



Trade Science Inc.

Organic CHEMISTRY

*An Indian Journal**Full Paper*

OCAIJ, 8(6), 2012 [206-210]

A convenient one-pot three component synthesis of 1,4-dihydropyridines using basic alumina as a catalyst in aqueous media under microwave irradiation

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Received: 29th September, 2011 ; Accepted: 29th October, 2011

ABSTRACT

A simple and convenient one-pot multi-component reaction has been described for the synthesis of 1,4-dihydropyridines from substituted benzaldehydes, β -keto esters and ammonium acetate catalyzed by basic alumina (10 mol %) in aqueous medium under microwave irradiation in good yields. The recyclability of basic alumina as a catalyst has been demonstrated and a comparative study between basic, acidic and neutral alumina is made. The generality and functional tolerance of this convergent and environmentally benign method is presented. © 2012 Trade Science Inc. - INDIA

KEYWORDS

Basic alumina;
1, 4-dihydropyridine;
Microwave irradiation.

INTRODUCTION

Multi-component reactions (MCRs) has emerged as an important method in the field of synthetic chemistry because the synthesis of complicated molecules can be achieved in a very fast, efficient, and time saving manner without going through the process of isolation of the intermediate. As a result, minimum effort is required in carrying out the reaction while drastically reducing the environmental loading and is therefore acceptable from the 'Green Chemistry' point of view^[1].

Nitrogen heterocycles, especially pyridine derivatives, are important pharmacophores in drug design and are among the most frequently cited heterocyclic compounds. Amongst these, 1,4-Dihydropyridine substance frameworks forming an important class of Ca^{+2} channel blockers such as Nifedipin and Amlodipine are clinically significant antihypertensive drugs^[2-5]. Although, a

number of modified methods under improved conditions have been reported comprising the use of microwaves^[6], ionic liquids^[7], and the use of catalysts such as $TMSCl-NaI$ ^[8], $InCl_3$ ^[9], I_2 ^[10], $SiO_2/NaHSO_4$ ^[11], $SiO_2/HClO_4$ ^[12], CAN ^[13], Na- and Cs-Norit carbons^[14], tetrabutylammonium hydrogen sulfate^[15], and metal triflates^[16], many of them suffer from drawbacks such as unsatisfactory yields, high temperatures, and long reaction times, and the use of stoichiometric and/or relatively expensive reagents. Moreover, the main disadvantage observed in almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. The application of reusable catalyst is scantily addressed. Therefore it is important to find better catalyst for the synthesis of DHPs in terms of operational simplicity, reusability, economic viability, and greater selectivity.

In achieving an efficient synthesis, organic reactions/

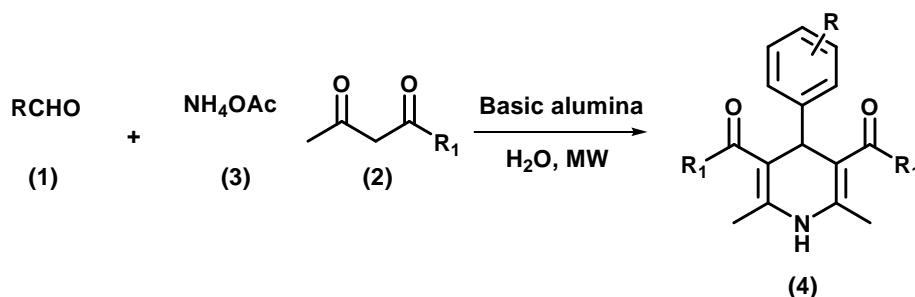
transformations on solid supported catalysts represent a viable and convenient alternative to traditional synthetic processes realized under homogeneous conditions^[17]. Current developments in the use of these heterogeneous catalysts in combination with aqueous media are attracting a great deal of interest^[18]. Because, solid supports like alumina, which are basically inorganic oxides, possess excellent ability to adsorb the organic compounds on their surface without absorbing or restricting the transmission of energy, especially in microwave irradiation^[19]. Besides this, the homogenous dispersion of active sites, associated selectivity and easy work-up schedule make the solid supported reactions more advantageous over the conventional reactions.

As a part of our current interest in the development of newer synthetic methods for heterocyclic compounds and the use of alumina in organic synthesis^[20], we wish to explore its utility and reusability as one of the reagents in one-pot three component reactions. Herein, we report an efficient and time-saving one-pot protocol for the three-component condensation of substi-

tuted aldehydes, β -keto esters and ammonium acetate in water using basic alumina as a catalyst under microwave irradiation. It is to be noted that, for the first time, a comparative study of basic, acidic and neutral alumina has been carried out for the synthesis of 1,4-dihydropyridines.

RESULTS AND DISCUSSION

In the initial experiment, a mixture of 4-chlorobenzaldehyde (1 mmol), methyl acetoacetate (2.1 mmol) and ammonium acetate (1 mmol) in acetonitrile (5 mL) was treated with 10 mol % of basic alumina under reflux condition gave 4a in 15 % yield. The same reaction when performed under controlled microwave irradiation afforded 4a with an increased yield of 28 % along with unreacted methyl acetoacetate. The product was characterized from ¹H NMR, ¹³C NMR, Mass spectra and by elemental analysis. It is quite clear that the product 4a was obtained *via* a three component cyclo-condensation reaction.



Scheme 1

Various trial reactions were performed by reacting 4-chlorobenzaldehyde, methyl acetoacetate and ammonium acetate under reflux as well as under controlled microwave irradiation for the optimization of the amount of catalyst used and the choice of appropriate solvent, to maximize the product yield. These observations are summarized in TABLE 1. It is evident from the Table that a catalytic amount of basic alumina (10 mol%) accomplishes the reaction successfully and the use of microwave irradiation further enhances the yield of the product considerably with dramatic reduction in the reaction time, the best result being obtained using 120W at 100°C in 3 minutes. It has also been observed that tap water is the best solvent for the present reaction among various other solvents.

Subsequently, a series of DHPs was prepared in the presence of basic alumina (10 mol %) involving different aldehydes and the products were isolated by simple filtration, work-up and purification (4a-n, TABLE 2). The reactions of various aldehydes possessing either electron-donating or electron-withdrawing substituents with methyl acetoacetate and ammonium acetate in the presence of a catalytic amount of basic alumina (10 mol %) produced high yields of the corresponding 1,4-DHPs (70–86 %). The results are presented in TABLE 2. Similarly, the reactions with other β -keto esters, like ethyl acetoacetate, also produced the corresponding DHP derivatives in good yields (TABLE 2, entries 4h-n). It is evident from these observations that the alkoxy (-OR) moiety present in the β -keto ester

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TABLE 1 : Optimization of reaction conditions and the catalyst recyclability for the synthesis of functionalized DHPs 4a.

Entry	Solvent	Reaction Conditions	Microwave				Conventional		
			MW Watt	Temp ° C	Time /(min)	Yield ^a (%)	Temp ° C	Time (h)	Yield ^a (%)
1	CH ₃ CN	No catalyst	120	100	5	0	100	8	Nil
2	CH ₃ CN	Basic alumina (10%)	120	100	5	28	100	8	15
3	Tap water	Basic alumina (5%)	120	100	5	74	100	5	30
4	Tap water	Basic alumina (10%)	120	100	3	86	100	2.5	35
5	Tap water	Basic alumina (20%)	120	100	3	83	100	5	34
6	Tap water	Basic alumina (30%)	120	100	3	84	100	5	34
7	Tap water	Basic alumina (recycled once,10%)	120	100	3	83	100	6	30
8	Tap water	Basic alumina (recycled twice, 10%)	120	100	3	80	100	6	30
9	Tap water	Basic alumina (recycled three times, 10%)	120	100	5	78	100	7	28
10	EtOH	Basic alumina (10%)	120	100	5	0	100	10	Nil
11	Tap water	Neutral alumina (10%)	120	100	10	38	100	4	48
12	Tap water	Acidic alumina (10%)	120	100	10	52	100	10	48
13	Tap water	Silica gel 60	120	100	5	65	100	4	60

^aIsolated yields.

TABLE 2 : Basic alumina catalyzed one-pot three component reaction of DHPs

Entry	Compounds	Substrate (1) R	Substrate (2) R ₁	Microwave ^b		Conventional		M.p (° C) ^c
				Time (min)	Yield ^a %	Time (h)	Yield ^a %	
1	4a	4-ClC ₆ H ₄	OCH ₃	3	86	2.5	51	195-197
2	4b	4-MeC ₆ H ₄	OCH ₃	3	79	3	53	175-177
3	4c	4-NO ₂ C ₆ H ₄	OCH ₃	4	76	4	57	197-199
4	4d	3,4,5-(OMe) ₃ C ₆ H ₂	OCH ₃	3	80	3	63	176-179
5	4e	Furyl	OCH ₃	3	94	3	58	196-198
6	4f	4-OMeC ₆ H ₄	OCH ₃	3	75	2.5	52	188-190 ^[22]
7	4g	CH ₃ CH ₂ -	CH ₃	4	81	3	59	126-128
8	4h	3,4-(OMe) ₂ C ₆ H ₃	OC ₂ H ₅	3	75	3	58	147-149
9	4i	2-ClC ₆ H ₄	OC ₂ H ₅	3	81	2.5	62	129-131 ^[21a]
10	4j	3-NO ₂ C ₆ H ₄	OC ₂ H ₅	4	72	3	52	170-172 ^[21a]
11	4k	C ₆ H ₅	OC ₂ H ₅	3	79	4	65	156-158 ^[21b]
12	4l	4-OHC ₆ H ₄	OC ₂ H ₅	3	70	3	62	166-168 ^[21b]
13	4m	2-OHC ₆ H ₄	OC ₂ H ₅	4	73	2.5	53	118-120
14	4n	Crotonyl	OC ₂ H ₅	5	82	3	55	116-119

^a Isolated Yield. ^b Microwave heating performed on 120 Watt power and 100 °C temperature. ^cReference.

does not have any effect on the overall yields of the products.

Next, a comparative catalytic efficiency of basic alumina, acidic alumina and neutral alumina for the synthesis of DHPs 4 was examined by executing a series of reactions using 10 mol % of each of the catalysts at the optimized reaction condition. It was found that the reactions performed with neutral and acidic alumina exhibited low efficiency with the formation of side products compared to basic alumina which gave maximum yields of the products and little or no side products at all (TABLE 3).

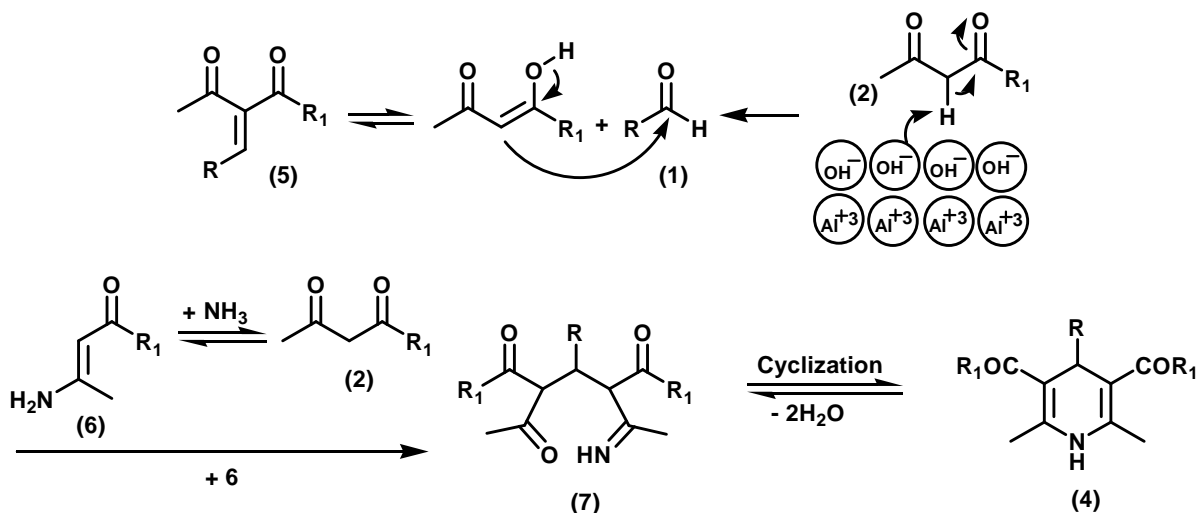
TABLE 3 : Comparative study of basic alumina, acidic alumina and neutral alumina catalyst for the synthesis of 4 under microwave irradiation

Entry	Product 4	Time (min)	Yield ^a (%)		
			Basic alumina	Acidic alumina	Neutral alumina
1	4a	3	86	52	38
2	4c	4	76	53	39
3	4d	3	80	57	43
4	4h	3	75	58	48
5	4k	3	79	64	54
6	4m	4	73	59	32

^a Isolated Yields.

A probable mechanism for basic alumina-catalyzed synthesis of substituted DHPs has been proposed in (Scheme 2). The first step of this reaction can be visualized as the basic alumina-catalyzed formation of Knoevenagel product 5. A second key intermediate is

ester enamine 6, produced by condensation of the second equivalent of the β -ketoester with ammonia. Condensation of these two fragments gives intermediate 7, which subsequently cyclizes to the 1,4-dihydropyridine 4.



Scheme 2 : Plausible mechanism.

EXPERIMENTAL SECTION

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. IR spectra were recorded on a Perkin-Elmer FT-IR instrument. The ^1H - and ^{13}C -NMR spectrum were recorded on a Bruker Avance II 400 NMR machine. Unless otherwise specified, CDCl_3 was used as solvent. Mass spectra were recorded with a Water ZQ-4000 equipped with ESI and APCI mass detector and CHN was done on Perkin-Elmer PE 2400 Series II. CEM Discover microwave reactor was used for microwave reaction.

General conventional procedure for synthesis of dihydropyridines (DHPs) 4

To a mixture of aldehyde (1 mmol) and methyl acetoacetate (2.1 mmol) in tap water (5 mL) was added basic alumina (10 mol %) and the resulting mixture was stirred at room temperature. A precipitation took place within 5-10 minutes, after which ammonium acetate (1 mmol) was added while continuing the stirring. The reaction mixture was subsequently refluxed for 2.5-4 hrs. On completion of the reaction (monitored by TLC), it was cooled and water was evaporated in *vacuo*. The

reaction was treated with ethyl acetate and filtered through a sintered funnel and washed thoroughly with the same solvent. The combined filtrate was evaporated in *vacuo* to afford the crude product which was purified by column chromatography over silica gel (100-200 mesh) using ethyl acetate/ hexane (3:7) as the eluent to afford pure compound 4.

General microwave procedure for synthesis of dihydropyridines (DHPs) 4

Aldehyde (1 mmol), methyl acetoacetate (2.1 mmol), basic alumina (10 mol%), ammonium acetate (1 mmol) and tap water (5 mL) were mixed and placed in a sealed pressure regulation 10-mL pressurized vials with "snap-on" cap and was irradiated in the CEM Discover microwave reactor at 120W power and 100°C temperature for 3-5 minutes. After the completion of reaction (TLC), the mixture was cooled and water was evaporated in *vacuo*. The reaction was treated with ethyl acetate and filtered through a sintered funnel and washed thoroughly with the same solvent. The combined filtrate was evaporated in *vacuo* to afford the crude product which was purified by column chromatography over silica gel (100-200 mesh) using ethyl acetate/ hexane (3:7) as the eluent to afford pure compound 4.

Same procedure was followed for the reaction when

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acidic alumina and neutral alumina were used as catalyst during the comparative study.

Dimethyl 4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4a, TABLE 2)

Off white solid, mp 195-197°C. IR ν_{\max} (KBr): 3343, 3237, 2965, 1699, 1653, 1487, 1440, 1314, 1215, 1116, 1036 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ 7.03-6.87 (m, 4H, CH_{arom}), 5.50 (s, 1H, NH), 4.72 (s, 1H, CH), 3.40 (s, 6H, OCH_3), 2.10 (s, 6H, CH_3) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ 167.9, 146.0, 144.5, 131.8, 129.1, 128.1, 103.6, 103.4, 51.1, 38.9, 19.5 ppm. MS (ESI) Calcd for $\text{C}_{17}\text{H}_{18}\text{ClNO}_4$ 335.09; Found m/z 358.0 ($\text{M}+\text{Na}$)⁺. Elemental Analysis for $\text{C}_{17}\text{H}_{18}\text{ClNO}_4$ Calcd. C, 60.81; H, 5.40; N, 4.17; Found C, 60.76; H, 5.44; N, 4.10.

CONCLUSION

In conclusion, we have demonstrated the superiority of basic alumina as a recyclable catalyst for the synthesis of dihydropyridines (DHPs) in water under microwave irradiation. The reaction scheme provides good yield and almost no side products. We have also presented a comparative study between basic, acidic and neutral alumina where the efficiency of basic alumina over the others is highlighted. The salient features of this protocol are good yields, mild reaction conditions, environmentally benign, superior atom economy, the readily accessibility of the catalyst, cost effectiveness and the recyclability of the catalyst.

ACKNOWLEDGEMENTS

M.R. thanks the UGC-RGNF for financial assistance and SAIF, NEHU for providing analytical supports.

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