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Sulfamic Acid: An Efficient, Cost-Effective, and Reusable Solid Acid Catalyst for the Synthesis of 1,8-Naphthyridines Under Solvent-Free Heating and Microwave Irradiation

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Abstract: An efficient and convenient method is described for the synthesis of 1,8-naphthyridines in excellent yields by condensation of 2-aminonicotinaldehyde with various active methylene compounds in the presence of sulfamic acid as the catalyst in a solvent-free media using both conventional heating and microwave irradiation.

Keywords: Microwave irradiation, 1,8-naphthyridines, solvent-free, sulfamic acid

INTRODUCTION

1,8-Naphthyridines and their derivatives are pharmacologically important because their wide range of biological and therapeutic properties, and there are numerous reports that highlight their chemistry and therapeutic use.[1] Thus, 1,8-naphthyridines and their derivatives have emerged as powerful tools in organic synthesis. 1,8-Naphthyridines are prepared by using either the Friedlander condensation[2] or the Knoevenagel reaction.[3] Even though various procedures are reported, disadvantages, including low yields, prolonged reactions times, use of an excess of

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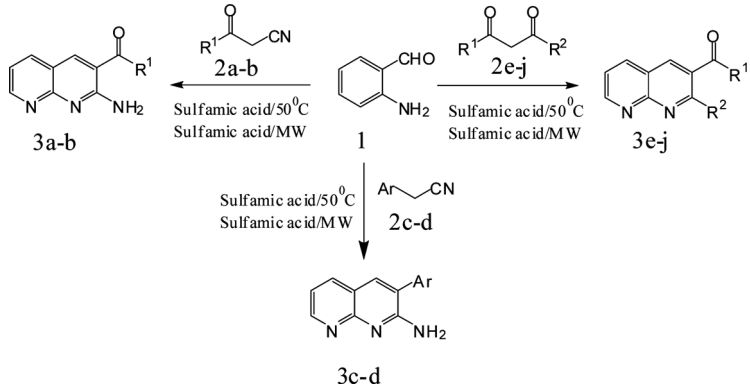


Scheme 1. Sulfamic acid (SA)-catalyzed synthesis of 1,8-naphthyridines.

reagents/catalysts, and use of toxic organic solvents necessitate the development of an alternative route for the synthesis of 1,8-naphthyridines.

Recently, sulfamic acid has emerged as a promising solid acid catalyst for acid-catalyzed reactions such as functional group protection and deprotection,[4] and synthesis of isoamyl acetate,[5] polymeric ether,[6] and xanthanes.[7] In addition, some important organic transformations, such as the Beckmann rearrangement,[8] Pechmann,[9] and Biginelli condensation[10] reactions have been performed successfully in the presence of a catalytic amount of sulfamic acid. In recent years, organic reactions in solvent-free conditions (solid state) have been increasingly attractive to synthetic organic chemists because of their simplicity and synthetic value.[11–13] Moreover, solvent-free reactions have many advantages, including ecofriendliness, commercial viability, and simplicity in processing, handling, and workup. In continuation of our work[7,14–16] on the development of new synthetic methodologies using acid catalysts and microwave irradiation, we have observed that sulfamic acid (SA) is an efficient catalyst for the synthesis of 1,8-naphthyridines from 2-aminonicotinaldehyde and active methylene compounds in solvent-free media utilizing both conventional heating and microwave irradiation (Scheme 1).

RESULTS AND DISCUSSION

In the microwave irradiation procedure for the synthesis of 1,8-naphthyridines, the reaction mass containing 2-aminonicotinaldehyde and active methylene compound was irradiated in a domestic microwave oven at 300 w over 30-s intervals in an open vessel for 2–5 min. The

Table 1. Effect of five acid catalysts on the reaction of 2-aminonicotinaldehyde with *N*-phenyl acetoacetamide under conventional and microwave heating

Catalyst	Method A		Method B	
	Time (min)	Yield (%)	Time (h)	Yield (%)
Sulfamic acid	3	93	1	82
Silica sulfuric acid	3	68	1	56
p-TsOH	3	62	1	48
H_2SO_4	3	42	1	35

1,8-naphthyridines were also conventionally prepared at 50°C over 1–2 h. The structures of all newly synthesized 1,8-naphthyridines were confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectral data.

To study the efficiency of a number of acidic catalysts compared to sulfamic acid in the synthesis of the 1,8-naphthyridines, we conducted a model reaction between 2-aminonicotinaldehyde and *N*-phenyl acetoacetamide in the presence of either sulfamic acid, silica sulfuric acid, *p*-toluenesulfonic acid, or sulfuric acid (all at 10 mol%) under both microwave irradiation (Method A) and conventional heating (Method B) conditions (Table 1). In this study, it was found that, compared to the other acid catalysts utilized, sulfamic acid was a more effective catalyst with respect to reaction time and yield of the resulting 1,8-naphthyridines (Table 1).

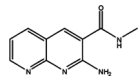
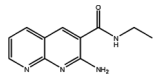
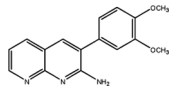
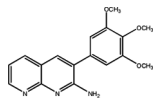
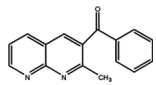
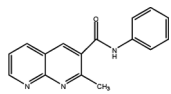
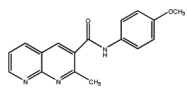
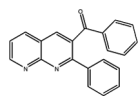
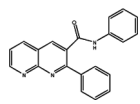
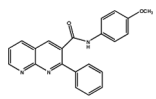
A variety of 2,3-disubstituted 1,8-naphthyridines were also synthesized via the conventional heating and microwave procedures all of which were obtained in good yields (Table 2), illustrating the versatility of methods A and B.

Analytical Data of Novel Compounds

3-(3,4-Dimethoxyphenyl)-[1,8]-naphthyridin-2-yl-amine (Table 2, entry **3c**): Pale yellow solid: mp 253 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.92$ (s, 3H), 3.95 (s, 3H), 5.5 (bs, 2H), 7.00–7.06 (m, 4H), 7.73 (s, 1H), 7.95 (dd, 1H), 8.87 (dd, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.33, 56.36, 111.88, 112.02, 118.38, 118.88, 121.42, 126.08, 129.41, 136.26, 137.19, 149.40, 149.56, 152.69, 159.18, 158.22; HRMS (EI^+): m/z found 281.1166; calcd. $C_{16}H_{15}N_3O_2$ (EI^+): 281.1164.

3-(2,3,4-Trimethoxyphenyl)-[1,8]-naphthyridin-2-yl-amine (Table 2, entry **3d**): Pale yellow solid: mp 266 °C. ^{1}H NMR (300 MHz, $CDCl_3$):

Table 2. Sulfamic acid (SA)–catalyzed synthesis of 1,8-naphthyridines via Scheme 1

		Method A		Method B		
Entry	Product	Time (min)	Yield (%)	Time (hrs)	Yield (%)	Mp (°C)
3a		3.0	92	1.5	78	222[17]
3b		4.0	90	2.0	75	220[17]
3c		3.0	95	1.2	85	257
3d		3.0	92	1.5	80	242
3e		4.0	90	2.0	75	143[2b]
3f		3.0	93	1.0	82	215[2b]
3g		2.0	90	1.2	80	150[2b]
3h		1.5	78	5.0	93	160[2b]
3i		1.0	76	4.0	91	280[2b]
3j		1.5	74	3.0	93	218[2b]

[a]Yields refer to pure products and all products were characterized by comparison of their physical data and ^{1}H NMR, ^{13}C NMR, and mass spectral data with those of authentic samples.

$\delta = 3.94$ (s, 6H), 3.96 (s, 3H), 5.6 (bs, 2H), 6.98–7.02 (m, 3H), 7.71 (s, 1H), 7.98 (dd, 1H), 8.88 (dd, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.33, 56.36, 111.88, 112.02, 118.38, 118.88, 121.42, 126.08, 129.41, 136.26, 137.19, 149.40, 149.56, 152.69, 159.18, 158.22; HRMS (EI^+): m/z found 311.1273; calcd. $C_{17}H_{17}N_3O_3$ (EI^+): 311.1270.

EXPERIMENTAL

General Procedure: Microwave Irradiation Method (Method A)

Sulfamic acid (0.1 mmol) was added to a mixture of 2-aminonicotinaldehyde **1** (1 mmol) and active methylene compound **2** (1 mmol), and the mixture was inserted in a microwave oven (BPL, 800 T model) and irradiated at 300 W for the appropriate time (Table 2). Completion of the reaction was indicated by thin-layer chromatography (TLC). After completion, the reaction mass was cooled to room temperature, water was added, and the mixture was stirred for 5 min. The resultant solid was filtered, washed with water, and recrystallized from an appropriate solvent to afford pure crystalline 1,8-naphthyridine derivative **3**.

Conventional Heating Method (Method B)

A mixture of 2-aminonicotinaldehyde **1** (1 mmol), active methylene compound **2** (1 mmol), and sulfamic acid (0.1 mmol) was stirred at 50 °C for the appropriate time (Table 2). Completion of the reaction was indicated by TLC analysis. The reaction was cooled to room temperature and treated with water. The resultant solid was filtered, washed with water and recrystallized from an appropriate solvent to afford pure crystalline 1,8-naphthyridine derivative **3**.

CONCLUSION

We have demonstrated an efficient and very simple procedure for the synthesis of 1,8-naphthyridines via the condensation of 2-aminonicotinaldehyde with various active methylene compounds in solvent-free media under conventional heating and microwave irradiation using sulfamic acid, which is inexpensive, nontoxic, and a readily available solid acid catalyst. Prominent among the advantages of this new procedure are easy workup, good yields, short reaction times, and operational simplicity.

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