One-Pot Synthesis of 1, 4-Dihydropyridines in PEG Under Catalyst-Free Conditions

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Abstract—A simple, inexpensive, and efficient one-pot synthesis of 1,4-dihydropyridine via Hantzsch reaction was achieved in good to excellent yields under catalyst free conditions by using PEG400 as solvent. In this reaction, PEG-400 was used as the solvent, which has such advantages: absolutely nontoxic, inexpensive, thermally stable, recoverable and easy to dispose in the reaction. And the corresponding products: 1,4-Dihydropyridine derivatives are very important in organic chemistry and medicine industry, by the using of PEG, the yields of the reaction were all very high(most above 95%). Finally, as to the inexpensive of PEG-400 and the high yields of the reaction, also because of the easy-treated procedures, this kind of reaction could be easier to produce in industrial. So, Polyethylene glycol offers a convenient, inexpensive, non-ionic liquid, non-toxic and recyclable reactions .

Keywords-1,4-Dihydropyridines, Hantzsch reaction, Multicomponent synthesis, PEG400, Catalyst free.

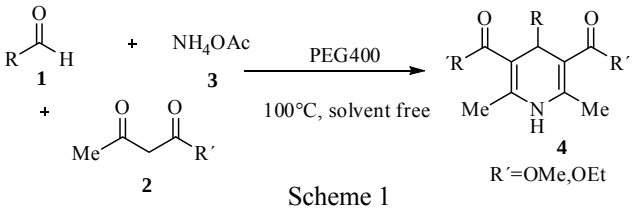
I. INTRODUCTION

1,4-Dihydopyridines (1,4-DHPs) have received considerable attention because of their significant biological activitie.[1] The well-known 1,4-DHPs antagonists are among the most widely used drugs for cardiovascular diseases.[2] And these simple heterocyclic scaffolds have also been found possessing a wide range of other pharmacological activities[3,4] and playing important role in chemical delivery systems.[5] As several different strategies are presently available for the synthesis of 1,4-DHPs, multicomponent reactions are recognized as the most powerful and facile tactic in term of providing structurally diverse 1,4-DHPs.[6] The most classical multicomponent synthesis of 1,4-DHPs involves the one-pot condensation of an aldehyde, ethyl acetoacetate and ammonia in either acetic acid or refluxing alcohol. However, yields of 1,4-DHPs obtained from Hantzsch method are generally low in most cases, particularly when aliphatic and unsaturated aldehydes were used. Although numerous modified methods have been reported,[7] many of them suffer from drawbacks such as harsh reaction conditions, low yield of products, expensive catalyst, cumbersome workup procedures or long reaction time. Therefore, it is still desirable to develop efficient catalyst system for the one-pot synthesis of 1,4-dihydropyridines, better in the manner of mild conditions with recyclable resources as well as good tolerance to acid-sensitive functional groups.

PEG and its monomethyl ethers are inexpensive, thermally stable, recoverable and nontoxic media for a broad range of different reactions,[8-9] However, this kind of environmentally benign media have not been yet used for the synthesis of 1,4-DHPs via Hantzsch reaction.

II. EXPERIMENT

In continuation of our interest on PEG organic reactions, we wish to report herein the one-pot synthesis of 1,4-Dihydopyridines by Hantzsch reaction using various aldehydes, ethyl acetoacetate and ammonium acetate in the presence of PEG-400 under catalyst-free conditions (Scheme 1).



Scheme 1

In a beginning, the reaction of benzaldehyde, ethyl acetoacetate and ammonium acetate in a 1 : 2 :1 ratio was performed by stirring in 0.4 g PEG-600. The product was obtained by recrystallization of the crude product from anhydrous ethanol after reaction time of 10 h, and provided the yield of 60%. Several kinds of PEGs were then investigated for this model reaction, and the corresponding results were showed in Table I. It was found that PEG-400 was the best media for the reaction.

TABLE I.. Effect of different kinds of PEGa

Entry	PEG	Time/h	Yield(%)[b]
1	PEG-200	4	75
2	PEG-400	4	93
3	PEG-600	4	82
4	PEG-800	4	80
5	PEG-1000	4	76
6	PEG-2000	4	70

[a] Reaction conditions: benzaldehyde (1 mmol), NH_4OAc (2 mmol), ethylacetoacetate (2 mmol), PEG-400 (0.8 g), at 100 ºC.

[b] Isolated yields.

With the optimized experimental conditions, various substituted aldehydes containing either electron donating or withdrawing groups were smoothly converted to corresponding 1,4-DHPs with excellent yields in the presence of PEG-400. The results are summarized in Table II. Both ethylacetoacetate and methylacetoacetate also smoothly reacted with aldehydes and ammonium acetate under standard reaction conditions. However, the yields of the products 4e and 4m are slightly lower than other entries probably due to thee steric hindrance effect of the ortho-OH in the structure. All the products were characterized by comparing their physical and spectral (IR and 1HNMR) data with corresponding data reported in literature.[7]

TABLE II PEG-promoted synthesis of 1,4-dihydropyrimidinones under solvent-free conditions[a]

Entry	Product	R	R'	Time/h	Yield(%)[b]
1	**4a**	C_6H_5	OMe	4	95
2	**4b**	$4\text{-}CH_3OC_6H_4$	OMe	4	99
3	**4c**	$4\text{-}(CH_3)_2NC_6H_4$	OMe	4	95
4	**4d**	$4\text{-}HOC_6H_4$	OMe	3.5	97
5	**4e**	$2\text{-}HOC_6H_4$	OMe	4	83
6	**4f**	$4\text{-}ClC_6H_4$	OMe	3.5	93
7	**4g**	$4\text{-}NO_2C_6H_4$	OMe	3.5	93
8	**4h**	2-Furyl	OMe	0.5	99
9	**4i**	C_6H_5	OEt	4	93
10	**4j**	$4\text{-}CH_3OC_6H_4$	OEt	4	98
11	**4k**	$4\text{-}(CH_3)_2NC_6H_4$	OEt	4	96
12	**4l**	$4\text{-}HOC_6H_4$	OEt	3.5	95
13	**4m**	$2\text{-}HOC_6H_4$	OEt	4	84
14	**4n**	$4\text{-}ClC_6H_4$	OEt	3.5	92
15	**4o**	$4\text{-}NO_2C_6H_4$	OEt	3.5	91
16	**4p**	2-Furyl	OEt	0.5	98

[a] Reaction conditions: aldehyde (1mmol), NH_4OAc (3 mmol), β-dicarbonyl compound (2 mmol), PEG-400 (0.8 g) at 100 ºC.

[b] Isolated yields.

To investigate the effect of PEG, the model reaction was then performed by heating at 100 ºC for 2 h in the absence of PEG. It was found that no reaction occurred, indicating that PEG was an essential promoter for this reaction. In addition, we also studied the PEG promoted Hantzsch condensation of benzaldehyde, ammonium acetate and ethyl acetoacetate in the presence of various solvents, such as water, acetonitrile, and toluene (1 ml). These results are presented in Table III. According to these results, it is clear that in the presence of these additional

solvents, the yields of 1,4-dihydropyrimidine derivatives were found comparatively lower.

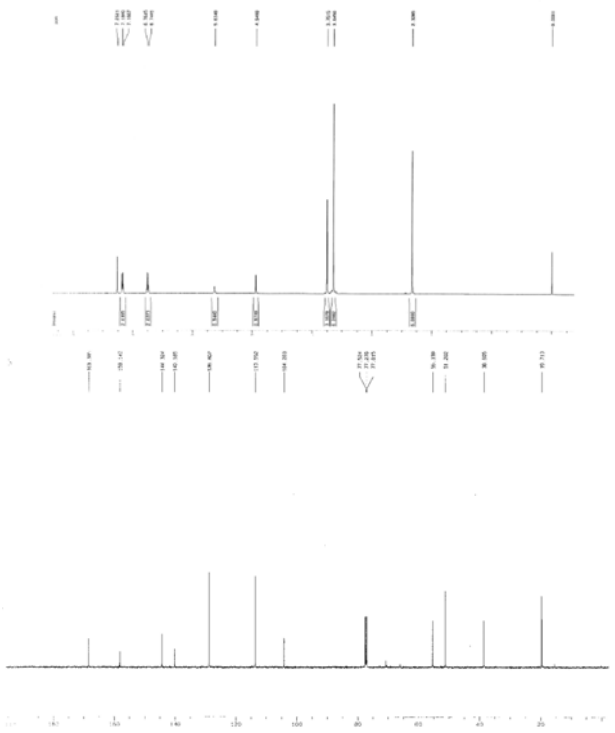
TABLE III Effect of different solvents[a]

Entry	Solvents	Time/h	Yield(%)[b]
1	Acetonitrile	6	84
2	chloroform	6	76
3	Toluene	6	72
4	Water	10	65

[a] Reaction conditions: benzaldehyde (3 mmol), NH_4OAc (3 mmol), ethylacetoacetate (2 mmol), PEG-400 (0.8 g), solvent (1 ml) under refluxing condition.

[b] Isolated yields.

Experimental General procedure: A mixture of aldehyde (1mmol), β-di-carbonyl compounds (3mmol), ammonium acetate (3mmol) and PEG400 (0.8 g) was heated at 100 ºC with stirring for 30-240min. After the completion of reaction as indicated by TLC, the reaction mixture was washed with ice cold water and extracted with Et2O, followed by water and brine solution and dried with anhydrous Na2SO4. The solution was concentrated in vacuum to afford the crude product. Then, the cure product was purified by recrystallization using ethanol. All compounds were fully characterized by mp, IR, 1H NMR, 13C NMR spectroscopy. The (4i-4p) data are in full agreement with those previously reported in the literature.[7c, 7d] data.



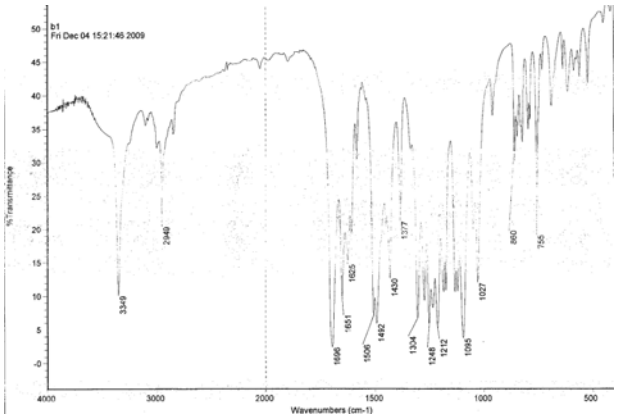


Figure 1. Spectrum of Key compounds 4b

Dimethyl 4-(4-Methoxyphenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(4b) Mp 177-179 ºC. 1H NMR(500MHz, CDCl3): δ = 2.32 (s, 6H), 3.64 (s, 6H), 3.75 (s, 3H), 4.94 (s, 1H), 5.63 (s, 1H), 6.75 (d, J = 8.7Hz, 2H), 7.17 (d, J = 8.65Hz, 2H). 13C HMR(125MHz, CDCl3): δ = 19.7, 38.6, 51.2, 55.3, 104.2, 113.6, 128.8, 140.2, 144.3, 158.1, 168.4. FT-IR(KBr): 3349, 1696, 1651, 1492, 1212, 1095, 755 cm-1(Fig.1.).

III. CONCLUSION

In summary, we have developed the catalyst system consisted of PEG-400/heating for Hantzsch synthesis of 1,4-DHPs under catalyst-free conditions. The environmentally friendliness of PEG medium, chromatogram-free purification process as well as the broad application scope are main advantages of present protocol. This facile and efficient synthetic method should be reasonably useful as complement for those know results on Hantzsch reaction.

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