A NOVEL SYNTHESIS OF SUBSTITUTED 4-HYDROXY- 1,8-NAPHTHYRIDINES

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(Received: March 19, 2009- Accepted: August 29, 2009)

ABSTRACT

Michael addition of 2-aminopyridines with methylpropiolate to afforded the addition compound 1^{a-g}, which on further cyclisation at higher temperature in dowtherm-A to yield cyclised product 2^{a-g}, with respective yields depends on the nature of the substituents.

Key words: Propionic acid methyl ester, 2-aminopyridine and 3-(Pyridin-2-ylamino)-acrylic acid methyl ester.

INTRODUCTION

Nitrogen containing heterocyclic compounds have extensive pharmaceutical applications and biologically activity. 1,8-Naphthyridines are one of the important class of such compounds as they have an excellent biological activity¹, and their chemistry is recently reviewed¹⁻³. As a step in this direction and in the continuation of our work on 1, 8-Naphthyridines⁴⁻⁷, synthesis of the compounds depicted in the title is carried out. The general synthetic procedures used in the preparation of these compounds involve the Michael type addition⁸⁻¹². Several substituted 4-hydroxy-1,8-naphthyridine and 4-Hydroxy-7-amino-1,8-naphthyridines have been prepared by condensation of substituted amino pyridines with methyl propiolates in methanol to give intermediates 3-(Pyridin-2-ylamino)-acrylic acid methyl ester derivatives, further these intermediates are cyclised in Dowtherm- A at higher temperature, to yield hydroxy naphthyridines.

Reaction Scheme:

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. ¹H NMR spectrum is taken on a Varian 500 MHz instrument with TMS as internal standard. The chemical shifts are expressed in ppm and the solvent used is DMSO-d₆. Mass spectrum is taken on Hewlett Packard mass spectrometer operating at 70 eV. All the compounds are recrystallised from ethanol.

General procedure for the preparation of compounds (1^{a-g}):

2-Amino pyridines (10.60 mmol) is dissolved in 10 ml of dry methanol and is added with Propionic acid methyl ester (16.0 mmol) drop wise at room temperature and stirred for about 16 hours. The methanol is evaporated completely under the reduced pressure. A reddish colour solids were obtained. The resulting reddish colour solids were recrystallised in ethyl acetate in hexane, yielded a light yellow coloured solids in very good yields.

General procedure for the preparation of 1,8-naphthyridines (2^{a-g}):

Compounds (1^{a-g}), (7.86 mmol) is taken in Dowtherm-A (14 mL) and refluxed about 250°C for 40-50 minutes. The reaction mixture is cooled to 30°C and poured in hexane (100 mL). A black coloured solids is precipitated which is filtered and washed twice with hexane. The resulting solids are recrystallised from ethanol to offer title compounds as brown coloured solids in good yields.

1,8-Naphthyridin-4-ol (2^a) :

¹H NMR (DMSO-d₆, 500MHz): 6.42 (s, 1H), 6.90-6.98 (t, 1H), 7.10-7.20

(d, 1H), 7.60-7.75 (t, 1H), 8.10-8.21 (d, 1H); ¹³C-NMR (500 MHz, DMSO-d₆ / TMS) δ: 82.3, 87.4 (2CH), 128.2 (1CH), 141.3 (1CH), 156.4 (1CH), 158.4 (1CH), 167.4 (1CH), 177.4 (1CH); IR (KBr pellet): 3320 (OH), cm⁻¹; Mass (m/z): 147 [M+1]; Yield 74 %.

7-Amino-1,8-naphthyridin-4-ol (2^b) :

¹H NMR (DMSO-d₆, 500MHz): 4.46 (s, 2H, NH₂), 5.24 (s, 1H, OH), 6.80-6.95 (m, 2H), 7.63-7.76 (t, 1H), 8.90-8.99 (d, 1H); ¹³C-NMR (500 MHz, DMSO-d₆ / TMS) δ: 89.3, 92.3 (2CH), 118.2 (1CH), 142.3 (1CH), 155.4 (1CH), 159.3 (1CH), 165.4 (1CH); IR (KBr pellet): 3315 (OH), 2875 (NH₂), cm⁻¹; Mass (m/z): 162 [M+1]; Yield 68 %.

5-Methyl-1,8-naphthyridin-4-ol (2^c) :

¹H NMR (DMSO-d₆, 500MHz): 2.21 (s, 3H, CH₃), 5.72 (s, 1H, OH), 6.83-6.97 (m, 1H), 7.43-7.66 (t, 1H), 8.92-8.96 (d, 1H); ¹³C-NMR (500 MHz, DMSO-d₆ / TMS) δ: 33.2, (CH₃), 85.2, 94.3 (2CH), 128.2 (1CH), 143.3 (1CH), 151.4 (1CH), 156.3 (1CH), 163.4 (1CH); IR (KBr pellet): 3318 (OH), cm⁻¹; Mass (m/z): 162 [M+1]; Yield 65 %.

6-Methyl-1,8-naphthyridin-4-ol (2^d) :

¹H NMR (DMSO-d₆, 500MHz): 2.25 (s, 3H, CH₃), 5.68 (s, 1H, OH), 6.73-6.87 (m, 1H), 7.23-7.36 (t, 1H), 8.82-8.86 (d, 1H); ¹³C-NMR (500 MHz, DMSO-d₆ / TMS) δ: 34.2, (CH₃), 84.2, 92.3 (2CH), 126.2 (1CH), 133.3 (1CH), 153.4 (1CH), 157.3 (1CH), 166.4 (1CH); IR (KBr pellet): 3324 (OH), cm⁻¹; Mass (m/z): 162 [M+1]; Yield 69 %.

7-methyl-1,8-naphthyridin-4-ol (2^e) :

¹H NMR (DMSO-d₆, 500MHz): 2.28 (s, 3H, CH₃), 5.64 (s, 1H, OH), 6.78-6.92 (m, 1H), 7.25-7.38 (t, 1H), 8.52-8.66 (d, 1H); ¹³C-NMR (500 MHz,

DMSO_d / TMS) δ: 36.4, (CH₃), 83.2, 91.3 (2CH), 124.2 (1CH), 132.3 (1CH), 152.4 (1CH), 158.3 (1CH), 164.4 (1CH); IR (KBr pellet): 3322 (OH), cm⁻¹; Mass (m/z): 162 [M+1]; Yield 69 %.

6-Chloro-1,8-naphthyridin-4-ol (2^f) :

¹H NMR (DMSO-d₆, 500MHz): 4.64 (s, 1H, OH), 6.93 (m, 1H), 7.25-7.38 (t, 1H), 8.82-8.93 (d, 1H); ¹³C-NMR (500 MHz, DMSO_d / TMS) δ: 36.4, (CH₃), 83.2, 91.3 (2CH), 124.2 (1CH), 132.3 (1CH), 152.4 (1CH), 158.3 (1CH), 164.4 (1CH); IR (KBr pellet): 3318 (OH), cm⁻¹; Mass (m/z): 181 [M+1]; Yield 75 %.

7-Methoxy-1,8-naphthyridin-4-ol (2^g) :

¹H NMR (DMSO-d₆, 500MHz): 4.18 (s, 3H, OCH₃), 6.17 (s 1H), 7.02-7.17 (d 1H), 8.33 (s 1H), 8.89 (d 1H), 9.51 (s 1H); ¹³C-NMR (500 MHz, DMSO_d / TMS) δ: 61.4, (OCH₃), 81.2, 94.3 (2CH), 121.2 (1CH), 137.3 (1CH), 155.4 (1CH), 159.3 (1CH), 163.4 (1CH); 177; Mass (m/z): (M⁺+1); Yield 71 %.

Characterization table of 4-Hydroxy 1,8-naphthyridines 2^{a-g}

Compd	R ¹	R ²	R ³	M. Formula	Melting Points	Analysis %		
						C	H	N
2a	H	H	H	C ₈ H ₆ N ₂ O	244-246	65.75	4.14	19.17
2b	H	H	NH ₂	C ₈ H ₇ N ₃ O	262-264	59.62	4.38	26.07
2c	Me	H	H	C ₉ H ₈ N ₂ O	225-227	67.49	5.03	17.49
2d	H	Me	H	C ₉ H ₈ N ₂ O	232-234	67.49	5.03	17.49
2e	H	H	Me	C ₉ H ₈ N ₂ O	246-248	67.49	5.03	17.49
2f	H	Cl	H	C ₈ H ₅ ClN ₂ O	272-274	53.21	2.79	15.51
2g	H	H	OMe	C ₉ H ₈ N ₂ O ₂	278-280	61.36	4.58	15.90

CONCLUSIONS

We have developed an economical, efficient cyclisation of amino pyridines with propiolic acid methyl ester, which can be a viable alternative to the Friedlander condensation. In the synthesis of all the derivatives, the same reaction conditions are provided. By this cyclisation one can prepare many of the 1, 8-naphthyridine derivatives, which are useful intermediates to carryout the research.

ACKNOWLEDGEMENT

Authors are thankful to the Principal, Kakatiya Institute of Technology and Science-Warangal for providing necessary laboratory facilities and the Director ICT-Hyderabad, for providing spectral data.

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