm^{-1} (N-H stretch) for all the synthesized piperidinederivatives in the infrared spectra.

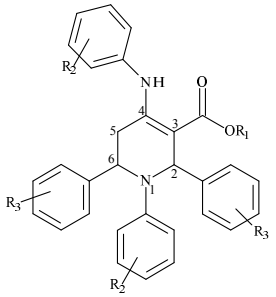


Fig.2 General structure of piperidine derivatives

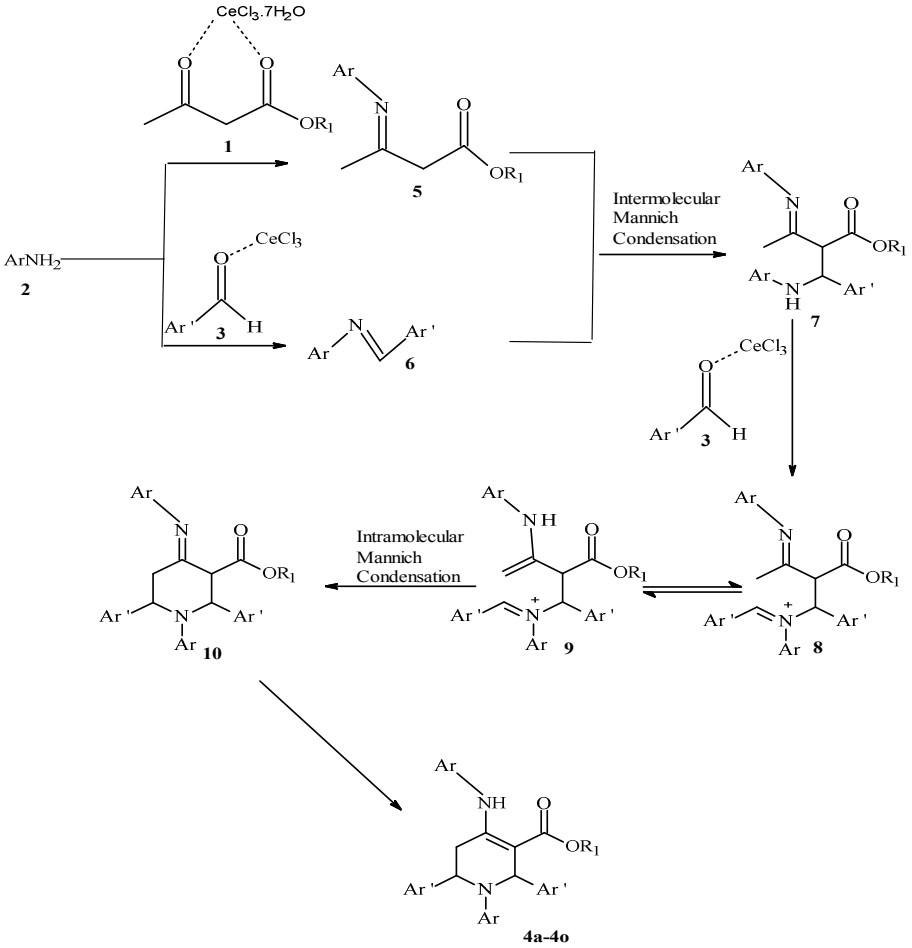
The characteristic features observed from the ^1H NMR spectra of all the products are illustrated below. A sharp singlet in the range 10.00 – 10.60 ppm indicates the presence of the N-H proton. While the methine proton on C-6 appears in the region 5.00 to 5.40ppm, the two protons at C-5 which are diastereotopic, are seen in most of the cases as two doublets of doublets in the region 2.70-2.73 and 2.81-2.84 ppm. A multipletin the 6.30 - 7.50 ppm range indicates the aromatic protons. In the case of **4a**, the benzylic methyl groups appear at 2.15 and 2.26 ppm as singlets. Thus, the presence of the expected peaks in the proton spectrum confirms the structures of the synthesized products.

Characteristic peaks for the aromatic carbons were observed in the ^{13}CNMR spectrum of all the compounds. All the products show a peak in the region 165.0-169.0 ppm which can be attributed to the C = O group. The peak in the region 153.0 – 155.0 ppm is very characteristic and is due to the C = C at C-4. Comparison of melting points and spectral data of the synthesized products with that reported in literatureestablished the structures of all the products without any ambiguity.

In this reaction, the recyclability of the solvent was attempted. Once we confirmed that all of the products and reactants are removed,the filtratewas reused for consecutive reactions. The

yields obtained in the two consecutive trials performed were comparable to the original. Thus, the solvent – catalyst mixture was recycled without appreciable loss in activity.

Based on the availableliterature and the results obtained, we propose a possible pathway for the reaction of aryl amine, β-ketoester, and substituted aldehyde in the presence of $CeCl_3.7H_2O$ catalyst. The latter is a mild Lewis acid capable of enhancing its reactivity by coordinating with the carbonyl oxygen. The pathways suggested by Abbasi *et al.* in the synthesis of piperidine derivativesusing $TiCl_2.2H_2O$ as catalyst[li] and by Kidwai *et al* in the $CeCl_3.7H_2O$ catalysedMannichreaction[lii]is utilized in the mechanism proposed. **(Scheme 4).**



Scheme 4: Proposed mechanism for the synthesis of substituted piperidine derivatives

The β-enaminone **5**is obtained by the reaction of aryl amine **2** and β-ketoester**1**in the presence of $CeCl_3.7H_2O$. Similarly, the corresponding imine **6** is obtained by condensation of arylamine**2** with aryl aldehyde**3**. The β-enaminone **5**undergoes an intermolecular Mannich reaction with the imine **6** to generate the intermediate product **7**. This on reaction with the second molecule of aryl aldehyde **3** (activated by $CeCl_3.7H_2O$) produces **8** which undergoes tautomerization to **9**. This tautomer**9**undergoes intramolecular Mannich type addition to form the intermediate product **10** which is converted to the final product.

Experimental Section

All the reagents were supplied by SD Fine Chem Limited (India) and Thomas Baker (India) and were used directly without any further purification. The physical constants of the

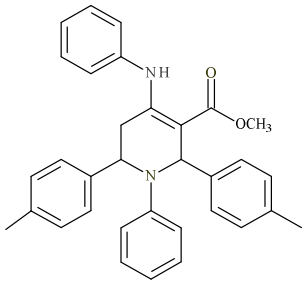
products were calculated by observing the spectra of the products. These values were then compared with the literature values and thus the products were characterized. Veego digital melting point apparatus was used to record all the melting points and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at ambient temperatures with $CDCl_3$ as the solvent on a 500 MHz BRUKER AVANCE DRX-500 instrument.

Experimental procedure for the synthesis of substituted piperidine derivatives (4a-4o)

β-ketoester**1** (1mmol), aryl amine **2** (2mmol) and cerium chloride heptahydrate ($CeCl_3.7H_2O$, 10 mol%) were taken in 5 mL ethyl alcohol and stirred at RT for 20 minutes. The aryl aldehyde **3** (2 mmol) was then added and the stirring was continued under reflux. A thin-layer chromatography (TLC) using n-hexane:ethyl acetate (3:7) as the solvent system was used to monitor the progress of the reaction. After completion of the reaction as indicated by TLC, the resulting thick solid was filtered off and washed with ethanol (3 x 2mL). The impure product was recrystallised from ethyl alcohol.

Physical and spectral characterization of model compound 4a

Methyl-2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-etrahydropyridine-3-carboxylate (4a)[xxix]



White solid (213-214◦C, 82% yield)

^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 2.15 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.73 (dd, 1H, *J* = 14.7, 3.2 Hz, H-5), 2.82 (dd, 1H, *J* = 15.2, 5.6 Hz, H-5), 3.92 (s, 3H, OCH_3), 5.11 (d, 1H, *J* = 3.5 Hz, H-6), 6.15 (d, 2H, *J* = 8.0 Hz, ArH), 6.42 (s, 1H, H-2), 7.43 – 6.33 (m, 16H, ArH), 10.16 (s, 1H, NH),

^{13}C NMR (151MHz, $CDCl_3$, δ, ppm) : 21.0, 22.3, 33.9, 51.3, 55.3, 58.0, 98.5, 113.1, 116.1, 125.4, 125.9, 126.0, 126.2, 128.1, 128.9, 129.3, 129.5, 136.0, 136.7, 138.1, 139.4, 140.2, 147.8, 156.2, 168.0.

Conclusions

The present work suggests a simple and uncomplicated protocol to synthesize substituted piperidine derivatives using $CeCl_3.7H_2O$ in refluxing ethanol. This protocol follows principles of green chemistry such as use of easily available starting materials, reuse of solvent and catalyst and high atom economy. $CeCl_3.7H_2O$ is a stable and effective Lewis acid. The reaction gives fair yields of the desired products for all systems. In comparison to other reports, this method provides a quicker and much cleaner method to synthesize the target molecules with the added advantage of using a green catalyst. The solvent and the catalyst could be recycled at least twice without apparent decrease in yields.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding

This work did not receive funding from external sources.

Supplementary Information (SI)

The supplementary information gives the experimental details, physical constants, and ^{1}HNMR and^{13}CNMR data for all the synthesised functionalized piperidine derivatives.

Acknowledgements

The authors thank the Homi Bhabha Centre for Science Education for the use of laboratory facilities and the Tata Institute of Fundamental Research (TIFR), for providing the NMR spectra.

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Received on October 20, 2019