

Nano Al₂O₃/KF: a versatile catalyst for the preparation of some Hantzsch type products

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Abstract

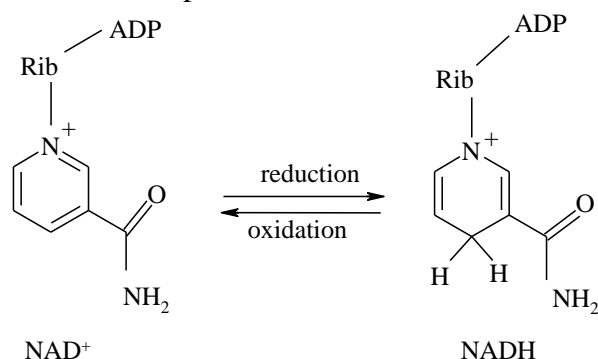
A protocol for the synthesis of 1,4-dihydropyridines (Hantzsch type-products) was developed through a three-component condensation of aldehydes, β -dicarbonyl compound and ammonium acetate in the presence of nano Al₂O₃/KF as catalyst. This reaction was carried out under different conditions including i) solvent-free conditions, ii) refluxing in different solvents. However, the reactions proceed in refluxing ethanol (10 mL). The reported protocol has the advantages of consistently excellent yields and short reaction times. The catalyst could be recovered easily.

Keywords: Hantzsch type-products; 1,4-dihydropyridines; nano Al₂O₃/KF; ethanol; different solvents.

Introduction

In all living cells, a nicotinamide adenine dinucleotide (NAD) is founded as coenzyme. The NAD is a dinucleotide compound which consists of two nucleotides joined through their phosphate groups. This compound

contains two heterocyclic cores, such as an adenine base and the nicotinamide. NAD exists in two forms, an oxidized and a reduced form abbreviated as NAD⁺ as well as NADH, respectively (Scheme 1) [1].



Scheme 1. Structural of NAD⁺ and NADH compounds

Therefore, in 1882 A. Hantzsch reported the synthesis of 1,4-dihydropyridine compound (1,4-DHP) for the first time, which is analogous to NADH coenzymes [2]. After that,

several protocols for the synthesis of 1,4-DHPs have been developed to improve and modify the reaction [3-5]. Traditionally, catalysts i.e. Amberlite IRA 900 [6], *t*-BuOK [7], hexagonal

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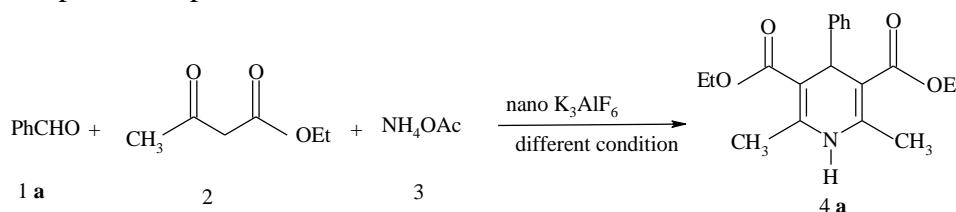
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mesoporous silicate (HMS) [3], silica gel/sulfonic acid catalyst ($\text{SiO}_2\text{-SO}_3\text{H}$) [8] and $\text{Yb}(\text{OTf})_3$ [9], had been significantly used for the synthesis of these compounds. Some of the 1,4-DHPs are used as drugs for the treatment of cardiovascular diseases, including hypertension [10]. However, some of these compounds have the potential to treat Alzheimer's disease [11]. Furthermore, the core of 1,4-DHP is a common feature of various bioactive compounds [12]. However, this report describes a one-pot multicomponent process for the

synthesis of 1,4-DHPs products using nano $\text{Al}_2\text{O}_3/\text{KF}$ as catalyst.

Results and discussion

Initially, we studied the Hantzsch-type reaction of benzaldehyde (**1a**), ethyl acetoacetate (EAA), and ammonium acetate in 1:2:1.2 molar ratio by nano $\text{Al}_2\text{O}_3/\text{KF}$ as catalyst in different solvents under different conditions. (Scheme 2, Table 1). The effects of different factors were examined, including solvents, temperature and the catalyst amount. The results have been summarized in Table 1.



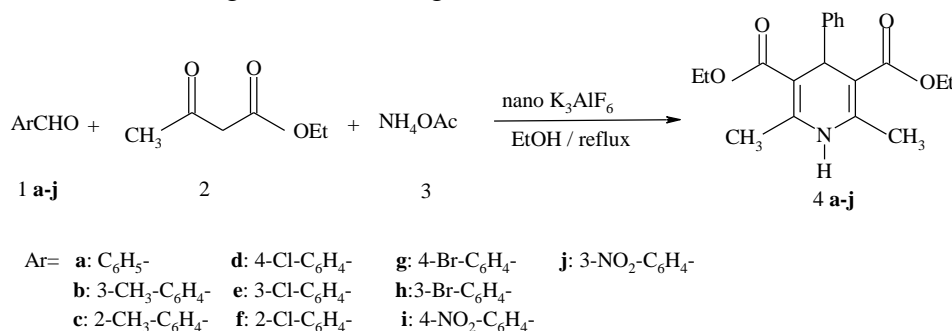
Scheme 2. Synthesis of **4a** by nano $\text{Al}_2\text{O}_3/\text{KF}$

This reaction was studied in the presence of 0.1 g of nano $\text{Al}_2\text{O}_3/\text{KF}$ and in different solvents, such as H_2O , EtOH , CHCl_3 , acetonitrile in refluxing status and solvent-free condition at 100°C .

In the next step, the model reaction has been performed using differing amounts of nano $\text{Al}_2\text{O}_3/\text{KF}$. The increase in the amount of nano $\text{Al}_2\text{O}_3/\text{KF}$ from 0.05 g to 0.1 g resulted in an increase in the reaction yield from 60 % to 85 %. Also, the reaction time decreased from 6.4 h to 4 h (Table 2, Entries 1 and 2). Using 0.15 and 0.2 g

of this catalyst, the same reaction yield was generated. But the reaction time increased unexpectedly to 6 h (Table 2, Entries 3 and 4). Therefore, nano $\text{Al}_2\text{O}_3/\text{KF}$ (0.1 g) was sufficient for catalyzing the reaction effectively.

According to the data reported in Tables 1 and 2 the reaction of aldehydes (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1.2 mmol) in the presence of nano $\text{Al}_2\text{O}_3/\text{KF}$ (0.1 g) in refluxing ethanol (10 mL) has been performed. The results are reported in Table 3, Scheme 2.



Scheme 3. Synthesis of the 1,4-DHPs (**4 a-j**) using nano $\text{Al}_2\text{O}_3/\text{KF}$ as catalyst

Table 1. Nano Al₂O₃/KF (0.1g) catalyzed synthesis of 1,4-DHP product (2a) under different conditions

Entry	T (°C)	Solvent (mL)	Time (h) ^a	Yield (%) ^b
1	r.t	Solvent-free	6	<15
2	100	Solvent-free	4	60
3	Reflux	Ethanol (10)	4	85
4	Reflux	CH ₃ CN (10)	4	70
5	Reflux	CHCl ₃ (10)	6	60
6	Reflux	H ₂ O (10)	6	40

^aTimes are given after maximum progress of reaction.^bIsolated yield.**Table 2.** Influence of nano Al₂O₃/KF amount for the synthesis of 1,4-DHP (2a) in refluxing ethanol (10 mL)

Entry	Al ₂ O ₃ /KF (g)	Time (h)	Yield (%)
1	0.1	4	85
2	0.05	6.4	60
3	0.15	6	85
4	0.2	6	85

Apparently, the nature of the substituent in the aromatic moiety does

not significantly affect the yield of the reactions.

Table 3. nano Al₂O₃/KF catalyzed synthesis of the Hantzsch 1,4-dihydropyridines 4a-j

Comp.	Ar	Time (h)	Yield (%)	m.p (°C)	
				measured	Reported
4a	C ₆ H ₅ -	4	85	158-160	160-161 [3]
4b	3-Me-C ₆ H ₄ -	4	85	125-126	124-125[3]
4c	2-Me-C ₆ H ₄ -	4	80	130-131	128-129.5[13]
4d	4-Cl-C ₆ H ₄ -	4	85	150-151	149-150 [3]
4e	3-Cl-C ₆ H ₄ -	4	85	136-138	138-139[14]
4f	2-Cl-C ₆ H ₄ -	4	85	120-122	122-124[3]
4g	4-Br-C ₆ H ₄ -	4	75	161-163	163-164 [3]
4h	3-Br-C ₆ H ₄ -	4	85	118-119	116-118 [3]
4i	4-NO ₂ -C ₆ H ₄ -	4	80	129-131	130-131[3]
4j	3-NO ₂ -C ₆ H ₄ -	4	85	161-162	163-164 [3]

Experimental section

Melting points were determined using an Electrothermal IA 9100 digital melting point apparatus and were uncorrected. The IR spectra were recorded for solid samples using KBr discs on a Perkin Elmer FT-IR apparatus Prestige 21. The ^1H NMR spectra (CDCl_3 , standard TMS) were recorded with a Bruker 300 MHz instrument. They are reported as follows: chemical shifts, (multiplicity and number of protons).

In a general procedure, the reaction of aldehydes (1 mmol), ethyl acetoacetate (2 mmol), and ammonium acetate (1.2 mmol) in the presence of nano $\text{Al}_2\text{O}_3/\text{KF}$ (0.1 g) in refluxing ethanol (10 mL) ethanol has been performed. The progress of the reaction followed by TLC using n-hexane/ethyl acetate (7:1) as solvent. When the reaction was completed, the mixture was filtered and the solid product residue was washed with water (20 mL). Then the crude product was purified by recrystallization from a mixture of EtOH and H_2O (5:1). In this step the catalyst was removed from product by filtration of hot solution.

All products are characterized by FT-IR, ^1H NMR, ^{13}C NMR and melting points. The spectral and analytical data for the selected compound is presented below.

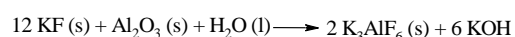
Diethyl 1,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a)

FT-IR (KBr): ν 3339.15 (N-H), 2880.44 (C-H), 1694.07-1727.51 (C=O), 1489.15 (C=C), 1274.83 (C-O) cm^{-1} . ^1H NMR (CDCl_3): δ = 1.51 (t, J = 7.1 Hz, 6 H), 2.22 (s, 6 H), 4.0 (q, J = 7.01 Hz, 4

H), 4.93 (s, 1 H), 9.2 (brd s, 1 H), 7.04-7.22 (m, 5 H) ppm. ^{13}C NMR (CDCl_3): δ = 14.26, 19.40, 39.63, 59.74, 103.93, 126.1, 127.84, 127.98, 144.23, 147.85, 167.81 ppm.

Preparation of Nano $\text{Al}_2\text{O}_3/\text{KF}$

Weinstock et al. have argued that $\text{KF}/\text{Al}_2\text{O}_3$ derives its basicity from the formation of KOH in the initial preparation of the solid supported material by the reaction of KF with the alumina support [15].



Many fluorides complexes derivatives with the general $\text{A}_2\text{BB}'\text{X}_6$ composition are known as crystallizing in the elpasolite (K_2NaAlF_6) (or ordered double perovskite) structure. The information is available on $\text{Al}_2\text{O}_3/\text{KF}$ being compared with its closest analogues cryolite Na_3AlF_6 and elpasolite K_2NaAlF_6 . It has been reported that the $\text{Al}_2\text{O}_3/\text{KF}$ has a tetragonally distorted elpasolite-type structure at room temperature, which transforms into the high symmetric cubic phase above 300–310 °C [16,17]. $\text{KF}\cdot 2\text{H}_2\text{O}$ (20 g) was dissolved in water (80 mL), and then basic Al_2O_3 (30 g) was added. The resulting mixture was stirred at 65–75 °C for 1 h. The water was removed under reduced pressure at 100 °C, and the resulting powder was dried at 120 °C for 4h to give active $\text{Al}_2\text{O}_3/\text{KF}$ [18]. The morphology and particle size of nano $\text{Al}_2\text{O}_3/\text{KF}$ catalyst were investigated by TEM and SEM (Figure 1). The average $\text{Al}_2\text{O}_3/\text{KF}$ particle sizes are changed from 17.16 to 40.40 nm.

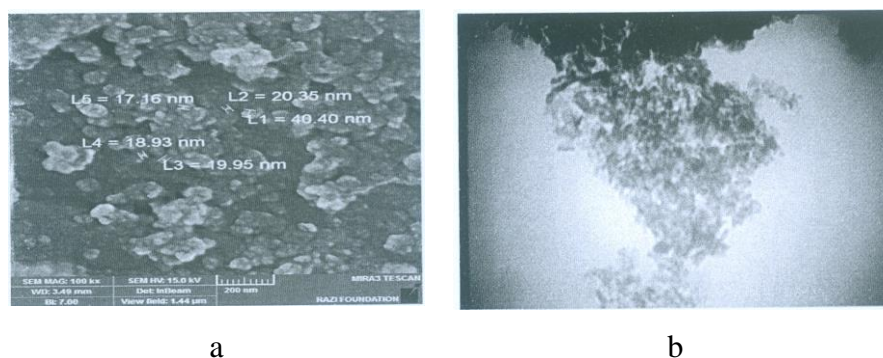


Figure 1. SEM (a) and TEM (b) images of nano Al₂O₃/KF

Conclusion

In summary, we have found a practical condensation procedure for the preparation of 1,4-dihydropyridines catalyzed by nano Al₂O₃/KF, which gives excellent yields. It has many other advantages, such as milder reaction conditions, shorter reaction time, and easy recovery of catalyst. Its performance has been compared with that of other heterogeneous base catalysts, such as HMS, silica gel/sulfonic acid catalyst (SiO₂-SO₃H) and Yb(OTf)₃. As a result Al₂O₃/KF is known to be a useful and interesting heterogeneous catalyst for base-induced organic reactions.

Acknowledgements

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References

- [1] N. Pollak, C. Dölle, M. Ziegler, *Biochem. J.*, **2007**, *402*, 205-218.
- [2] A. Hantzsch, J. Liebig, *Ann. Chem.*, **1882**, *215*, 1-82.
- [3] A. Farhadi, T. Hamoule, M.A. Takassi, T. Arizavipour, *Bulg. Chem. Commun.*, **2015**, *47*, 101-104.
- [4] H.R. Memarian, M. Abdoli-Senejani, D. Döpp, *Z. Naturforsch.*, **2006**, *61b*, 50-56.
- [5] J.S. Mojarrad, Z. Zamani, H. Nazemiyeh, S. Ghasemi, D. Asgari,

Adv. Pharm. Bull., **2011**, *1*, 1-10.

- [6] S.R. Jetti, N. Babu G, S. Jain, *Der Pharma Chemica*, **2015**, *7*, 344-349.
- [7] A. Debache, L. Chouguat, R. Boulcina, B. Carboni, *Open Organic Chemistry Journal*, **2012**, *6*, 12-20.
- [8] R. Gupta, R. Gupta, S. Paul, A. Loup, *Synthesis*, **2007**, 2835-2838.
- [9] L.-M. Wang, J. Sheng, L. Zhang, J.-W. Han, Z.-Y. Fan, H. Tian, C.-T Qian, *Tetrahedron*, **2005**, *61*, 1539-1543.
- [10] F. Bosset, H. Meyer, E. Wehinger, *Angew. Chem. Int. Ed. Engl.*, **1981**, *20*, 762-769.
- [11] B. Jansone, I. Kadish, T. Groen, U. Beitnere, D.R. Moore, A. Plotniece, K. Pajuste, V. Klusa, *Plos One*, **2015**, *10*, 1-15.
- [12] R. Manhold, B. Jablonka, W. Voigt, K. Schoenafinger, K. Schrauan, *Eur. J. Med. Chem.*, **1992**, *27*, 229-235.
- [13] S.M. Pitzenberger, B.M. Trost, *Patents*, US4780538 A, **1988**.
- [14] H.S. Sohal, A. Goyal, R. Sharma, R. Khare, *Eur. J. Chem.*, **2014**, *5*, 171-.
- [15] L.M. Weinstock, J.M. Stevenson, *Tetrahedron Lett.*, **1986**, *27*, 3845-3848.
- [16] K. Grojtheim, J.L. Holm, S.A. Mikhael, *Acta Chem. Scand.*, **1973**, *27*, 1299-1306.
- [17] E.G. Steward, H.P. Rooksby, *Acta Crystallogr.*, **1953**, *6*, 49-52.
- [18] S.X. Wang, *Ultrasonics Sonochem.*, **2002**, *9*, 159-161.