Convention Special Issue - 2019

J. Indian Chem. Soc.,
Vol. 96, October 2019, pp. 1351-1354

Microwave-induced Montmorillonite-mediated synthesis of dihydropyridine

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Manuscript received online 14 May 2019, accepted 10 September 2019

A simple, inexpensive and efficient one-pot synthesis of 1,4-dihydropyridine derivatives using 10 wt.% of Montmorillonite K-10 clay as catalyst is developed under microwave irradiation. A most probable mechanism is also advanced.

Keywords: 1,4-Dihydropyridine (DHPs), Montmorillonite K-10, microwave, solid catalyst, Hantzsch reaction.

Introduction

Dihydropyridines (DHP) are important organic molecules with diverse biological activities. For example, they have vasodilator, anti-atherosclerotic, antitumor, and antidiabetic activities[1–7]. Owing to vast chemotherapeutic application and unique structural motif, various methods are reported for the synthesis of this class of molecules[8–17]. Hantzsch reaction is a very good method for the preparation of DHP[13], although numerous other methods are available for the synthesis of these molecules. Molecular iodine[8,18,19], lithium bromide[20], bismuth nitrate[21], ruthenium trichloride[22], Zn-proline complex[23], bakers' yeast[24] and ionic liquid[25] are used for this purpose. However, the existing methods suffer certain limitation like high temperature, longer reaction time, low yield and cost related issues. Therefore, the development of simple, efficient and versatile methods for the synthesis of 1,4-dihydropyridyl scaffold is immensely desirable. In recent years, the use of clay as catalyst especially Montmorillonite, has been extensively explored in organic synthesis[26–29]. The major advantages of this catalytic system over other existing catalyst include process recyclability, readily availability, easy handling process, nontoxic nature of the catalyst, inexpensive and noncorrosive nature.

As a part of our ongoing interest in clay-mediated organic transformation towards the search of anticancer drugs molecule[30–35] we studied the catalytic and non-catalytic effects of Montmorillonite K-10.

This paper describes clay-induced microwave-mediated novel synthesis of dihydropyridines in excellent yield. In comparison to existing methods, clay-mediated reactions have a much wider scope since this reaction is solventless, fast, and economical. The product can be isolated without conducting any tedious workup.

Results and discussion

In some of our previous publications, the use of Montmorillonite was demonstrated[36–38]. Interestingly, this clay is compatible in the presence of microwave irradiation and absorbs energy readily. Numerous dihydropyridines derivatives were prepared following microwave-assisted Montmorillonite-mediatedreaction of aldehyde **1a-e**, dicarbonyl compound **2** in presence of ammonium acetate **3** under solvent-free con-

ditions following the principles of multi-component reactions. This reaction became successful and dihydropyridines were obtained in good yield (Scheme 1).

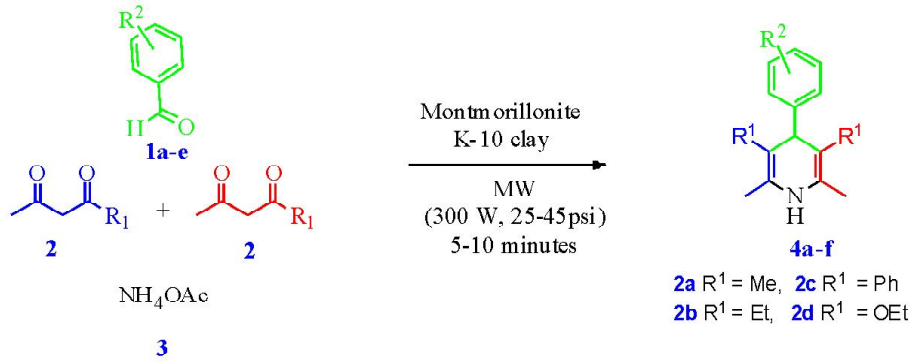
Initially, reaction of benzaldehyde (1 mmol) (**1a**), acetylacetone (2 mmol) (**2a**) and ammonium acetate (**3**) in presence 10 wt.% of catalyst Montmorillonite K-10 under microwave irradiation (power level 5) for 3 min, without using any solvent was performed. Only 60% of the product **4a** was realized after purification of the crude products. To improve the reaction yield and optimize the reaction condition, we increased the catalyst loading from 10–20 wt.% and carried out the reaction under the same condition. Surprisingly a noticeable improvement in the yield of compound **5a** (80% Y) was recorded.

This optimistic result encouraged us to further investigate the reaction to identify the best condition. In this connection we investigated this reaction with diverse substituted aromatic aldehydes **1b-e** with different 1,3-di-carbonyl esters **2b-d** under the delineated condition. An increase the amount of Montmorillonite K-10 from 10–25 wt.% further improved the product yield (70–90% Y) and also reduced the reaction time significantly.

It was worthy to note that the sterically hindered phenyl group viz benzoyl acetone generally reduced the yield of 1,4-dihydropyrdyl compounds moderately (Scheme 1, Table 1, entry 7).

No oxidation to pyridines was observed during our investigation. But some of the reported methods produced pyridine as a side product.

The formation of the products can be explained through

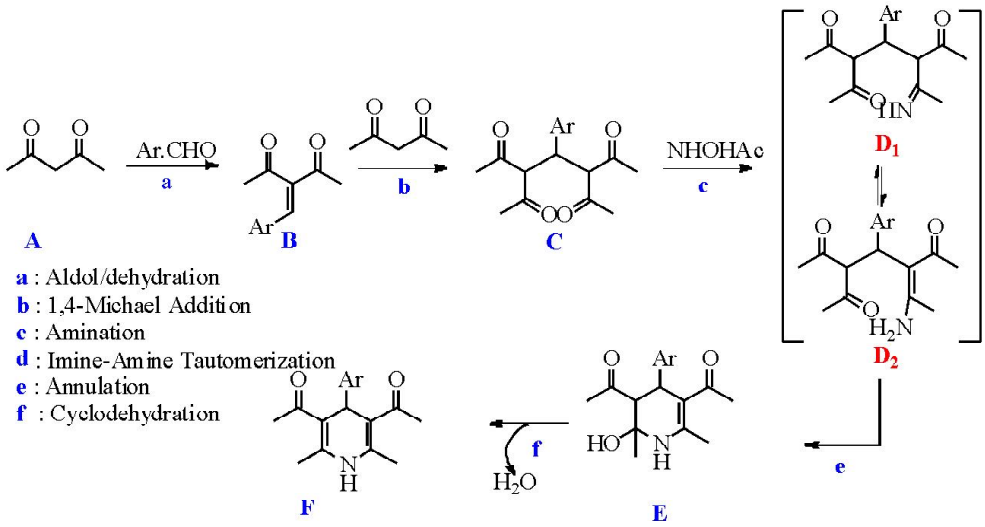


Scheme 1. Montmorillonite K-10 clay catalysed synthesis of 4-substituted 1,4-dihydropyridine derivatives under microwave condition through Hantzsch reaction.

Table 1. Synthesis of 1,4-dihydropyridines (1,4-DHPs) derivatives catalyzed by Montmorillonite K-10 under microwave irradiation

Entry	Aldehyde	1,3-DCs	1,4-DHPs	Catalyst	Time	Yield[a]
	1	**2**	**4**	(wt.%)	(min)	(%)
	[**a-c**]	[**a-d**]	[**a-e**]			
	R^2	R^1	R^2/R^1			
1	**1a** (H)	**2a** (Me)	**4a** (H, Me)	20	5	80
12	**1b** (Me)	**2a** (Me)	**4b** (Me, Me)	15	5	75
	1c (OMe)	**2a** (Me)	**4c** (OMe, Me)	15	8	90
	1d (F)	**2a** (Me)	**4d** (F, Me)	25	10	70
	1e (Cl)	**2a** (Me)	**4e** (Cl, Me)	20	10	75
	1c (OMe)	**2b** (Et)	**4f** (OMe, Et)	15	8	70
	1c (OMe)	**2c (Ph)**	**4g** (OMe, Ph)	20	10	65
	1c (OMe)	**2d** (OEt)	**4f** (OMe, OEt)	20	8	80

[a]Isolated yield after column chromatography.



Scheme 2. Mechanism of Hantzsch synthesis of 1,4-dihydropyridin (DHPs).

Hantzsch reaction mechanism (Scheme 2). The reaction occurred through aldol condensation between the aldehyde and diketone to form an intermediate that reacted further through Michael addition with another molecule of diketone.

An amination to form the imine intermediate (D_2) was occurred at the last step through a reduction rearrangement to form dihydropyridine.

It is important that clay can be used as a solid support and acidic material to obtain the desired products. A number of studies indicated that the proportion of clay to function as an appropriate catalyst depends on the power of microwave irradiation. For example, the reaction went to completion at high power microwave irradiation conditions even with much lower proportion of clay (for 1 mmol of the substrate, 25 mg of clay is sufficient at high power microwave irradiation).

Experimental

To the reactants (1 mmol each) were added clay (25 mg) and the reaction mixture was thoroughly mixed. It was then irradiated in a microwave oven for 2–3 min. To the reaction mixture was added dichloromethane (5 mL) and it was then filtered to remove the clay. The crude product which was sufficiently pure was obtained by evaporation of the solvent.

Acknowledgement

BKB is grateful to US NIH, US NCI and the Kleberg Foundation of USA for the support of this research.

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