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Microwave Assisted One Pot Synthesis of Functionalized Fused Benzo [1,8]Naphthyridine Scaffolds

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ABSTRACT

An interesting development method for the synthesis of 5, 6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine derivatives were prepared by microwave irradiation. A facile and rapid procedure by one pot three component reaction of 2-chloroquinoline-3-carbaldehydes (1a-e), 1-tetralone (2) and Ammonium acetate (3) using strong base in polar aprotic solvent is described.

KEY WORDS: 5, 6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine, Ammonium acetate, benzo-naphthyridine, nitrogen heterocycles, microwave synthesis, three component protocol.

1. INTRODUCTION

[1, 8] naphthyridine scaffolds have been isolated from natural products which possess a wide spectrum of biological activities. [1,8]Naphthyridine derivatives exhibit a broad range of interesting physiological activities, such as anti-inflammatory, (Baba, 1996; Barbosa-Filho, 2006) analgesic, (Roma, 2000) antiaggressive, (Atanasova, 2007) anticancer, (Kuramoto, 2003) antibacterial, (Chen, 1997) antitumor, (Ferrarini, 2000) antihypertensive, (Sherlock, 1988) and antiallergitic (Barlin, 1984). Additionally, some [1,8]naphthyridine derivatives show their outstanding optical properties for developing the fluorescent dyes, (Sun, 2006; Li, 2010) and sensors (Fang, 2004; Ghosh, 2007) Microwave-assisted (MW) reactions have significant method in organic synthesis have given a considerable attention in the past decade (Raghukumar, 2003; Shintani, 2003). More importantly, Microwave irradiation often carries the features such as remarkably easier workup, decreased reaction time and increased yield. In conjunction with continued interest, a convenient reaction sequence in combinatorial synthesis (Tu, 2007) was explored the use of microwave assisted combinatorial synthesis of nitrogen heterocycles.

The simple method provided a convenient operation of naphthyridine analogs which was very difficult to lead the synthesis using conventional synthetic route (Pitchai, 2013). In the past, the synthesis of heterocycles and macro molecules using microwave methodology have been well documented in the literature (Katritzky, 2003). A new series of heterocyclic compounds, involving naphthyridine analogs were successfully synthesized under microwave irradiation which resulted the advantages of short simple operation, increased safety and synthetic rigid route for small-scale rapid synthesis for biomedical screening. These green technique provided an efficient small naphthyridine skeletons for medicinal chemistry fields (Han, 2009). The method of solvent free microwave irradiation chemical reactions was used in synthetic area with the importance due to environmentally friendly processes, as compared to conventional method (Loupy, 1998). The Friedlander condensation under microwave irradiation in presence of montmorillonite K10 clay or LiCl in solvent free conditions afforded the [1,8]naphthyridine analogs in fairly good yields (Mogilaiah, 2006).

The present study have been reported a one pot microwave assisted synthesis of 5, 6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine 4(a–d) from easily available and cheap precursor, namely 2-chloro-quinoline-3carbaldehyde (1a-e), 1-tetralone (2), ammonium acetate (3).

2. EXPERIMENTAL PROCEDURE

Melting points determined using a Raga melting point apparatus, were uncorrected. IR spectra were recorded on Shimadzu FTIR-8201 PC spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR and ^{13}C NMR were determined on Bruker Avance III-400 MHz spectrometer in DMSO- d_6 solution. J values are in Hz. Chemical shifts are expressed in ppm down field from internal standard TMS. Mass spectrum (MS) was recorded on a Finnigan LCQ ion-trap mass spectrometer (Thermo Finnigan Corporation, San Jose, CA) Ionization Electrospray Ionization (ESI) or Atmospheric Pressure Chemical Ionization (APCI). Elemental analysis was performed on a Vario EL III CHNS Analyzer and a Perkin Elmer 2400 Series II CHNS analyzer. The purity of the compounds was checked by TLC on silica gel plates using 4:1 petroleum ether and ethyl acetate. The microwave used is a CEM microwave synthesizer (Model No: 908010) operating at 180/264 V and 50/60 Hz with microwave power maximum level of 300 W and microwave frequency of 2455 MHz.

General procedure for the synthesis of 5,6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine (4a-e): A mixture of 2-chloroquinoline-3-carbaldehydes (1a-e) (500mg, 2.4mmol), 1-tetralone (2) (0.48mL, 3.6mmol), Ammonium acetate (3) (462mg, 6mmol) (1:1.5:2.5 ratio), NaH (10 mol %) in dry DMF (10mL), which was taken in a flask, was introduced into the microwave oven at 240W and irradiated for 10-12 min as indicated in Table.1. After completion of the reaction (monitored by TLC), the solution was treated with cold water and acidified with dil. HCl till complete

precipitation and the solid so formed, was filtered, dried and chromatographed using silica gel over petroleum ether–ethyl acetate (95:5) as eluent and then recrystallized using ethanol:DMF(1:1).

10-methoxy-5,6-dihydro-naphtho[*g*]benzo[*b*][1, 8]naphthyridine 4a: Yield 72%, m.p. 175-177^{0}C; IR (KBr, *v*, cm^{-1}) 1641(C=N); ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ (ppm) 3.00(t, 2H, *J*=6.4Hz, CH$_2$), 3.05(t, 2H, *J*=5.6Hz, CH$_2$), 3.92(s, 3H, OCH$_3$), 7.40(t, 2H, *J*=7.6Hz, ArH), 7.47-7.49(m, 1H, ArH), 7.50-7.52(m, 1H, ArH), 7.60-7.64(m, 1H, ArH), 7.77(s, 1H, ArH), 7.89(d, 1H, *J*=9.2Hz, ArH), 8.01-8.03(dd, 1H, *J*=7.2Hz, ArH), 8.45(s, 1H, ArH); ^{13}C NMR (DMSO-d$_6$, 100 MHz) δ (ppm) 28.8, 33.9, 56.7, 120.2, 122.7, 123.3, 126.1, 127.0, 128.4, 129.1, 130.4, 136.1, 136.6, 137.8, 138.3, 143.6, 143.8, 148.1, 157.1; Anal. Calcd. For $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.94. Found C, 80.82; H, 5.22; N, 8.99.

12-methoxy-5,6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine 4b: Yield 68%, m.p. 171-173^{0}C; IR (KBr, *v*, cm^{-1}) 1638(C=N); ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ (ppm) 2.74-2.93(m, 4H, 2CH$_2$), 3.63(s, 3H, OCH$_3$), 7.17(d, 1H, *J*=7.6Hz, ArH), 7.21(t, 2H, *J*=7.2Hz, ArH), 7.23(d, 1H, *J*=7.2Hz, ArH), 7.30-7.33(m, 2H, ArH), 7.48(s, 1H, ArH), 7.94(d, 1H, *J*=7.2Hz, ArH), 8.17(s, 1H, ArH); Anal. Calcd. For $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.94. Found C, 80.85; H, 5.24; N, 8.98.

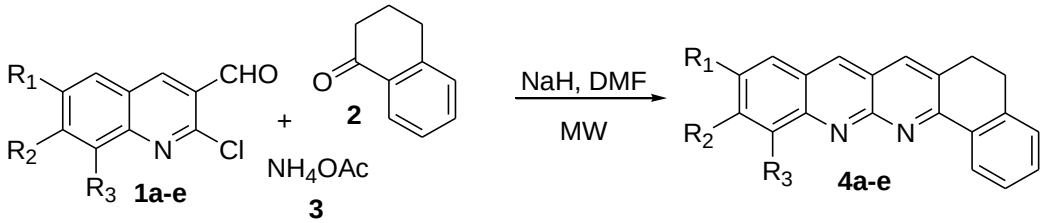
11-methyl-5,6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine 4c: Yield 80%, m.p. 190-192^{0}C; IR (KBr, *v*, cm^{-1}) 1640(C=N); ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ (ppm) 2.43(s, 3H, CH$_3$), 2.96(t, 2H, *J*=6.4Hz, CH$_2$), 3.11(t, 2H, *J*=6.6Hz, CH$_2$), 7.15(t, 2H, *J*=8Hz, ArH), 7.30(d, 1H, *J*=8.8Hz, ArH), 7.44(d, 1H, *J*=7.6Hz, ArH), 7.57(s, 1H, ArH), 7.62(d, 1H, *J*=8Hz, ArH), 7.84(s, 1H, ArH), 7.96(d, 1H, *J*=7.2Hz, ArH), 8.32(s, 1H, ArH); MS m/z(%) found [M$^+$] 296.3 (30%), Anal. Calcd. For $C_{21}H_{16}N_2$ [M$^+$] 296.1.

10-methyl-5,6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine 4d: Yield 82%, m.p. 194-196 ^{0}C; IR (KBr, *v*, cm^{-1}) 1637(C=N); ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ (ppm) 2.35(s, 3H, CH$_3$), 2.88(t, 2H, *J*=5.6Hz, CH$_2$), 2.93(t, 2H, *J*=7.2Hz, CH$_2$), 7.23(t, 2H, *J*=8.4Hz, ArH), 7.41(d, 1H, *J*=8.8Hz, ArH), 7.45(d, 1H, *J*=7.2Hz, ArH), 7.49(s, 1H, ArH), 7.56(d, 1H, *J*=7.2Hz, ArH), 7.81(s, 1H, ArH), 7.86(d, 1H, *J*=7.2Hz, ArH), 8.17(s, 1H, ArH); Anal. Calcd. For $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found C, 85.21; H, 5.52; N, 9.58.

5,6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine 4e: Yield 76%, m.p. 203-205^{0}C; IR (KBr, *v*, cm^{-1}) 1648(C=N); ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ (ppm) 2.93(t, 2H, *J*=6.4Hz, CH$_2$), 3.08(t, 2H, *J*=7.2Hz, CH$_2$), 7.28(t, 2H, *J*=8.8Hz, ArH), 7.34(t, 2H, *J*=8Hz, ArH), 7.56(d, 1H, *J*=7.6Hz, ArH), 7.63-7.66(m, 2H, ArH), 7.91(s, 1H, ArH), 8.06(d, 1H, *J*=7.6Hz, ArH), 8.48(s, 1H, ArH); Anal. Calcd. For $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found C, 85.20; H, 5.17; N, 9.98.

3. RESULTS AND DISCUSSION

Herein we report the synthesis of 5,6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine by three component reaction of 2-chloroquinoline-3carbaldehyde (1a-e), 1-tetralone (2) and ammonium acetate (3) under microwave irradiation in presence of NaH catalyst in DMF. The Starting material 2-chloroquinoline-3carbaldehyde (1a-e) was prepared according to the reported method (Meth-Cohn, 1978). Equimolar amounts of substituted 2-chloroquinoline-3-carbaldehyde was reacted with 1-tetralone and ammonium acetate in presence of 10 mol % of NaH in DMF solvent to give the corresponding substituted [1,8]naphthyridine scaffolds (4a-e) in (68-82%) yields. All three reactants were taken in the molar ratio 1:1.5:2.5 in each experiments. This protocol offered a variety of substituted naphtho-benzo [1,8]naphthyridine derivatives. Table.1, showed the reaction conditions for the three component reaction to offer various [1,8]naphthyridine derivatives in good yields. Interestingly, methyl derivatives exhibited high yields compared with other derivatives.



Scheme.1. synthesis of 5,6-dihydro-naphtho[*g*]benzo[*b*][1, 8] naphthyridine (4a-e)

Table 1. Synthesis of 5, 6-dihydro-naphtho[*g*]benzo[*b*] [1, 8] naphthyridine (4a-e)

Product	R_1	R_2	R_3	Time (mint)	Yields (%)*
4a	OCH_3	H	H	10	72
4b	H	H	OCH_3	12	68
4c	H	CH_3	H	10	80
4d	CH_3	H	H	12	82
4e	H	H	H	12	76

*Yields noted after column purifications

All compounds were characterized by IR, NMR, Mass and elemental analysis. The FTIR spectrum of compound 4a showed the band at 1641 cm^{-1} for C=N stretching. Further ^1H NMR spectrum of 4a displayed two triplet for aliphatic group at δ 3.00 and 3.05 ppm. A sharp singlet was observed for methoxy proton at δ 3.92 ppm. In addition, nine aromatic protons of compound 4a were noted at δ 7.40-8.01 ppm. In C^{13} NMR, three signals were obtained at δ 28.8, 33.9, 56.7 ppm for aliphatic groups and aromatic signals were found at δ 120.2-157.1 ppm. Finally, observed mass spectrum value m/z (%) [M^+] 296.3 (30%) of the compound 4c was consistent with the calcd. mass 296.1 for $C_{21}H_{16}N_2$ [M^+].

4. CONCLUSION

We have developed an efficient, rapid and regioselective one pot three component procedure for 5,6-dihydro-naphtho[*g*]benzo[*b*][1,8]naphthyridine compounds using inexpensive, cheap catalyst in aprotic solvent. This reaction sequence offer several features that include save time, easy workup, high selectivity and satisfactory yields.

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