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Microwave assisted synthesis of 1,4-dihydropyridines

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Summary. A novel method, which is eco-friendly, cost effective, solvent free, was developed for the synthesis of 1,4-dihydropyridines from ethyl acetoacetate, aldehyde and ammonium acetate under domestic microwave oven.

Key words: Hantzsch synthesis, microwave.

Introduction. Described more than one century ago by Hantzsch [1] dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (1,4-DHP) have now been recognized as vital drugs in the treatment of angina and hypertension. Some of them Amlodipine, Felodipine, Isradipine, Lacidipine, Nicardipine, Nifedipine, Nimodipine, Nitredipine etc. have been commercialized and it has been proven that their therapeutic success is related to their efficiency to bind to calcium channels and consequently to decrease the passage of the transmembrane calcium current associated in smooth muscle with a long tasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart [2—4].

Aromatization of 1,4-DHP has also attracted considerable attention in recent years as Bocker [5] has demonstrated that metabolism of those drugs involves a cytochrome P-450 catalyzed oxidation in the liver. The so-obtained pyridines are devoid of the pharmacological activity of the parent heterocycles and are further transformed by additional chemical modifications.

High-speed microwave-assisted chemistry has attracted a considerable amount of attention in recent years and has been applied successfully in various fields of synthetic organic chemistry [6—12], including cycloaddition reactions [7], heterocycle synthesis [8], the rapid preparation of radio-labeled materials [9], transition-metal-catalyzed processes [10], solvent-free reactions [11], and phase-transfer catalysis [12]. In fact, it is becoming evident that microwave approaches can be developed for most chemical transformations requiring heat. The main benefits of performing reactions under controlled microwave-irradiation conditions in sealed vessels are the significant rate-enhancements and the higher product yields that can frequently be observed [6—12]. We were therefore interested in developing a rapid, microwave-assisted protocol for synthesis of DHP of the Hantzsch type.

In 1882 Hantzsch reported the first synthesized of 1,4-DHP. The classical method for the synthesis of 1,4-dihydropyridines is a one-pot condensation of an aldehyde with ethyl acetoacetate, and ammonia either in acetic acid or refluxing in alcohol [13]. However, the yields of 1,4-dihydropyridines obtained by this method are generally low. Recently the solvent free synthesis of 1,4-DHP [14] was reported. However this method required more time for the synthesis especially when electron withdrawing group present on aromatic ring. With these observation and our continuous research for the synthesis of 1,4-dihydropyridine derivatives [15, 16] we

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Table 1

Synthesis of 1,4-dihydropyridine derivates under microwave condition at 90 W

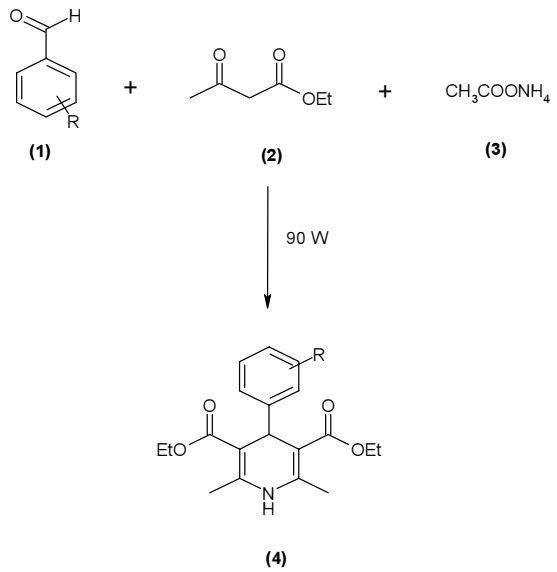
Entry	R	Time		Yield (%)	
		Reported [14]	Found	Reported [14]	Found [a]
4a	C_6H_5	1.5 hr	3 min.	93	92
4b	2-Br C_6H_4	45 min.	3 min.	96	94
4c	3-Br C_6H_4	45 min.	3 min.	96	95
4d	4-Br C_6H_4	1.45 hr	4 min.	97	94
4e	3-NO_2 C_6H_4	2 hr	4 min.	99	95
4f	4-NO_2 C_6H_4	3.5 hr	4 min.	99	94
4g	2-OMe C_6H_4	1.4 hr	3 min.	92	90
4h	2-Pyridil	2 hr	5 min.	98	92
4i	3-Pyridil	5 hr	4 min.	97	93
4j	4-Pyridil	4.5 hr	4 min.	95	92
4k	2-Furyl	10 min.	3 min.	91	92
4l	2-Thienyl	15 min.	3 min.	86	90
4m	Pr	15 min.	3 min.	90	90
4n	H	45 min.	3 min.	87	85
4o	Me	30 min.	3 min.	83	85
4p	Et	45 min.	3 min.	93	85

a = isolated yield after column chromatography.

have developed an efficient and versatile method for the preparation of 1,4-dihydropyridines that provides scope for further improvement towards milder reaction conditions and improved yields.

The present investigation discloses a modern development of solvent free Hantzsch reaction by using microwave irradiation. The yield of 1,4-DHP enhanced while the reaction time was reduced. It has not only resulted in economical automation but also minimized hazard of pollution to achieve eco-friendly process. The present procedure is equally effective for aromatic and aliphatic aldehydes. The compatibility with various functional groups, mild reaction conditions, and shorter reaction time are the advantages of the present procedure.

Scheme 1.
Facile one-pot synthesis of 1,4-dihydropyridine



Experimental section. A mixture of benzaldehyde (10 mmoles) ethyl acetoacetate (20 mmoles) and ammonium acetate (30 mmoles) was taken in a Pyrex cylindrical tube and heated in a domestic MW oven (CE2977N Samsung) 90W for 3—5 min. at appropriate time mentioned in table 1 to give corresponding dihydropyridines in 85—95 % yield. After completion the content was cooled to room temperature and poured into crushed ice and filtered through a sintered funnel. The crude compounds were purified by silica gel (60—120 mesh) column chromatography eluting with methanol : chloroform (2 : 8), to get the desired compounds in pure form.

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Синтез 1,4-дигідропіридинів із застосуванням мікрохвильової печі

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Резюме. Розроблено новий, екологічно безпечний, економічно вигідний, такий, що не потребує розчинника, метод синтезу 1,4-дигідропіридинів з етилацетоацетату, альдегіду й ацетату амонію з використанням побутової мікрохвильової печі.

Ключові слова: синтез Ганча, мікрохвильова піч.

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