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An environmentally friendly one-pot synthesis method of 1,4 dihydropyridines through Hantzsch reaction

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Introduction

The effectiveness of medications in treating various ailments has a significant impact on life quality. It is well acknowledged that developing organic chemical processes, particularly heterocyclic synthesis, is necessary to create the necessary raw materials for medications. It is common knowledge that reducing waste formation during the synthesis of materials is crucial for safeguarding both human health and the environment. Green chemistry concepts can be used to reduce the amount of toxic waste produced. Heterogeneous catalysis is essential for the development of environmentally friendly, environmentally safe chemical processes as well as for demonstrating how they protect the environment and lower process costs. Given their wide spectrum of pharmacological uses and actions, such as vasodilation, HIV protease inhibition, radioprotection, bronchodilation, anticancer, and hepatoprotective effects, 1,4-dihydopyridines (1,4-DHPs) have received considerable attention.The traditional Hantzsch method involves condensing a large number of aldehydes in a single pot with ethyl acetoacetate and ammonia either at room temperature in acetic acid or over an extended period of time in ethanol. this protocol suffers from severe drawbacks such as extended reaction times and low product yields.

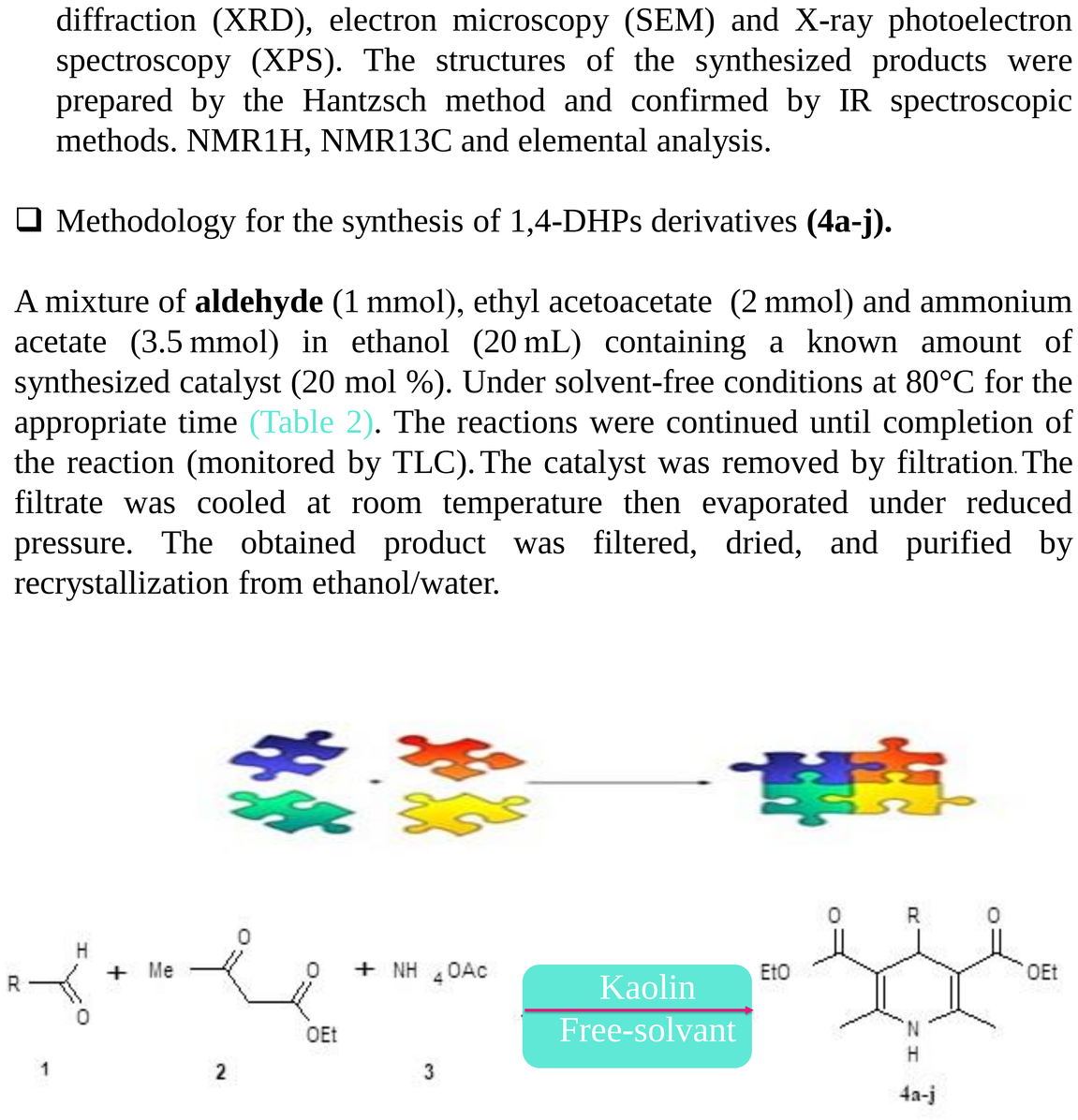
In this work, we report an effective and environmentally friendly method for the solvent-free synthesis of 1,4-DHP employing kaolin as a heterogeneous catalyst made from natural materials. By using scanning electron microscopy (SEM) and X-ray diffraction (XRD), the crystallinity and morphology of the catalyst were investigated (SEM). Through the use of X-ray photoelectron spectroscopy, the surface condition was studied (XPS). This research provides a new, efficient, and dependable technique for the synthesis of 1.4-DHP with outstanding yields and a quick reaction time using an environmentally friendly, reusable catalytic device.

Materials and Method

- The catalyst was prepared by a simple method from natural elements and characterized by various physico-chemical techniques such as X-ray diffraction (XRD), electron microscopy (SEM) and X-ray photoelectron spectroscopy (XPS). The structures of the synthesized products were prepared by the Hantzsch method and confirmed by IR spectroscopic methods. NMR1H, NMR13C and elemental analysis.

- Methodology for the synthesis of 1,4-DHPs derivatives **(4a-j).**

A mixture of **aldehyde** (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (3.5 mmol) in ethanol (20 mL) containing a known amount of synthesized catalyst (20 mol %). Under solvent-free conditions at 80°C for the appropriate time (Table 2). The reactions were continued until completion of the reaction (monitored by TLC). The catalyst was removed by filtration. The filtrate was cooled at room temperature then evaporated under reduced pressure. The obtained product was filtered, dried, and purified by recrystallization from ethanol/water.



Scheme 1. synthesis of 1.4-DHP derivatives via the Hantzsch reaction.

Results and discussion

- Fig. 1 shows the XRD patterns of Kaolin was formed essentially by three phases identified as kaolinite 1A ($Al_2Si_2O_5(OH)_4$) corresponding to 2θ values at 24.98°, 26.68°, 34.89°, 38.61°,45.40°, 55.25°, 59.85°, 62.26° and 73.3°(JCPDS 14-0164), Mica 2M1 $KAl_2(Si_3Al)O_{10}(OH,F)_2$ for 2θ values of 30.08°, 35.00°, 37.74° and 42.44°(JCPDS 06-0263) and quartz SiO_2 was detected at 2θ = 20.87°, 50.11° and 68.06° (JCPDS 33-1161).

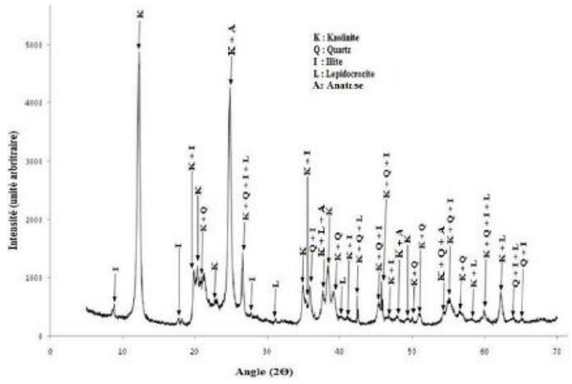


Fig.1

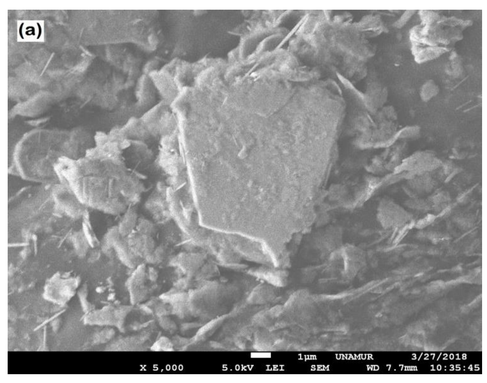


Fig.2

- The morphology of Kaolin is shown in SEM photomicrographs of **Fig.2**. Kaolin SEM micrograph revealed platelets of different sizes with hexagonal edges.
- Reaction optimization using different conditions (Table 1)

entry	Solvant	catalyst	Amm of catayst mol%	Time (h)	Yield(%)[b]
3	EtOH	Q_3	5	3	80
4	EtOH	Q_3	10	3	84
5	EtOH	Q_3	15	3	81
6	EtOH	Q_3	20	2	81
7	Free solvant	Q_3	20	1	85
8	THF	Q_3	20	5	63
9	CH_3CN	Q_3	20	5	73
10	Cyclohexane	Q_3	20	5	58
11	MeOH	Q_3	20	4	82

Table 1

entry	R	Product	Reaction time (h)	Yield[a] %	M.p(°C) Measure
1	Ph	4a	2.75	80	156-158
2	2-NO_2-C_6H_4	4b	3.5	76	170-172
3	3-NO_2-C_6H_4	4c	1.0	85	163-165
4	4-NO_2-C_6H_4	4d	3.0	82	131-133
5	3-OH-C_6H_4	4e	3.5	74	172-174
6	4-OH-C_6H_4	4f	3.0	82	126-128
7	4-Br-C_6H_4	4g	2.5	73	160-162
8	5-Br-2-OMe-C_6H_3	4h	5.0	75	161-163
9	C_6H_4-CH=CH	4i	3.0	76	122
10	2-furyl	4j	4.0	81	160-162

Table 2

- The optimal conditions for the Biginelli reaction catalyzed by kaolin is 20 mol of Q3 without solvent for 1 hour.**(Table 1, 7).**
- Considering these results, a series of aromatic and heteroromantic aldehydes have been employed according to the same procedure. We have found that with aromatic carbocyclic aldehydes bearing electron-withdrawing or electron-donating substituents, the yields are good, as are heterocyclic aldehydes **(Table 2).**

Conclusion

A simple, environmentally friendly and highly efficient method has been developed for the synthesis of 1,4-dihydropyridine (1,4-DHPs) compounds via one-pot Hantzsch reaction with good yields (70-90%). These compounds were synthesized in a solvent-free environment using kaolin as catalyst, an aromatic aldehyde, ethyl acetoacetate, and urea. X-ray diffraction (XRD), scanning electron microscopy (SEM), and X-ray photoelectron spectroscopy (XPS) techniques were used to characterize the kaolin. This environmentally friendly method has a number of advantages, including the capacity to recover and reuse the heterogeneous catalyst repeatedly, a green and economical process, a good yield, and quick reaction time.

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