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$TiCl_2 \cdot 2H_2O$ catalyzed one-pot synthesis of highly functionalized tetrahydropiperidines and evaluation of their antimicrobial activities

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Abstract: One-pot condensation reaction of ethyl acetoacetate, various substituted benzaldehydes and anilines in the presence of $TiCl_2 \cdot 2H_2O$ yields highly functionalized tetrahydropiperidines. Atom economy, efficiency, and short reaction times are the advantages of the method, which is carried out under mild conditions using easily accessible and inexpensive chemicals. The antimicrobial activity of the synthesized products was evaluated against three Gram-positive and three Gram-negative bacteria, a yeast and a fungus strain using disc diffusion and minimum inhibitory concentration methods.

Keywords: antibacterial activity; multicomponent reaction; $TiCl_2 \cdot 2H_2O$; tetrahydropiperidine.

Introduction

In multicomponent reactions (MCRs), three or more different starting materials undergo a reaction to form diverse complex molecules in a one-pot strategy with reducing waste, good efficiency, high selectivity, time saving, and high safety [1–3]. Tetrahydropiperidine and their derivatives are an important class of heterocyclic molecules found in numerous natural products and biologically active compounds [4–9]. They have also shown biological properties such as antihypertensive [10], antibacterial [11], anti-inflammatory [12], and antimalarial activity [13]. Tetrahydropiperidines have also been utilized as useful synthetic precursors for the preparation of other compounds. Various methods have been developed for the synthesis of functionalized piperidines in the presence of catalysts such as L-proline/TFA [13], $InCl_3$ [14], 1-methyl-2-oxopyrrolidinium hydrogen sulfate ([Hpyro][HSO_4]) [15], tetrabutylammonium tribromide (TBATB) [7], $ZrOCl_2 \cdot 8H_2O$ [16], $Bi(NO_3)_3 \cdot 5H_2O$ [17], SPINOL-phosphoric acids [18], $BF_3 \cdot SiO_2$ [19], trityl chloride (Ph_3CCl) [20], $FeCl_3/SiO_2$ nanoparticles [21], cerium ammonium nitrate (CAN) [22], molecular iodine (I_2) [23], and picric acid [24]. Despite the large number of reported catalysts for the synthesis of functionalized piperidines, many of the methods suffer from disadvantages such as long reaction times, need for excess amounts of the reagent, low yields, use of toxic or expensive reagents, tedious work-up procedures, and high temperature conditions. Therefore, there is a need for alternative methods that avoids these problems. In continuation of our interest in developing protocols for the synthesis of heterocyclic compounds [25, 26], herein we report $TiCl_2 \cdot 2H_2O$ as a new catalyst for the fast, facile, and efficient synthesis of highly functionalized piperidine derivatives by the direct condensation of a variety of anilines with aryl aldehydes and ethyl acetoacetate under mild reaction conditions (Scheme 1).

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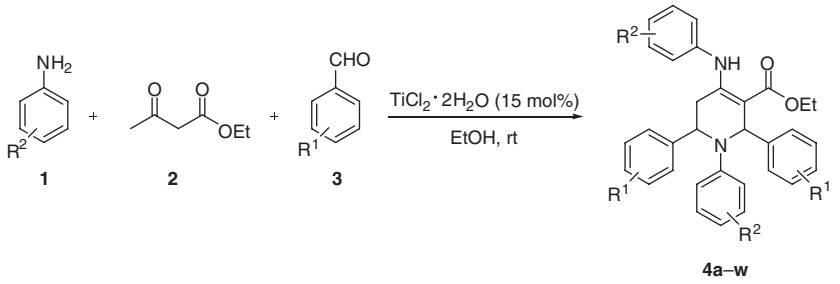
Results and discussion

Initially, in order to find an efficient catalyst, the model reaction of benzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol) in the presence of various potential catalysts in ethanol at ambient temperature was studied. The results are summarized in Table 1. As can be seen, the best result was obtained using $TiCl_2 \cdot 2H_2O$.

Then, the model reaction was optimized by using several solvents. The results presented in Table 2 show



Scheme 1 Synthesis of compounds **4a–w**. For definition of the substituents R^1 and R^2, see Table 3.

Table 1 Synthesis of piperidine **4a**[a] in the presence of various catalysts.

Entry	Catalyst (10 mol%)	Time (h)	Yield (%)
1	$Sr(NO_3).6H_2O$	24	10
2	NaH_2PO_4	24	Trace
3	$Al(NO_3)_3.9H_2O$	20	25
4	$(NH_4)_3PMo_{12}O_{40}.6H_2O$	20	40
5	$Co(NO_3)_3.6H_2O$	18	45
6	$IrCl_3.3H_2O$	12	62
7	$TiCl_2.2H_2O$	7	73

[a]Experimental conditions: benzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol) in ethanol (5 mL) at room temperature.

Table 2 The effect of different solvents and different amounts of $TiCl_2{\cdot}2H_2O$ on the yield of **4a** at room temperature.

Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)
1	Neat	15	4	47
2	MeOH	15	4	85
3	CH_3CN	15	8	76
4	EtOAc	15	12	40
5	H_2O	15	20	–
6	CH_2Cl_2	15	20	Trace
7	EtOH	15	4	90
8	EtOH	–	18	–
9	EtOH	5	10	55
10	EtOH	10	7	73
11	EtOH	20	4	88

that EtOH is the solvent of choice. Running the synthesis of model compound **4a** in the absence of solvent leads to a 47% yield at room temperature (Table 2, entry 1).

Different molar ratios of the catalyst were also investigated. The best result was obtained in the presence of 15 mol% $TiCl_2{\cdot}2H_2O$ in EtOH at room temperature (Table 2, entry 7). An increase in the amount of catalyst does not improve the yield and in its absence no product is obtained even after 18 h (Table 2, entries 8–11).

To explore the scope and substrate limitations of the reaction, various substituted benzaldehydes and anilines were allowed to react with ethyl acetoacetate under the optimized conditions. The results are summarized in Table 3. The method is efficient and superior in comparison with the reported literature preparations. Various derivatives were obtained in relatively high yields. The electron withdrawing or electron donating nature of the aryl group affects the reaction rate, but no clear substitution effect on the yield is observed. The structures of the synthesized products were identified by comparison of their spectroscopic data and melting points with those of literature reports. The structures of new compounds **4j** and **4s** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis data.

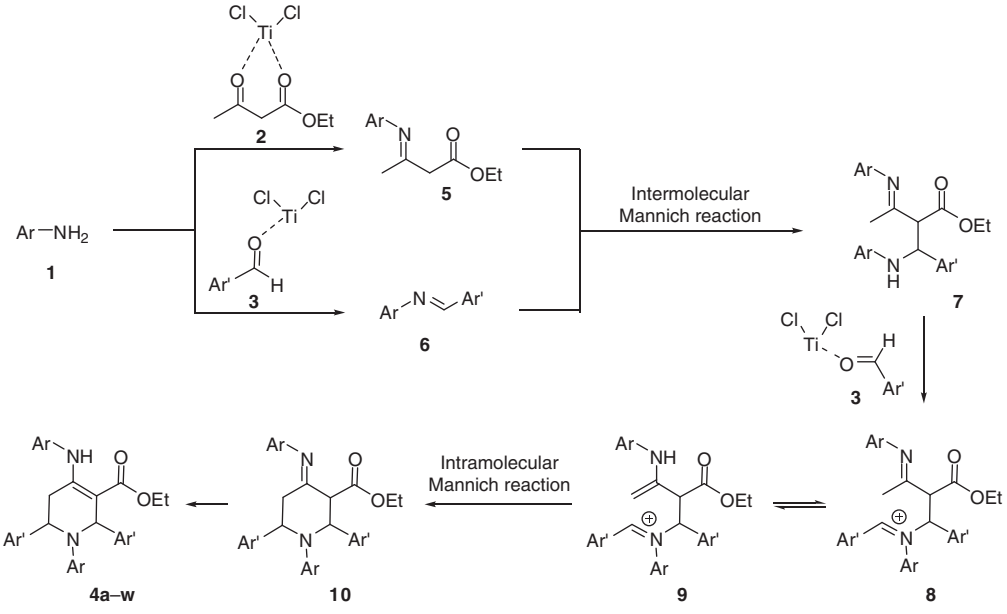
A plausible mechanism for the discussed synthesis is shown in Scheme 2. Initially, the reaction of arylamine **1** and ethyl acetoacetate **2** gives the β-enaminone **5** in the presence of $TiCl_2{\cdot}2H_2O$ [27]. In a similar way, condensation of arylamine **1** with arylaldehyde **3** generates the corresponding imine **6**. Then, the intermolecular Mannich reaction of β-enaminone **5** with the imine **6** activated by $TiCl_2{\cdot}2H_2O$ affords the intermediate product **7** [27]. The reaction of **7** with the second activated molecule of arylaldehyde produces the intermediate compound **8**. Then, **8** undergoes tautomerization to **9** which is stabilized by intramolecular hydrogen bond. Finally, the intramolecular Mannich-type reaction of **9** generates the intermediate product **10** which is a direct precursor to the final product **4a–w** [17].

The antimicrobial activity evaluations of selected compounds **4** against three Gram-positive containing *(Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus subtilis)* and three Gram-negative (*Klebsiella pneumonia*, *Escherichia coli*, and *Salmonella enterica*) bacteria, a yeast (*Candida albicans*), and a fungus (*Aspergillus niger*) strain are presented in Table 4. As can be seen, only a few compounds show antibacterial activity against the

Table 3 Synthesis of tetrahydropiperidines **4a–w** in the presence of $TiCl_2 \cdot 2H_2O$ at room temperature.

Entry	R^1	R^2	Time (h)	Lit. time (h)	Yield[a] (%)	Lit. yield (%)	Mp (°C)	Lit. mp (°C)	[Ref]
4a	H	H	8	20	84	81	169–171	175–176	[22]
4b	H	4-Cl	3.5	14	89	85	196–198	201–202	[14]
4c	H	4-Br	4	22	91	81	197–198	197–199	[22]
4d	H	3-I	5	20	89	75	170–172	170–172	[17]
4e	H	4-Me	4	24	90	86	197–198	196–198	[17]
4f	H	4-OMe	6	24	91	74	174–176	172–173	[17]
4g	4-Me	H	5	23	87	68	229–231	230–231	[22]
4h	4-F	H	5	20	89	83	205–207	204–208	[22]
4i	3-Me	H	6	23	84	74	153–154	155–157	[22]
4j	3-Me	4-Me	8	–	86	–	181–182	–	
4k	4-NO_2	H	6	18	87	80	249–251	247–250	[22]
4l	4-Me	4-Br	5.5	28	89	88	237–239	234–236	[22]
4m	4-Me	4-Cl	5	14	88	79	217–219	218–220	[14]
4n	4-Me	4-F	7	16	85	80	186–187	183–185	[14]
4o	4-Me	3-I	6	20	89	74	205–207	205–207	[17]
4p	4-Me	4-OMe	4	17	91	65	219–220	221–224	[22]
4q	4-Cl	4-Me	4.5	21	92	70	227–228	227–229	[14]
4r	4-Cl	4-F	4	18	89	84	223–224	219–222	[14]
4s	4-Cl	3-I	5	–	87	–	189–190	–	
4t	3-Cl	4-OMe	4	17	90	73	226–227	167–169	[22]
4u	4-OMe	4-Cl	4.5	21	90	84	183–185	180–181	[22]
4v	4-OMe	4-Br	7	21	88	76	184–186	184–186	[22]
4w	4-NO_2	3-I	5	14	75	77	139–141	140–142	[14]

[a]Isolated yields.



Scheme 2 A plausible mechanism for the synthesis of piperidines **4a–w**.

mentioned bacteria strains. Compound **4w** with nitro and iodo substituents displays the highest activity, while compounds separately substituted with either a nitro group or an iodine atom are devoid of activity.

Conclusions

A facile and efficient method for the synthesis of highly substituted piperidines was developed. Some of the

Table 4 Antibacterial activity of the synthesized piperidine derivatives and reference drugs.

Compound	*S. enterica*		*E. coli*	
	DD[a]	MIC[b]	DD	MIC
4q	11	750	–	–
4s	10	>1000	–	–
4t	9	NA	–	–
4w	12	750	13	500
Streptomycin (standard)	10	125	15	100
Rifampicin (standard)	10	150	12	125

Compounds with no sensitivity are not reported.
[a]Diffusion diameter (mm).
[b]Minimum inhibitory concentration (μg/mL).

synthesized products exhibit noticeable antibacterial activity.

Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. Melting points were recorded on an Electrothermal type 9300 apparatus. FT-IR spectra were recorded using KBr disks on an Avatar 370 FT-IR Thermo Nicolet spectrometer. ^{1}H NMR and ^{13}C NMR spectra were collected on a Bruker Avance 400 spectrometer. Mass spectra were obtained on a Varian Mat CH-7 spectrometer. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

General procedure for the preparation of piperidines 4a–w

A solution of aniline or substituted aniline (2 mmol), ethyl acetoacetate (1 mmol), $TiCl_2{\cdot}2H_2O$ (15 mol%) in 96% EtOH (5 mL) was stirred at room temperature. After 20 min, benzaldehyde or substituted benzaldehyde (2 mmol) was added and the mixture was stirred for the time indicated in Table 3. After the completion of the reaction as monitored by TLC using $CHCl_3$/MeOH (9:1) as eluent, the resulting solid was filtered off, washed with EtOH (2×20 mL) and crystallized from EtOH. The crude product found in the mother liquor was further purified by column chromatography using $CHCl_3$/MeOH (20:1) as eluent and then crystallized from EtOH. Products prepared previously are listed in Table 3.

Ethyl 2,6-di-m-tolyl-1-(p-tolyl)-4-(p-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4j) White solid; mp 181–182°C; IR (KBr): 3249, 3068, 2956, 2869, 1649, 1585, 1452, 1372, 1249, 1075 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (3H, t, J = 7.2 Hz, CH_3), 2.17 (3H, s, CH_3, at phenyl), 2.27 (3H, s, CH_3, at phenyl), 2.32 (6H, m, CH_3, at phenyl), 2.70 (1H, dd, J = 15.2, 2.2 Hz, C_5-H′), 2.83 (1H, dd, J = 15.2, 5.4 Hz, C_5-H″), 4.33 (1H, m, OCH_2), 4.47 (1H, m, OCH_2), 5.08 (1H, m, C_6-H), 6.15 (2H, m, ArH), 6.37 (1H, s, C_2-H), 6.45 (2H, m, ArH), 6.89 (3H, d, J = 10.5 Hz), 6.95 (2H, d, J = 7.6 Hz), 7.03–7.26 (7H, m, ArH), 10.19 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 20.5, 21.2, 21.7, 34.4, 56.2, 58.2, 60.1, 95.1, 113.5, 125.2, 125.5, 127.3, 127.6, 127.8, 128.7, 126.5, 127.2, 128.8, 129.3, 130.1, 135.2, 138.9, 139.4, 146.3, 154.4, 169.6; MS (EI, 70 eV): *m/z* 530 [M$^+$]. Anal. Calcd for $C_{36}H_{38}N_2O_2$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.40; H, 7.43; N, 5.34.

Ethyl 2,6-bis(4-chlorophenyl)-1-(3-iodophenyl)-4-((3-iodophenyl) amino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4s) White solid; mp 189–190°C; IR (KBr): 3234, 3069, 2956, 2875,1657, 1604, 1459, 1375, 1249, 1075 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (3H, t, J = 7.5 Hz, CH_3), 2.69 (1H, dd, J = 14.6, 2.7 Hz, C_5-H′), 2.82 (1H, dd, J = 14.6, 5.4 Hz, C_5-H″), 4.35 (1H, m, OCH_2), 4.47 (1H, m, OCH_2), 5.06 (1H, m, C_6-H), 6.26 (1H, s, C_2-H), 6.37–6.46 (4H, m, ArH), 6.55 (1H, s, ArH), 6.74 (2H, d, J = 7.6 Hz, ArH), 6.93–7.24 (9H, m, ArH), 10.29 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 33.9, 55.4, 59.1, 61.9, 99.2, 113.4, 117.4, 121.7, 123.8, 124.2, 125.4, 128.4, 128.8, 129.2, 129.6, 129.9, 130.2, 131.4, 131.7, 133.9, 134.7, 141.4, 142.5, 142.8, 147.9, 155.8, 168.9; MS (EI, 70 eV): *m/z* 793 [M$^+$]. Anal. Calcd for $C_{32}H_{26}Cl_2I_2N_2O_2$: C, 48.33; H, 3.30; N, 3.52. Found: C, 48.39; H, 3.21; N, 3.69.

Antimicrobial activity assays

Antimicrobial activity was determined against three Gram-positive bacteria (*S. epidermidis* ATCC 12228, *S. aureus* ATCC 29737, and *B. subtilis* ATCC 6633) and three Gram-negative bacteria (*S. enteriae* PTCC 1188, *E. coli* ATCC 10536, and *K. pneumonia* ATCC 10031), an yeast (*C. albicans* ATCC 10231), and a fungus (*A. niger* ATCC 16404). Antimicrobial activities of the samples were determined by disc diffusion method through determination of a diameter of inhibition zones [28]. Bacterial strains which were sensitive to the samples in the disc diffusion assay were chosen to study minimal inhibition concentration (MIC) using a micro-well dilution assay method [29]. Streptomycin and rifampicin for bacteria and nystatin for yeast were used as standard reference drugs under concentration conditions identical to that of test compounds.

References

[1] Brauch, S.; Van Berkel, S. S.; Westermann, B. Higher-order multicomponent reactions: beyond four reactants. *Chem. Soc. Rev.* **2013**, *42*, 4948–4962.
[2] Gu,Y. Multicomponent reactions in unconventional solvents: state of the art. *Green Chem.* **2012**, *14*, 2091–2128.
[3] Shaabani, S.; Shaabani, A.; Ng, S. W. One-pot synthesis of coumarin-3-carboxamides containing a triazole ring via an isocyanide-based six-component reaction. *ACS. Comb. Sci.* **2014**, *16*, 176–183.
[4] Marcus, B.; Pankaj, C.; Robert, H.; Gerhard, R.; Dieter, E. Asymmetric synthesis of tetrahydropyridines via an organocatalytic one-pot multicomponent michael/aza-Henry/cyclization triple domino reaction. *Org. Lett.* **2014**, *16*, 6012–6015.

[5] Mateeva, N. N.; Winfield, L. L.; Redda, K. K. The chemistry and pharmacology of tetrahydropyridines. *Curr. Med. Chem.* **2005**, *12*, 551–571.
[6] Duttwyler, S.; Lu, C.; Mercado, B. Q.; Bergman, R. G.; Ellman, J. A. Regio- and stereoselective 1,2-dihydropyridine alkylation/addition sequence for the synthesis of piperidines with quaternary centers. *Angew. Chem. Int. Ed.* **2014**, *53*, 3877–3880.
[7] Khan, A. T.; Lal, M.; Khan, M. M. Synthesis of highly functionalized piperidines by one-pot multicomponent reaction using tetrabutylammonium tribromide (TBATB). *Tetrahedron Lett.* **2010**, *51*, 4419–4424.
[8] Mohite, A. R.; Sultane, P. R.; Bhat, R. G. BF_3·Et_2O and trifluoroacetic acid/triethyl amine-mediated synthesis of functionalized piperidines. *Tetrahedron Lett.* **2012**, *53*, 30–35.
[9] Viegas, C.; Bolzani, J. V. S.; Furlan, M.; Barreiro, E. J.; Young, M. C. M.; Tomazela, D.; Eberlin, M. N. Further bioactive piperidine alkaloids from the flowers and green fruits of *Cassia spectabilis*. *J. Nat. Prod.* **2004**, *67*, 908–910.
[10] Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; et al. Synthèses et activités psychotropes de 3,4-diarylpipéridines. Corrélation structure-activité et recherche d'une activité antihypertensive. *Eur. J. Med. Chem.* **1991**, *26,* 19–32.
[11] Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S. Synthesis and antitumor activity of indolylpyrimidines: Marine natural product meridianin D analogues. *Bioorg. Med. Chem.* **2007**, *15*, 1206–1211.
[12] Ho, B.; Crider, A. M.; Stables, J. P. Synthesis and structure–activity relationships of potential anticonvulsants based on 2-piperidinecarboxylic acid and related pharmacophores. *Eur. J. Med. Chem.* **2001**, *36*, 265–286.
[13] Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. Organocatalyzed highly atom economic one pot synthesis of tetrahydropyridines as antimalarials. *Bioorg. Med. Chem.* **2009**, *17*, 625–633.
[14] Clarke, P. A.; Zaytzev, A. V.; Whitwood, A. C. Pot, atom and step economic (PASE) synthesis of highly functionalized piperidines: a five-component condensation. *Tetrahedron Lett.* **2007**, *48*, 5209–5212.
[15] Sajadikhah, S. S.; Hazeri, N.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Beigbabaei, A.; Lashkari, M. A one-pot multi-component synthesis of *N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates catalysed by oxalic acid dihydrate. *J. Chem. Res.* **2013**, *37*, 40–42.
[16] Mishra, S.; Ghosh, R. Efficient one-pot synthesis of functionalized piperidine scaffolds via $ZrOCl_2$·$8H_2O$ catalyzed tandem reactions of aromatic aldehydes with amines and acetoacetic esters. *Tetrahedron Lett.* **2011**, *52*, 2857–2861.
[17] Brahmachari, G.; Das, S. Bismuth nitrate-catalyzed multicomponent reaction for efficient and one-pot synthesis of densely functionalized piperidine scaffolds at room temperature. *Tetrahedron Lett.* **2012**, *53*, 1479–1484.
[18] Li, X.; Zhao, Y.; Qu, H.; Mao, Z.; Lin, X. Organocatalytic asymmetric multicomponent reactions of aromatic aldehydes and anilines with β-ketoesters: facile and atom-economical access to chiral tetrahydropyridines. *Chem. Commun.* **2013**, *49*, 1401.
[19] Ramachandran, R.; Jayanthi, S.; Jeong, Y. T. One-pot synthesis of highly diversified tetrahydropyridines by tandem condensation of aldehydes, amines, and β-ketoesters. *Tetrahedron* **2012**, *68*, 363–369.
[20] Sajadikhah, S. S.; Hazeri, N.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Willis, A. C. Trityl chloride as an efficient organic catalyst for one-pot, five-component and diastereoselective synthesis of highly substituted piperidines. *Res. Chem. Intermed.* **2014**, *40*, 723–736.
[21] Safaei-Ghomi, J.; Ziarati, A. An efficient $FeCl_3$/SiO_2 NPs as a reusable heterogeneous catalyzed five-component reactions of tetrahydropyridines under mild conditions. *J. Iran. Chem. Soc.* **2013**, *10*, 135–139.
[22] Wang, H. J.; Mo, L. P.; Zhang, Z. H. Cerium ammonium nitrate-catalyzed multicomponent reaction for efficient synthesis of functionalized tetrahydropyridines. *ACS. Comb. Sci.* **2011**, *13*, 181–185.
[23] Khan, A. T.; Khan, M. M.; Bannura, K. K. Iodine catalyzed one-pot five-component reactions for direct synthesis of densely functionalized piperidines. *Tetrahedron* **2010**, *66*, 7762–7772.
[24] Mukhopadhyay, C.; Rana, S.; Butcher, R. J.; Schmiedekamp, A. M. First report of syn isomers in the diastereoselective synthesis of highly functionalized piperidines catalysed by wet picric acid: factors influencing the syn-anti ratios. *Tetrahedron Lett.* **2011**, 52, 5835–5840.
[25] Eshghi, H.; Khojastehnezhad, A.; Moeinpour, F.; Bakavoli, M.; Seyedi, S. M.; Abbasi, M. Synthesis, characterization and first application of keggin-type heteropoly acids supported on silica coated $NiFe_2O_4$ as novel magnetically catalysts for the synthesis of tetrahydropyridines. *RSC Adv.* **2014**, *4*, 39782–39789.
[26] Rahimizadeh, M.; Seyedi, S. M.; Abbasi, M.; Eshghi, H.; Khojastehnezhad, A.; Moeinpour, F.; Bakavoli, M. Nanomagnetically modified ferric hydrogen sulfate ($NiFe_2O_4$@SiO_2-FHS): a reusable green catalyst for the synthesis of highly functionalized piperidine derivatives. *J. Iran. Chem. Soc.* **2015**, *12*, 839–844.
[27] Shaterian, H. R.; Azizi, K. Acidic ionic liquids catalyzed one-pot, pseudo five-component, and diastereoselective synthesis of highly functionalized piperidine derivatives. *J. Mol. Liqiuds* **2013**, *180*, 187–191.
[28] Manjula, M. K.; Rai, K. M. L.; Gaonkar, S. L.; Raveesha, K. A.; Satish, S. Synthesis of new series of 5,6-dihydro-4 H-1,2-oxazines via hetero Diels-Alder reaction and evaluation of antimicrobial activity. *Eur. J. Med. Chem.* **2009**, *44*, 280–288.
[29] Oroojalian, F.; Kasra-Kermanshahi, R.; Azizi, M.; Bassami, M. R. Phytochemical composition of the essential oils from three Apiaceae species and their antibacterial effects on food-borne pathogens. *Food Chem.* **2010**, *120*, 765–770.