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Efficient Solid Phase Acid Catalyst One Pot Synthesis Of 1,8-Naphthyridines *Via* Microwave Irradiation

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ABSTRACT

A simple and efficient procedure has been developed for the synthesis of 1,8-naphthyrdines by using solid phase catalyst such as anhydrous aluminiumchloride. Products were prepared in a single step from readily available and inexpensive starting material 2-aminopyridine under microwave irradiation.

INTRODUCTION

Considerable interest has been shown in naphthyridines, on account of their excellent pharmacological activity. Antibiotic of this group are being widely used for the diagnostics and chemotherapy of infectious diseases of humans including AIDS. Some of new 1,8-naphthyridine derivatives have recently been patented as growth regulators, fungicides, bactericides, herbicides, insecticides, and nematho cides of new generation[1-5]. In recent years the number of publications devoted to various aspects of naphthyridine chemistry has sharply increased. More number of publications have appeared during last two decades 40% of them being patents.

The first derivative of naphthyridine obtained in 1893, since then number of methods has been appeared in the literature for the synthesis of 1,8-naphthyridine derivatives[1,6-8]. Among the variety of strategies for the construction of 1,8- naphthyridine moieties, one of the most important method is Friendlander condensation of 2-aminonicotinaldehyde with carbonyl compounds containg a-methylene group in the presence of an acid or base[9] catalyst. A recent report[10,11] described the synthesis of 1,8-naphthyridines starting from 2-aminonicotinaldehyde. However, potentially significant drawbacks of all these methods involves a number of steps, drastic conditions, long reaction time, low yields and more importantly the uses of expensive chemical 2-aminonico tinaldehyde as starting material, which is very difficult to synthesize and expensive one.

Although many synthetic methods for the synthesis of 1,8-naphthyridines have been reported, examination of literature reveals considerable scope for refinement of the existing procedures. Thus due to their great biological importance and this compound happens to be the starting material for the synthesis of heterocycles of biological interest, the development of effective ways to synthesize these compounds uti-

TABLE 1 : Microwave and thermal synthesis of 1,8-naphthyridines using anhydrous $AlCl_3$ catalyst

Product[a]	MP(^{0}C)	R	Microwave method irradiation		Thermal method	
			Time (min)	Yield[b] (%)	Time (hrs)	yield[c] (%)
2a	220	H	5	95	8	90
2b	223	CH_3	5	95	8	88
2c	221	OCH_3	6	90	9	89
2d	225	Cl	6	93	8	87
2e	223	Br	6	92	8	88
2f	225	NO_2	5	95	8	89
3a	170	H	5	90	8	88
3b	178	CH_3	4	95	8	90
3c	169	OCH_3	5	92	9	88
3d	174	Cl	4	94	8	90
3e	169	Br	6	90	9	87
3f	173	NO_2	6	92	8	90

[a]All the products were characterised by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra
[b]Yields of isolated products under MW irradiation
[c]Yields of isolated products under Thermal condition

lizing inexpensive reagent continues to be an active area of research for synthetic organic chemists.

For in-depth study and to evaluate the catalytic efficacy of various lewis acids in this reaction some other combinations have also been tried (TABLE 2). As is clear from this data in the TABLE 2, $AlCl_3$ is the most effective catalyst. Other combinations either give poor yields or are completely ineffective.

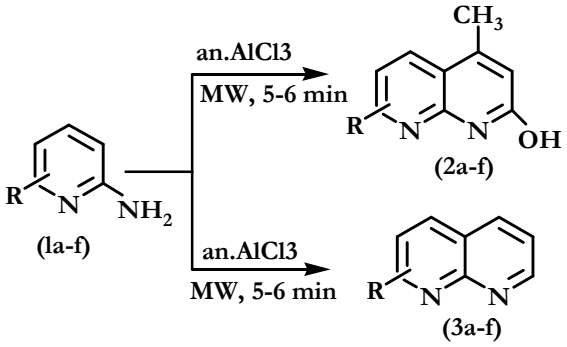
There is one report[12] on the synthesis of 1,8-naphthyridines by using inexpensive 2-aminopyridine as starting material, but the yield reported in this method between 10-30 % only. Hence, in search of an efficient high yield method and in continuation of our work on microwave assisted organic synthesis of condensed heterocycles[13-15], we have focused a simple and efficient procedure for the synthesis of 1,8-naphthyridines by using inexpensive starting material 2-amino pyridine in presence of solid phase catalyst such as anhydrous aluminiumchloride under microwave irradiation.

The cyclisation of 2-aminopyridine involves the reaction of 2-aminopyridine with ethylacetoacetate or crotonaldehyde independently in presence of solid phase catalyst such as $AlCl_3$ under thermal as well as microwave conditions. The reaction of 2-aminopyridine **(1a-f)** with ethylacetoacetate in presence of $AlCl_3$ catalyst under thermal conditions afforded 2-hydroxy-4-methyl-1,8-naphthyridines **(2a-f)** in 88-90% yields. Under the similar conditions, 2-

TABLE 2 : Synthesis of 1,8-naphthyridines in the presence of different catalyst

Entry	Catalyst	Time(h)	Time(min)	Yield(%)
1	$FeCl_3$	25	30	50
2	$FeCl_3$ +KI	19	25	65
3	$LiCl_3$	13	20	65
4	$FeCl_3.6H_2O$	13	20	n.r
5	$AlCl_3$. $6H_2O$	15	20	n.r
6	$AlCl_3$	8-9	5-6	85-90

aminopyridine **(1a-f)** reacts with crotonaldehyde gave 65-70% yield of 1,8-naphthyridines. Though both the reactions affording high yields of target products, 1,8-naphthyridines **(2a-f)** and **(3a-f)** the reaction needs a long time for completion(8-9h) at 120-130^{0}C (TABLE 1). However, in microwave oven the reaction proceeded with quantitative yields at a faster rate. Thus, the rate of the reaction is fast in the microwave irradiation as a result the reaction times are shorter and yields are high with easy isolation products. Hence, these results show that the microwave-assisted **(3)** reactions for the synthesis of 1,8-naphthyridines are more convenient, it shorter the reaction time from 8-9hrs to 5-6 min (TABLE 1) and also anhydrous AlCl3 proved to be anactive acid catalyst for the synthesis of 1,8-naphthtyridine under microwave irradiation.



SCHEME 1

The high yield protocol for the preparation of 1,8-naphthyridines provides a better alternative to the existing methodologies due to its shorter reaction time, simpler reaction procedure, utilization of inexpensive chemicals and the formation of cleaner products that can be used for synthetic applications without further purification.

EXPERIMENTAL

Melting points were determined in an open capillary tube with a Buchi melting point apparatus and are uncorrected. Elemental analyses were carried out using Perkin-Elmer 240C CHN-analyzer. IR spectra were recorded on a FT-IR infrared spectrophotometer. ^{1}H- NMR and ^{13}C-NMR spectra were run in $CDCl_3$ solvent at 300MHz and 75MHz on a NMR spectrophotometer(chemical shifts in δppm). Mass spectra were recorded on a LC MS Mass spectrometer.

Synthesis of 1,8-naphthyridines

General procedure

1. Thermal conditions

(a) A mixture of 2-aminopyridine(0.01mol) and ethylacetoacetate(0.01mol) and anhydrous aluminiumchloride(0.001mol) was heated at 120^{0}C for 8-9h. The reaction mixture was cooled and poured in ice cold water(50mL) and ethyl acetate(25mL). The organic layer was separated from the aqueous one and organic phase was washed with saturated solution of sodium bicarbonate(2×20mL) and water, dried over anhydrous Na_2SO_4, filtered and concentrated to yield yellow colour product and recrystalised from excess methanol to yield pure yellow product **(2a)**(TABLE 1).

(b) A mixture of 2-aminopyridine(0.01mol) and crotonaldehyde(0.01mol) and anhydrous aluminiumchloride(0.001mol) was heated at 120^{0}C for 8-9h. The reaction mixture was cooled and poured in ice-cold water(50mL) and ethyl acetate(25mL). The organic layer was separated from the aqueous one and organic phase was washed with saturated solution of sodium bicarbonate (2×20mL) and water, dried over anhydrous Na_2SO_4, filtered and concentrated to yield yellow colour product and recrystalised from excess methanol to yield pure yellow product **(3a)** (TABLE 1).

2. Microwave conditions

(a) A mixture of 2-aminopyridine (0.01mol) and ethylacetoacetate(0.01 mol) and anhydrous aluminiumchloride(0.001mol) was taken in a beaker and irradiated in MW at 160 W for 6 min. The completion of the reaction was checked by TLC and poured in ice-cold water (50mL) and ethyl acetate(25mL). The organic layer was separated from the aqueous one and organic phase was washed with saturated solution of sodium bicarbonate(2×20 mL) and water, dried over anhydrous Na_2SO_4, filtered and concentrated to yield yellow colour product and recrystalised from excess methanol to yield pure yellow product **(2a)**. (TABLE 1). FT-IR(KBr): 3440(O-H), 2956(C-H), 1580(C=N)cm^{-1}. ^{1}H-NMR (DMSO-d6, 300MHz): δ(ppm)=7.0-8.3(m, 4H, Ar-H), 8.34(3H, s), ^{13}C-NMR ($CDCl_3$): 135.0, 128.2, 148.3, 158.0, 139.4, 136.1, 140.1, 1270, 160.3. Mass, m/z; 162(M.+2). Anal.Calcd(%) for C9H8N2O: C; 67.49, H; 5.03, N; 17.49. Found: C; 67.48, H; 5.02, N; 17.47.

(b) A mixture of 2-aminopyridine(0.01mol) and crotonaldehyde(0.01mol) and anhydrous aluminiumchloride(0.001mol) was taken in a beaker and irradiated in MW at 160 W for 6 minutes. The completion of reaction was checked by TLC and poured in icecold water (50mL) and ethyl acetate(25mL). The organic layer was separated from the aqueous one and organic phase was washed with saturated solution of sodium bicarbonate(2×20mL) and water, dried over anhydrous Na_2SO_4, filtered and concentrated to yield yellow colour product and recrystalised from excess methanol to yield pure yellow product **(3a)**. (TABLE 1). FT-IR(KBr): 2956(C-H), 1557(C=N)cm^{-1}. ^{1}H-NMR (DMSO-d6, 300 MHz): δ(ppm)=6.9-8.7(m, 6H, Ar-H, Mass, m/z; 132 (M.+2). Anal.Calcd(%) for C8H6N2: C; 73.83, H; 4.65, N; 21.52. Found: C; 73.80, H; 4.63, N; 21.51.13C NMR ($CDCl_3$): 135.2, 128.4, 148.6, 158.8, 139.2, 136.4, 135.2, 127.9, 149.3.

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CONCLUSIONS

In conclusion the presented synthetic procedure is convenient, simple and high yielding microwave-assisted method for the synthesis of 1,8-naphthy ridines in the presence of anhydrous aluminium chloride by using inexpensive 2-aminopyridine. Anhydrous aluminiumchloride is envirofriendly, active acid catalyst. It could be the economical method and appear to be better than the reported methods and also would be useful to a large number of synthetic chemists working in this field.

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