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Silica sulfuric acid catalysed synthesis of 1,8-naphthyridines in the solid state under microwave irradiation

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ABSTRACT

Synthesis of 1,8-Naphthyridine derivatives *via* Friedländer condensation method from 2-amino-Pyridine-3-Carboxaldehyde in the presence of a catalytic amount of silica sulfuric acid (SSA) under solvent-free condition and microwave irradiation was described. A good range of simple ketones such as ethylacetoacetate and acetophenones.

KEYWORDS

1,8-Naphthyridines;
2-Amino-pyridine-3-Carboxaldehyde;
Ketones;
Silica sulfuric acid.

INTRODUCTION

Naphthyridines are an important class of pharma ceutically active compounds as they have excellent biologi cal activities, antibacterial[1,2], antimycobacterial[3], antitumor[4], antiinflam matory[5], antiplat elet[6], gastric antisecretary[7], antiallergic[8], local anaesthetic[9] and benzodia zepine receptor activity[10]. Nalidixic acid, for example, possesses strong antibacterial activity and used mainly for the treatment of urinary tract infections with gram negative pathogens[11]. In addition, Gemifloxacin is antimicrobial and antibacterial[12]. For these reasons their synthesis has always attracted the attention of synthetic organic chemists. Among the variety of strategies for the construction of 1,8-naphthyridine moiety, one of the most important methods is Friedlander condensation of 2-aminonicotinaldehyde with carbonyl compounds containing α-methylene group in the presence of an acid[13] or base[14] catalyst. This method has limitations such as harsh reaction conditions, longer reaction time period and tedious work-up. Therefore, it is important to develop a simple and environmentally safe solvent free method to synthesize 1,8-naphthyridine derivatives. In recent years, considerable interest has emerged in microwave induced reactions[15,16] and solvent-free organic synthesis mediated by microwave irradiation[17,18] offers significant advantages. In view of this and in continuation of our ongoing programme to develop synthetic protocols utilizing inorganic reagents under microwave irradiation[19-20], herein, we report a novel solvent-free synthesis of 1,8-naphthyridines which utilizes the relatively benign reagent such as silica sulfuric acid (SSA) and a clean energy source, microwave irradiation.

RESULTS AND DISCUSSION

The Friedlander condensation of 2-aminonicotinaldehyde with carbonyl compounds containing α-methylene group in the presence of silica sulfuric acid (SSA) under solvent-free condition and microwave irradiation afforded 1,8-naphthyridines in good yields (75-98%) in a short reaction time period (4-10 min). The present high yielding protocol for the prepa-

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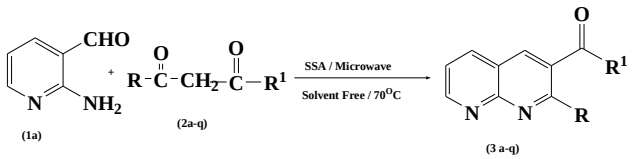
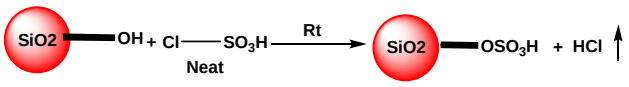
ration of 1,8-naphthyridines provides a better alternative to the existing methods due to its shorter reaction time period, simpler reaction procedure and the formation of cleaner products that can be used for synthetic applications without further purification. All the compounds prepared were characterized by IR and ^{1}H NMR spectroscopy and finally by comparison with authentic samples[14,21-24].



Scheme 1

All reagents used were commercial grade; melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were obtained on a varian 500 MHz instrument with TMS as internal Standard and chemical shifts are expressed δ ppm solvent used id $CDCl_3$ & $DMSOd_6$ and Mass spectrum on a Hewelett Packard mass spectrometer operating at 70ev, purity of the compounds were checked by TLC, which is performed with.E.Merch precoated silica gel plates (60F-254) with iodine as a developing agent. Acme,India silica gel, 60-120 and 230-400 mesh for column chromatography is used. All compounds are recrystalised in ethanol and methanol.

Silica sulfuric acid was easily prepared by reaction of silica gel with chlorosulfonic acid[25]. The reaction is very clean and not requiring any work-up procedure because the evolved HCl gas can be removed from the reaction vessel immediately.



Scheme 2 : Preparation of silica sulfuricacid

For the optimization of reaction conditions, 2-aminonicotinaldehyde and pentane-2,4-dione was selected as model substrate. It was found that, in the absence of solvent, the reaction is completed in the presence of 0.1 equivalents of SSA as catalyst and irradiation by microwave for 5 min. 1-(2-Methyl-[1,8]naphthyridin-3-yl)-ethanone **(1a)** was obtained in 94% yield. To demonstrate the generality of the method, we next extended the scope of this reaction to other model compounds, the results of which are summarized in TABLE 1. This method is equally effective for both cyclic and acyclic ketones.

EXPERIMENTAL

General experimental procedure for the preparation of 1,8-naphthyridines

2-aminonicotinaldehyde (500 mg, 4.09 mmol), pentane-2,4-dione (451 mg, 4.50 mmol) and silica sulfuric acid (57 mg, 0.04 mmol) were mixed together and irradiated under micro wave condition (Black & Deaker, 900 W, 80%) for 5 min (5 × 1 min). The mixture was washed with ethanol (2 ×10 ml) and filtered. After evaporation of the solvent, the desired product was recrystallized in hot ethanol and acetone to give **(3a)** in 94% yield.

The other 1,8-naphthyridines were characterized by comparison of their spectral (mp, ^{1}H-NMR, IR), TLC and physical data with the authentic samples.

Spectral data for selected compounds

2-Cyclopropyl-[1,8]naphthyridine-3-carboxylic acid ethyl ester (3g)

White solid; ^{1}H NMR (300 MHz, $DMSOd_6$): 9.12 (d, 1H, J = 6.5 Hz), 8.83 (s, 1H), 8.58 (d, 1H, J=6.2 Hz), 7.59, (t, 1H, J = 7.2 Hz), 4.41 (q, 2H, J= 8.0), 2.91 (m, 1H), 1.39 (t, 3H, J=6.8 Hz, CH_3), 1.23, (q, 2H, J= 6.8 Hz, CH_2), 1.12 (q, 2H, *J* =6.8Hz, CH_2); ^{13}C NMR (300 MHz, $DMSOd_6$): 171.5 (CO), 162.2,151.2, 148.3, 135.6, 134.8, 125.2, 124.6, 119.3, 58.3 (OCH_2), 14.6 (CH_3), 9.4 (CH), 7.2 ($2CH_2$) ; IR (ν/cm^{-1}); 1724 (CO); MS (EI): m/z (M+1) 243.3. Analysis (% Cal/fou) for $C_{14}H_{14}N_2O_2$, C: 69.41/ 69.38, H: 5.82/ 5.53, N: 11.56/ 11.48.

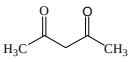
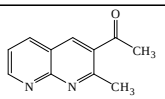
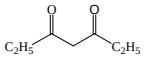
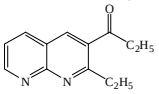
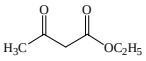
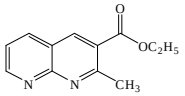
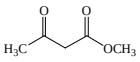
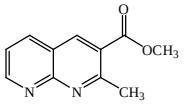
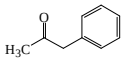
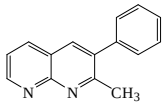
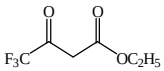
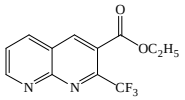
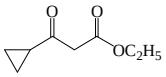
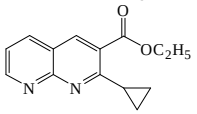
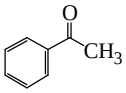
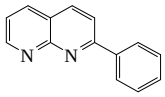
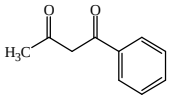
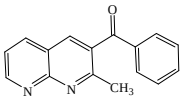
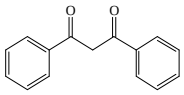
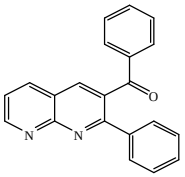
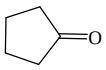
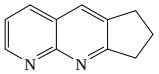
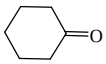
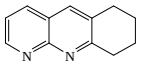
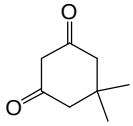
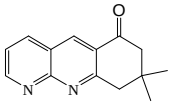
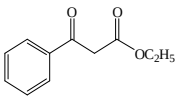
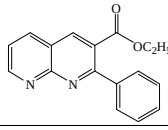
2-Phenyl-[1,8]naphthyridine (3h)

Light yellow solid, ^{1}H NMR (300 MHz, $DMSOd_6$): δ 7.42-7.56 (m, 5H, 5CH), 8.21,(d, 1H, J= 15 Hz, CH), 8.39-8.42 (m, 3H, 3CH), 8.91 (d, 1H, CH). ^{13}C-NMR (300 MHz, $DMSOd_6$/ TMS) δ: 121.3, 123.8, 124.4, 126.9, 129.3, 139.2, 149.2, 150.1, 158.3. (Mass (m/z): 207.2 [M+1].

6,7,8,9-Tetrahydro-benzo[b][1,8]naphthyridine (3l)

Cream colour solid; ^{1}H NMR (300 MHz, $DMSOd_6$) : δ 9.18 (d, 1H, J=6.4 Hz), 8.56, (d, 1H,

TABLE 1 : Friedlandler condensation of 2-aminonicotinaldehyde and ethylacetoacetates in presence of SSA

S.No	Substrate	Ketone	Product	Isolated Yields (%)	Time (min)	M.p.°C (Found/Lit)
1	3a			94	5	146/146-147 (ref.18)
2	3b			97	4	125/125 (ref.14)
3	3c			95	6	86/85-86 (ref.14)
4	3d			93	6	85/82-84 (ref.14)
5	3e			95	7	129/128-129 (ref.14)
6	3f			95	4	125/125 (ref.24)
7	3g			98	8	168 (ref.25)
8	3h			75	6	122
9	3i			85	5	142/143 (ref.22)
10	3j			90	5	161/160 (ref.22)
11	3k			85	8	164
12	3l			96	8	178
13	3m			91	10	122
14	3n			90	6	104/104 (ref.23)

Products were characterized by comparison of their spectroscopic data (^{1}H NMR and IR) and M.p's with those reported in the literature

J = 6.5 Hz), 8.11 (s, 1H), 7.51 (t, 1H, J=7.4 Hz), 3.19 (t, 2H, J=8.2 Hz, CH_2), 2.81 (t, 2H, J= 8.0 Hz, CH_2), 1.62 (m, 4H, $2CH_2$); NMR (300 MHz, $DMSOd_6$ / TMS) δ: 161.2, 147.3, 146.4,133.4, 132.3, 123.5, 121.2, 35.8 ($2CH_2$), 31.2 (CH_2), 28.3 (CH_2); IR (KBr pellet): 2210 (aliph. CH_2) cm $^{-1}$; MS

(EI): m/z (M+1) 185.4; Analysis (% Cal/fou) for $C_{12}H_{12}N_2$, C: 78.23/ 78.18, H: 6.57/ 6.53, N: 15.21/ 14.48.

8,8-Dimethyl-8,9-dihydro-7H-benzo[b][1,8] naphthyridin-6-one (3m)

Off-white solid; ^{1}H NMR (300 MHz, DMSOd_6): δ 9.21 (d, 1H, J=6.2 Hz), 8.62, (d, 1H, J = 6.6 Hz), 8.21 (s, 1H), 7.41 (t, 1H, J=7.4 Hz), 3.12 (s, 2H, CH_2), 2.55 (s, 2H, CH_2), 1.19 (s, 6H, 2CH_3); ^{13}C NMR (300 MHz, DMSOd6): 198.4 (CO), 171.2, 151.6, 150.2, 136.7, 135.1, 125.3, 124.6, 53.2, 47.5, 25.2, 23.5; IR (KBr pellet): 1735 (CO, keto); MS (EI): m/z (M+1) 227; Analysis (% Cal/fou) for $C_{14}H_{14}N_2O$, C: 74.31/ 74.18, H: 6.24/ 6.14, N: 12.38/ 12.05.

CONCLUSION

In conclusion, the SSA-promoted reaction reported here is a novel extension of 1,8-naphthyridine synthesis *via* condensation of different ketones and 2-amino-pyridine-3-carbo xaldehyde (Friedlander condensation). This is the very good, eco-friendly and economically very cheap for preparing the various 1,8-naphthyridines.

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