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REGULAR ARTICLE

Green catalyst-free one-pot synthesis of novel tetrahydropyridine-3-carboxamides by microwave-assisted approach

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Abstract. A clean, facile and catalyst-free four-component domino reaction of aromatic aldehyde, ethyl cyanoacetate, acetoacetanilide and ammonium acetate in ethanol under microwave irradiation (MWI) conditions is described. Eleven novel and diverse tetrahydropyridine-3-carboxamide derivatives were synthesized in excellent yields (91–97%) using this green protocol. The significant benefits of this method are simple handling, ethanol as solvent, catalyst-free reaction under mild conditions, short reaction times (<10 min) and excellent product yields. Easy workup procedure and simple purification technique of the target molecules evade column chromatography.

Keywords. Microwave-assisted; multicomponent reaction; green synthesis; one-pot protocol; tetrahydropyridine-3-carboxamides.

1. Introduction

Multicomponent reactions (MCRs) facilitate the fusion of three or more reactants in a single step to create a single product selectively with atom economy.[1,2] MCRs have gradually become vital for the synthesis of biologically active compounds, due to their green characteristics, such as atomic economy, lesser consumption of solvents and reduced chemical waste, when compared to multistep reactions.[3,4] Further, MCRs exhibit many benefits such as easy handling, shorter reaction times, and higher yields and no requirement for purification. Thus, they are linked to green chemistry toolbox.[5–7] Hence, chemists are increasingly becoming interested in developing novel and more efficient MCRs, for drug discovery and combinational chemistry.

The microwave irradiation (MWI) technique is known to promote selectivity that differs from the conventional methods and also it enhances differed selectivity between competitive reactions.[8,9] MWI is an alternative source of heat than the traditional sources in organic chemistry.[10] Interestingly, MWI dielectric heating is dependent on the polarity of the reaction medium to absorb microwave energy and then convert into heat.[11] In addition, the use of an MWI for organic synthesis in sealed vessel offers reduced energy consumption and reaction in shorter time.[10–12] It displays several advantages such as higher yields, chemo-selectivity, energy-saving, low cost and improved reaction rate compared to conventional methods.[11–13]

Heterocyclic compounds are an important class of molecules in organic chemistry, due to their fascinating applications in various pharmaceutical and agricultural arenas.[14,15] About 80% of commercialized drugs possess heterocyclic components.[18] The nitrogen-containing moieties, in particular, are the backbone to several natural products and biologically active compounds.[16,17] Therefore, the synthesis of these compounds has been on the forefront for combinational chemistry and drug discovery.[16–18] Most importantly, these compounds can be synthesized under rapid and environmentally-friendly synthetic procedures.[19] Pyridines and its analogues having nitrogen in a six-membered ring, show good activities

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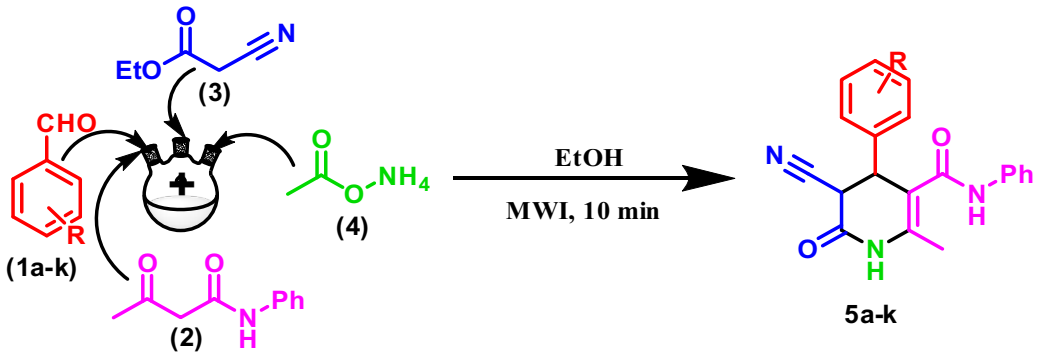


Scheme 1. Four-component green synthetic route for tetrahydropyridine-3-carboxamides.

Table 1. Optimization of various catalysts for the synthesis of tetrahydropyridine-3-carboxamides (**5a**)[a].

				Conventional		MWI	
Entry	Catalyst	Solvent	Condition	Time (h)	Yield [b] (%)	Time (h)	Yield [b] (%)
1	–	–	R.T/Heat	6.0	–	6.0	–
2	–	–	R.T/Heat	6.0	–	6.0	–
3	$FeCl_3$	EtOH	R.T	5.0	Trace	4.0	Trace
4	$ZnCl_2$	EtOH	R.T	5.0	Trace	5.0	Trace
5	HCOOH	EtOH	R.T	4.0	Trace	3.5	Trace
6	AcOH	EtOH	R.T	4.0	Trace	4.0	Trace
7	K_2CO_3	EtOH	R.T	3.0	39	1.0	54
8	piperidine	EtOH	R.T	3.5	31	1.0	41
9	TEA	EtOH	R.T	4.0	22	1.0	42
10	Urea	EtOH	R.T	3.0	29	1.0	59
11	$NaHCO_3$	EtOH	R.T	3.5	19	1.0	48
12	HBF_4	EtOH	R.T	4.0	–	1.0	–
13	[Hbim]Cl	EtOH	R.T	4.0	–	1.0	–
14	**–**	EtOH	R.T	**4.0**	**63**	**0.1**	**97**

[a]2-methoxy benzaldehyde (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.0 mmol) and ethyl cyanoacetate (1 mmol) in 5 mL EtOH in the presence of various catalysts.
[b]Isolated yield of the pure product.

with applications in biological and pharmaceutical fields.[20] They are also amongst the scaffolds that exhibit anti-proliferative,[21] antifungal,[22] antipsychotic,[23] anti-viral,[24] anti-mitotic,[25] anti-leishmanial,[26] anti-oxidant[27] and anti-malarial[28] properties. The presence of pyridine moieties in amrinone and milrinone drugs, as cardiotonic agents used for heart failure treatment, is noteworthy.[29] Furthermore, tetrahydropyridines were reported to possess anti-inflammatory properties and are identified as non-nucleoside reverse transcriptase inhibitors of human HIV.[30,31] Consequently, great scope exists in the development of newer and efficient synthetic approaches for diverse pyridine scaffolds of biologically active moieties.

In continuance of our research work on novel heterocyclic molecules, we have previously reported new protocols for various heterocyclic scaffolds, and many of which have displayed good biological activities.[32–35] We have also synthesized a series of different heterocyclic molecules *via* MCRs and by using several green technologies.[36–40] With the aim to afford the novel molecules of tetrahydropyridine-3-carboxamide derivatives, a green protocol of fusion of four components in one-pot is designed using EtOH solvent under MWI conditions. To the best of our knowledge, a catalyst-free, one-pot multicomponent reaction of acetoacetanilide, ethyl cyanoacetate, ammonium acetate and aromatic aldehydes has not yet been reported.

Table 2. The influence of different solvents on the synthesis of tetrahydropyridine-3-carboxamide[b].

Entry	Solvent	Time (min)	Yield (%)
1	DMF	60	38
2	THF	60	45
3	dioxane	60	38
4	MeCN	60	61
5	hexane	120	–
6	toulene	120	–
7	MeOH	45	76
8	EG	25	80
9	Glycerol	20	75
10	**EtOH**	**10**	**97**
11	H_2O	30	81

[a]2-methoxy benzaldehyde (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.0 mmol) and ethyl cyanoacetate (1 mmol) in the presence of various solvents.
[b]Isolated yield of the pure product.

2. Experimental

2.1 *General process for the preparation of tetrahydropyridine-3-carboxamides*

The mixture of aromatic aldehyde (1.0 mmol), acetoacetanilide (1.0 mmol), ethyl cyanoacetate (1.0 mmol) and ammonium acetate (1.0 mmol) in 5.0 mL EtOH was irradiated in a microwave vessel. After 5 min MWI at 50 °C, while reaction completion was monitored by TLC (eluent n-hexane: ethyl acetate 3:2 v/v), the crude product was collected by vacuum filtration. It was washed with water (5 mL) followed by ethanol, till a clear filtrate is observed. The product was recrystallized in ethanol if necessary, to obtain targeted pure product (Scheme 1). Structures of all synthesized compounds were confirmed based on the spectra analysis (^{1}H-NMR, ^{15}N-NMR, ^{13}C-NMR and HRMS). All spectral characterization data and instrumental details are incorporated in the Supplementary Information (SI-1).

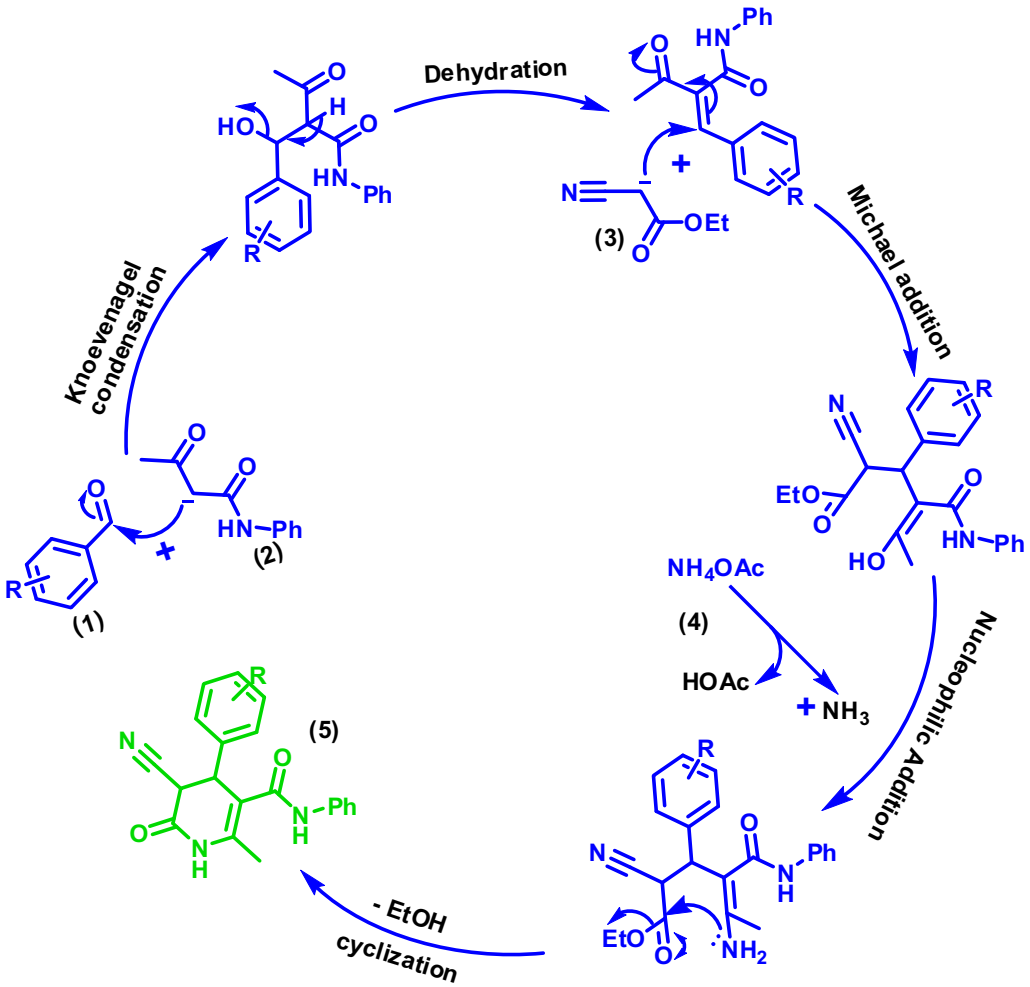
3. Results and Discussion

To accomplish appropriate conditions for the preparation of poly-substituted tetrahydropyridine-3-carboxamide, initially, different reaction conditions were examined. 2-methoxy benzaldehyde (1.0 mmol), acetoacetanilide (1.0 mmol), ammonium acetate (1.0 mmol) and ethyl cyanoacetate (1.0 mmol) were mixed as a typical reaction under conventional or microwave methods. The trail reaction conducted in the absence of any catalyst and any solvent systems at R.T. and heating conditions gave no anticipated product even after 6 h by both methods. The reaction was performed by evaluating the catalysts in ethanol solvent system, using $FeCl_3$, $ZnCl_2$, HCOOH and AcOH as acidic nature catalysts, offered trace yields after prolonged reaction time. Under the conventional method, use of various basic catalysts like K_2CO_3, TEA, urea, piperidine and $NaHCO_3$ at R.T. in EtOH solvent media revealed low reaction yields, but MWI gave the moderate yield in 1 h. No desired product was attained by the using of ionic liquids (HBF_4 and [Hbim]Cl) as a catalyst in both conditions even after 4 h. Remarkably the model reaction revealed excellent product yields (97%) within 10 min reaction time under catalyst-free, in EtOH by MWI (Table 1). MWI produces internal heating through coupling the MWI energy with

Table 3. MW-assisted synthesis of tetrahydropyridine derivatives under catalyst-free conditions.

Entry	R	Product[b]	Yield[c] (%)	M.p. °C	Lit. M.p. °C
1	2-OMe	**5a**	97	119-121	–
2	2,4-Cl	**5b**	95	136-137	–
3	3,4,5-OMe	**5c**	91	183-184	–
4	2-Cl,6-F	**5d**	94	200-201	–
5	2-thionyl	**5e**	91	197-198	–
6	4-OH	**5f**	94	239-241	–
7	2-CF_3	**5g**	96	176–177	–
8	2-Me	**5h**	97	246–248	–
9	2,4,5-Me	**5i**	91	221-223	–
10	3-Cl	**5j**	96	190-192	–
11	2,5-OMe	**5k**	97	239-241	–

[a]Aryl aldehyde (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.0 mmol) and ethyl cyanoacetate (1 mmol) in 5 mL EtOH under MW irradiation.
[b]The products were characterized by ^{1}H-NMR, ^{15}N-NMR, ^{13}C-NMR and HRMS analysis.
[c]Isolated yield of the pure product.nnn.



Scheme 2. Probable mechanism for the formation of tetrahydropyridine-3-carboxamide.

reactants in the reaction. The efficiency of such energy and heat dispersal is a function of the dielectric properties of the reactants and solvent. Hence, the molecules with higher dielectric constant values absorb MW energy more efficiently, while reagents with lower polarity or the crystalline materials absorb less.

Based on the positive results summarized in Table 1, the scope of various polar protic, polar aprotic and non-polar solvents in improving the reaction yields was assessed. DMF, THF, dioxane and MeCN gave moderate yields of the desired target molecule, but after relatively prolonged reaction time than with EtOH. In hexane and toluene, no desired product was obtained. MeOH, ethylene glycol (EG), Glycerol, EtOH and H_2O afforded excellent yields in short reaction time. These screening investigations proved EtOH as the best solvent, in terms of the product yield (97%) and reaction time (<10 min) (Table 2). This might be due to the theory that polar solvent couple with the MWI hence generating more heat during the reaction progress. It was noteworthy to mention that the EtOH proved ideal solvent with the MWI, in selective formation of tetrahydropyridine derivative.

After optimization of the reaction conditions, to expand the scope of this protocol, mostly in respect to library creation, it was screened by using acetoacetanilide, ethyl cyanoacetate, and ammonium acetate and diversity of functionalized aldehydes in the presence of EtOH solvent system under MWI conditions (Table 3). The positioning of the substituents and electronic effects on the phenyl ring did not show any noticeable effects in terms of product yields and the reaction conditions. Irrespective of nature of electron-withdrawing or donating substituents or at *para-, ortho- or meta-* positions on the aldehydes, all the reactions offered outstanding results (91–97%).

The probable mechanism for the formation of tetrahydropyridines, based on the experimental results

are illustrated in Scheme 2. The initial reaction involves the Knoevenagel condensation reaction between an aryl aldehyde (1) and acetoacetanilide (2). Thereafter, upon water removal, Michael addition reaction occurs with active ethyl cyan acetate (3), resulting in the formation of the intermediate. Its reactive ketone functional group being attacked by ammonium acetate (4), amino substitution occurs, *via* nucleophilic addition. The amidation reaction takes place between the amino group and ester, prior to the ring closure to give the final desired product, tetrahydropyridine (5).

4. Conclusions

In summary, we have optimised the MWI facilitated green reaction conditions for the design of eleven novel tetrahydropyridine molecules from the one-pot, four-component fusion. The significant benefits of the protocol are environmentally benignness, simple handling, less toxic, fast reaction, higher yields, evading column chromatography and mild reaction conditions.

Supplementary Information (SI)

All instrumental, product characterization data and spectral information is available at www.ias.ac.in/chemsci.

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