A FACILE ONE POT SYNTHESIS OF BENZO[*g*] PYRIDO [3,4- *b*] [1, 8] NAPHTHYRIDINE AND ITS DERIVATIVES

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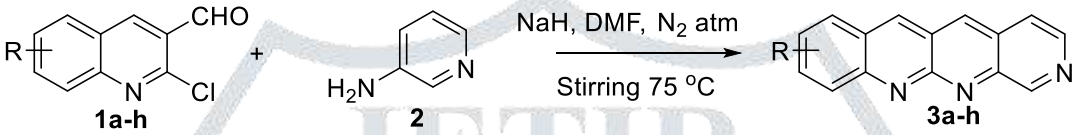
Abstract : A facile and unusual one-pot effective process of synthesizing benzo[*g*]pyrido[3,4-*b*][1,8]naphthyridine has been described in this article by using of the versatile precursor 2-chloro-3-formyl quinolines (1a-h) and 3-aminopyridine.



Keywords : *1*,8-naphthyridines, 2-chloro-3-formyl quinoline, benzo pyrido naphthyridines

1. Introduction

From the past decades, naphthyridines with fused rings like imidazo[1], dibenzo[2], benzopyrido, diazanaphtho, benzopyrazolo[3] and benzo quinoline have been widely reported. We have also much more attracted the development of synthetic routes for the above said *N*-heteroarenes for their variety of applications.[4-6] Particularly, they occupy a prominent place in the medicinal field with the characteristic properties of multifarious pharmacological[7-10] and chemotherapeutic activities. Hence, it was worthwhile to explore more alternative approaches that would provide a facile access to a wide variety of the above system. Our interests in developing new synthetic strategies using 3-amino pyridine recently made possible the development of an efficient route for the preparation of benzo pyrido naphthyridines from the precursor 2-chloro-3-formyl quinoline (**1**).

2. Results and Discussion

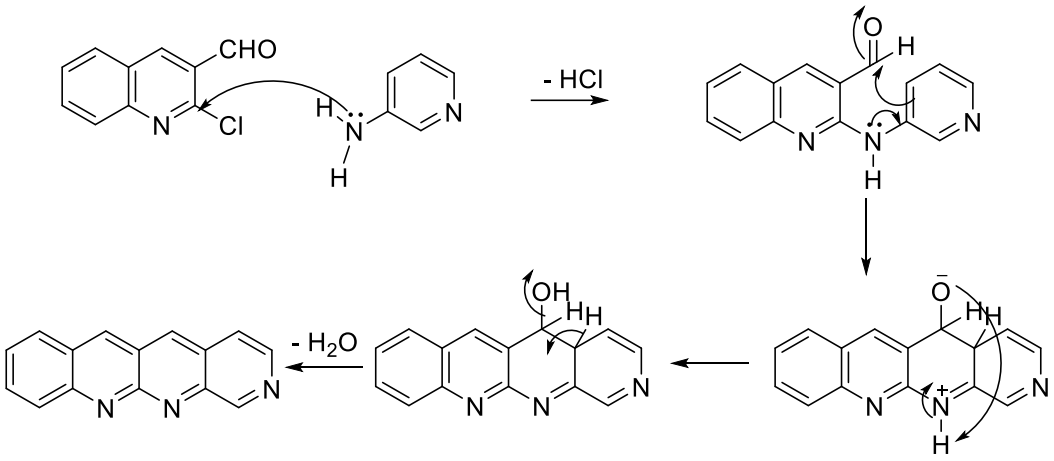
2.1 Synthesis of benzo[g]pyrido[3,4-b] [1, 8] naphthyridine (3)

Our group tried several methods for the substitution of amino group on compound **1** by replacing chloro group. For this, the convenient method was reported by us, using of the solvent DMF.[11] In this one pot method was very useful for constructing fused naphthyridine derivatives. Thus, we tried this method for making pyrido benzo naphthyridines using 2-aminopyridine[12] instead of aniline with the same precursor 2-chloro-3-formyl quinoline (**1**), but couldn't achieve positive result. The reason may be the basicity of aminopyridine. Keeping this in mind, made some changes in fusing methodology got positive result. Here, the addition of NaH and keeping the reaction mixture at nitrogen atmosphere which leads the positive way. On performing the same reaction under inert atmosphere with 3-aminopyridine which leads the titled product. After 48 hours of stirring the reaction mixture a well pronounced new spot was developed on TLC. Then, the solution was cooled and the solvent was removed under reduced pressure. The residue was purified by column chromatography using PE: EA (85:15)(v/v) to furnish the desired pale yellow solid product with yield 36 - 48%.

(i) NaH, DMF, N_2 atm, 48 hrs, stirring 75 °C

The reactions were extended to other derivatives **3a-h**.

The reaction can be summarized along with the following plausible mechanism.



3. Experimental

Preparation of benzo[g] pyrido [3, 4- b] [1, 8] naphthyridine(3): general procedure

To 1 part of 2-chloro-3-formylquinoline (0.0052 moL) in DMF (16 mL) was added 3-aminopyridine 1.2 part (0.0062 moL) and sodium hydride (0.0052 moL), then the mixture was stirred at 75 ºC for 48 hours under nitrogen gas atmosphere and then the DMF was removed under reduced pressure and the residue washed with 2N NaOH and water and dried. The residue was purified by column chromatography using PE: EA (85:15)(v/v) which yielded the benzo[*g*] pyrido [3,4- *b*] [1, 8] naphthyridine.

Benzo[*g*] pyrido [3,4- *b*] [1, 8] naphthyridine (3a)

Yield (36 %); mp: 156 -158ºC; IR (KBr, υ_{max}) cm^{-1}: 1623 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 7.2 – 8.6 (m, 7H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_9-H, C_{10}-H), 9.2 (s, 1H, C_1-H), 9.0 (d, 1H, C_3-H, *J* = 8.5 Hz); CHN analysis (%): Calcd. C 77.91, H 3.92, N 18.17; $C_{15}H_9N_3$ (231.25) Found: C 77.87, H 4.00, N 18.11.

8-methyl benzo[*g*] pyrido [3,4-*b*] [1, 8] naphthyridine (3b)

Yield (48 %); mp: 173 -174 ºC; IR (KBr, υ_{max}) cm^{-1} (**Fig.2.4**): 1614 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm] (**Fig.2.5**): 2.6 (s, 3H, C_8-CH_3), 7.2 – 8.6 (m, 6H, C_4-H, C_5-H, C_6-H, C_7-H, C_9-H, C_{10}-H), 9.2 (s, 1H, C_1-H), 9.0 (d, 1H, C_3-H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) [δ ppm] (**Fig.2.6**): 21, 126, 127, 128, 134, 136, 137, 139, 143,147. CHN analysis (%): Calcd. C 78.34, H 4.52, N 17.13; $C_{16}H_{11}N_3$ (245.28) Found : C 78.30, H 4.46, N 17 .08.

9-methyl benzo[*g*] pyrido [3,4-*b*] [1, 8] naphthyridine (3c)

Yield (46 %); mp: 170 -171 ºC; IR (KBr, υ_{max}) cm^{-1}: 1616 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 2.8 (s, 3H, C_9-CH_3), 7.2 – 8.4 (m, 6H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_{10}-H), 9.3 (s, 1H, C_1-H), 9.1 (d, 1H, C_3-H, *J* = 8.5 Hz); CHN analysis (%): Calcd. C 78.34, H 4.52, N 17.13; $C_{16}H_{11}N_3$ (245.28) Found: C 78.25, H 4.47, N 17.09.

10-methyl benzo[*g*] pyrido [3,4-*b*] [1, 8] naphthyridine (3d)

Yield (45 %); mp:168 -170 ºC; IR (KBr, υ_{max}) cm^{-1}: 1620 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 2.9 (s, 3H, C_{10}-CH_3), 7.2 – 8.2 (m, 6H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_9-H), 9.2 (d,1H, C_3-H, *J*= 8 Hz), 9.3 (s, 1H, C_1-H); CHN analysis (%): Calcd. C 78.34, H 4.52, N 17.13; $C_{16}H_{11}N_3$ (245.28) Found: C 78.27, H 4.49, N 17.09.

8-methoxy benzo[*g*] pyrido [3,4-*b*] [1, 8] naphthyridine (3e)

Yield (39 %); mp: 184 -185 ºC; IR (KBr, υ_{max}) cm^{-1}: 1617 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 3.98 (s, 3H, C_8-OCH_3), 7.2 – 8.3 (m, 6H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_9-H, C_{10}-H), 9.4 (s, 1H, C_1-H), 9.1 (d, 1H, C_2-H, *J* = 7.5 Hz); CHN analysis (%): Calcd. C 73.55, H 4.24, N 16.08; $C_{16}H_{11}N_3O$ (261.28) Found: C 73.45, H 4.20, N 16.17.

9-methoxy benzo[*g*] pyrido [3,4-*b*] [1, 8] naphthyridine (3f)

Yield (42 %); mp: 177 -179 ºC; IR (KBr, υ_{max}) cm^{-1}: 1623 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 3.95 (s, 3H, C_9-OCH_3), 7.2 – 8.1 (m, 6H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H, C_{10}-H), 9.3 (s, 1H, C_1-H), 9.1 (d, 1H, C_3-H, *J* = 7.5 Hz); CHN analysis (%): Calcd. C 73.55, H 4.24, N 16.08; $C_{16}H_{11}N_3O$ (261.28) Found: C 73.50, H 4.28, N 16.15.

10-methoxy benzo[*g*] pyrido [3,4-*b*] [1, 8] naphthyridine 3g)

Yield (41 %); mp: 182 – 183 ºC; IR (KBr, υ_{max}) cm^{-1}: 1619 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 3.90 (s, 3H, C_{10}-OCH_3), 7.2 – 8.4 (m, 6H, C_4-H, C_5-H, C_6-H, C_7-H, C_8-H,

C_9-H), 9.3 (s, 1H, C_1-H), 9.1 (d, 1H, C_3-H, *J* = 7.5 Hz); CHN analysis (%): Calcd. C 73.55, H 4.24, N 16.08; $C_{16}H_{11}N_3O$ (261.28) Found: C 73.47, H 4.27, N 16.13.

8, 10-Dimethyl benzo[*g*] pyrido [3,4-*b*] [1, 8] naphthyridine (3h)

Yield (45 %); mp: 189 - 190 ^oC; IR (KBr, υ_{max}) cm^{-1}: 1612(–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 2.7 (s, 3H, C_{10}-CH_3), 2.4 (s, 3H, C_8-CH_3), 7.2 – 8.3 (m, 5H, C_4-H, C_5-H, C_6-H, C_7-H, C_9-H), 9.4 (s, 1H, C_1-H), 9.2 (d, 1H, C_3-H, *J* = 8.0 Hz); CHN analysis (%): Calcd. C 78.74, H 5.05, N 16.20; $C_{17}H_{13}N_3$ (259.11) Found : C 78.67, H 5.13, N 16. 13.

4. Acknowledgement

The authors express their thanks to the University Grants Commission, Bahadurshah Zafer Marg, New Delhi for the financial assistance.

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