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PEG-400 mediated and microwave assisted one pot three-component coupling reactions: Expedient and rapid synthesis of Hantzsch 1,4-dihydropyridines devoid of use of catalyst

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ABSTRACT

Current study deals with three-component coupling reaction of aldehyde, 1,3-diketone or β -ketoester and ammonia in poly(ethylene glycol)-400, the US-FDA approved novel reaction media using microwave irradiation (MWI). A series of 1,4-DHPs were prepared within 1-5min using PEG-400 as a solvent without using any catalyst, gives 85-95% yields. No marginal changes in the yields were observed at high microwave power and at high temperature. Moreover, PEG-400 can be recovered and reused effectively up to five runs without significant loss of activity.

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KEYWORDS

PEG-400;
MWI;
Multi-component reaction;
Without catalyst.

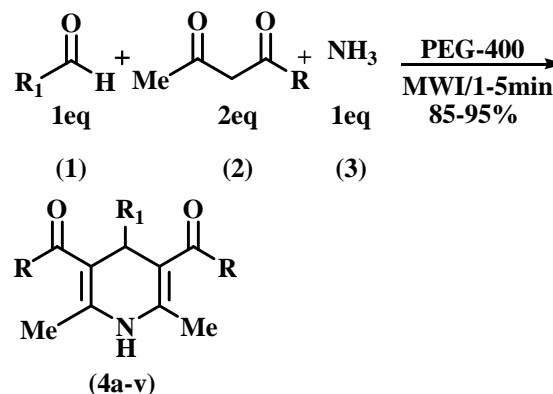
INTRODUCTION

Dihydropyridines are the important class of organic compounds in view of its ample of application in the pharmaceuticals^[1,3]. Arthur Hantzsch in 1882^[2] first reported the classical synthesis of 1,4-dihydropyridines (1,4-DHPs) which involves one pot three-component coupling reaction of 1 equivalent of alkyl or aryl aldehyde, 2 equivalents of β -ketoester and 1 equivalent of ammonia at reflux temperature using either acetic acid or ethanol as a solvent. However, the yield of 1,4-DHPs are generally low. Hence numerous methodologies with improved reaction conditions have been documented^[3]. Many of these still suffer some serious drawbacks such as unsatisfactory yields, tedious work-up procedure,

occurrence of side reactions including aromatization, economically non-viable, long reaction rate, high reaction temperature etc.

To overcome these problems, numerous modifications attempted including new Lewis acid catalyst, Zn{L-proline}₂^[4] under microwave condition. The catalyst is also recycled up to five runs but it appreciably loss the catalytic activity for the next successive runs and ultimately yield loss were observed. 1,4-DHPs were also synthesized by using water-ethanol solvent^[5] system using MWI, but this process fails at high microwave power, because reaction mixture is rapidly heated at high microwave power leading to solvent evaporation and hence precipitation of the reaction mixture were observed. The synthesis of 1,4-DHPs is also reported

in room temperature ionic liquids^[6] but the rate of reaction is sluggish than the microwave counterparts. Of all these methodologies, the ionic liquid medium is the sole protocol which allows the recycling of the solvent. There is despite the fact that, unlike several of 'neoteric solvent' like ionic liquids (ILs) where toxicity and environmental burden data are for the most part unknown while complete toxicity profiles are available for a range of polyethylene glycol (PEG) molecular weights and indeed, many are already approved for internal consumption by US-FDA^[7]. Moreover, the vapor density for low molecular weight PEG is greater than 1 and this is consistent with the industry standard for selection of alternative solvents to Volatile organic chemicals (VOCs)^[8]. In short, in viewing the benignity and superiority of PEG as a solvent over ionic liquids and other reported protocols for the synthesis of 1,4-DHPs, herein we disclose our findings by using PEG-400 as a recyclable solvent for the rapid microwave assisted multicomponent reaction (MCR) i.e. synthesis of 1,4-DHPs without using acid catalyst. (SCHEME 1) To our best knowledge this is the first report of multicomponent reaction which amalgamate the non-conventional heating technique and use of PEG-400, US-FDA's GRAS (Generally recognize as safe) list solvent.



SCHEME 1

RESULTS AND DISCUSSION

From the very beginning, the experiment was carried out with 1 eq of salicylaldehyde (Entry 6; TABLE 1), 2 eq of methyl acetoacetate, and 1 eq of ammonia in 10mL of PEG-400. Since all three substrates were taken in to PEG-400 and were subjected to microwave irradiation at 200W(80°C) using monomode open-vessel, TLC was taken after 1min, to our surprise that the reaction was found to complete with 95% yields, while conventionally it takes 30min to complete with poor yield(82%). Our second experiment with 4-

TABLE 1 : Synthesis of 1,4-DHPs by conventional heating and under microwave irradiation using 200W power at 80°C, using PEG-400 as a solvent without using acid catalyst

Entry	Aldehyde(R ₁)	R	Products	Microwave irradiation		Conventional heating		Ref
				Time(min)	Yield(%)	Time(h)	Yield(%)	
1	H	OMe	4a	2	92	1	75	-
2	C ₆ H ₅	OMe	4b	2	91	2.5	83	[6]
3	2-NO ₂ -C ₆ H ₄	OMe	4c	5	87	2	73	-
4	3-NO ₂ -C ₆ H ₄	OMe	4d	5	90	3.5	75	[6]
5	4-F-C ₆ H ₄	OMe	4e	3	93	3	79	-
6	2-OH-C ₆ H ₄	OMe	4f	1	95	0.5	82	-
7	2-Cl-C ₆ H ₄	OMe	4g	2	89	3	71	-
8	3-OCH ₃	OMe	4h	4	91	4	78	-
9	Cinnamaldehyde	OMe	4i	5	94	4.5	72	-
10	4-N,N-(Me) ₂ C ₆ H ₄	OMe	4j	5	85	8	70	-
11	Furfural	OMe	4k	3	95	1	85	[6]
12	H	OEt	4l	2	93	1.5	73	-
13	C ₆ H ₅	OEt	4m	2	93	1	80	[6]
14	3-NO ₂ -C ₆ H ₄	OEt	4n	4	89	2	75	[6]
15	2-Cl-C ₆ H ₄	OEt	4o	3	92	3	80	-
16	2-OH-C ₆ H ₄	OEt	4p	1	95	0.5	80	-
17	4-OCH ₃ -C ₆ H ₄	OEt	4q	5	90	4	74	-
18	9-anthraldehyde	OEt	4r	5	85	10	60	-
19	Cinnamaldehyde	OEt	4s	4	90	6	69	-
20	4-F-C ₆ H ₄	OEt	4t	2	91	4	81	-
21	2-Cl-C ₆ H ₄	Me	4u	3	90	3.5	78	-
22	2-OH-C ₆ H ₄	Me	4v	2	91	1.5	80	-

^aConventional heating refers the heating in ethanol

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N,N-dimethyl benzaldehyde(Entry 10; TABLE 1), the reaction was monitored at 2min time interval, it was furnished within 5min with 85% yields while conventionally the yield was found to be only 70% after 8h refluxing. Our third experiment with furfural(Entry 11; TABLE 1), the reaction was found to finish within 3min with 95% yields. This experiment proved that acid sensitive aldehyde, of course heterocyclic aldehyde is also appropriate under this solvent condition. In order to confirm the versatility of reaction, we bought ethyl acetoacetate as a source of β -ketoester with polyaromatic aldehyde i.e. 9-anthraldehyde(Entry 18; TABLE 1), the reaction was found to complete within 5min with 85% yields, while conventionally only 60% yields were obtained. The substrates were found to be unreacted after long refluxing in ethanol. Our second substrate with ethyl acetoacetate was cinnamaldehyde(Entry 19; TABLE 1), the reaction was finished within 4min with 90% yields while conventionally it takes 6h to complete(Yield 69%). In order to further broaden the scope of this protocol, we used acetyl acetone as a source of 1,3-diketone with 2-chloro benzaldehyde (Entry 21; TABLE 1) and salicylaldehyde(Entry 22; TABLE 1). Both the reactions were furnished within 3min and 2min with 90% and 91% yields respectively while conventionally yields were low. Spurred by the findings with above mentioned experiments, we carried out more experiments of TABLE 1. Overall, all these reactions proceed within short time than the conventional heating, with moderate to high yields.

Effect of microwave power

Effect of microwave power play a pivotal role in microwave assisted organic synthesis(MAOS). Microwave effects caused by the uniqueness of the microwave dielectric heating mechanism. This effect is termed as "specific microwave effect", and such can not be achieved or duplicated by conventional heating. The efficiency of "microwave flash heating" not only reduces

chemical reaction times from hrs to min but it is also known to reduce side reactions, increase yields and improved reproducibility of temperature. In order to check the effect of microwave power, we carried out five experiments at high microwave power i.e. 400W and 500W at two different temperatures i.e. 80°C and 150°C. The results are summarized in TABLE 2. There were no significant changes in the overall yields of the products were observed for 400W and 500W at 80°C. While at 150°C, partial yield loss was observed. From these experiments, we conclude that there were no significant decomposition of substrates or products were observed at high temperature and at high microwave power. And also due to high vapour pressure of PEG-400, even though the reaction mixture is rapidly heated at 400W or 500W, no solvent evaporation takes place. While in case of conventional solvents (i.e. ethanol or acetic acid) rapid heating of the reaction medium causes evaporation of solvent in open-vessel microwave and which may lead to precipitation. Moreover, PEG has been found to be stable to acidic or basic promoters and also at high temperature. Furthermore, it might be assume that high polarity of PEG-400 leads to high loss-factor value which will indicate the efficient absorption of microwave and consequently for rapid heating.

Recyclability study

The reusability of PEG-400 was carried out at 80°C and 200W power. In order to evaluate the recyclability of PEG-400, we carried out three different experiments with different substrates up to five runs (TABLE 3). After the initial experimentation of entry 2; TABLE 3, the reaction mixture was kept overnight, solid mass was obtained. PEG-400 was decanted and the product was collected. Substrates for the next run were charged into the resulting mother liquor and was subjected to microwave irradiation, we get 89% yield for the second run. By employing recycling procedure as mentioned above, the yields were found to be 88, 88 and 87% for the

TABLE 2 : Synthesis of 1,4-DHPs at high microwave power and at two different temperatures using PEG-400 as a solvent

Entry	Microwave irradiation at 80°C				Microwave irradiation at 150°C			
	Power(W)/ time(min)	Yield (%)	Power(W)/ time(min)	Yield (%)	Power(W)/ Time(min)	Yield (%)	Power(W)/ Time(min)	Yield (%)
7	400/2	87	500/2	86	400/2	87	500/2	83
11	400/3	93	500/3	92	400/3	90	500/3	85
12	400/2	92	500/2	92	400/2	90	500/2	87
13	400/2	89	500/2	88	400/2	88	500/2	84
14	400/3	89	500/3	88	400/3	87	500/3	86

^bEntry referrers according to reactions of SCHEME 1 and by using substrates from TABLE 1

TABLE 3 : Recyclability of PEG-400 with different substrates

Entry	Number of runs	MWI(200W) at 80°C	
		Time(min)	Yield(%)
2	2 nd run	2	89
2	3 rd run	2	88
2	4 th run	2	88
2	5 th run	2	87
20	2 nd run	2	89
20	3 rd run	2	89
20	4 th run	2	88
20	5 th run	2	87
22	2 nd run	3	90
22	3 rd run	3	89
22	4 th run	3	88
22	5 th run	3	88

^cEntry referrers according to reactions of Scheme 1 and by using substrates from TABLE 1

next successive runs. Similar procedure for recyclability was followed for Entry 20; TABLE 3. We get 89, 89, 88 and 87% yields for second, third, fourth and fifth run respectively. Moreover, the recyclability of PEG-400 was also studied for three component reactions of acetyl acetone, salicylaldehyde and ammonia(Entry 22, TABLE 3). Second, third, fourth and fifth run gives 90, 89, 88 and 88% yields respectively. The findings revealed that, PEG-400 can be recycled up to five runs without any remarkable yield loss. This method may represent a valuable alternative solvent in classical Hantzsch synthesis. In fact, current protocol is the unique protocol for the synthesis of 1,4-DHPs by blending of non-classical heating technique and banning the use of VOCs as a reaction medium.

CONCLUSION

In conclusion, the distinguishable features of this procedure are simple experimental process, rapid synthesis due to microwave heating, mild reaction condition, use of US-FDA's GRAS list solvent, harmless to environment by avoiding the use of VOCs, avoidance of acid catalyst, simplicity in operation, improved yields and accelerate the reaction rate, cleaner reaction profile, cheaper reaction media than ionic liquids i.e. [Bmin][BF₄] and [Bmin][PF₆], reusability of PEG-400 and superior to ionic liquids in terms of safety, toxicity and environmental risk which make it convenient, economic and user friendly process for the synthesis of calcium channel blockers 1,4-DHPs analogous.

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