A CONVENIENT ONE POT SYNTHESIS OF BENZO[*g*] PYRIDO [2,3- *b*] [1, 8] NAPHTHYRIDINE

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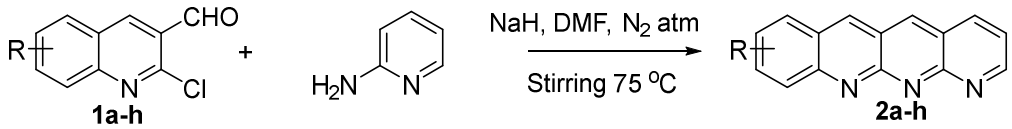
Abstract : A facile and effective one-pot unusual method for the synthesis of benzo[g]pyrido[2,3-b] by the reaction of 2-chloro-3-formyl quinolines (1a-h) and 2-aminopyridine is described. This may be a most convenient for the preparation of 1,8 naphthyridine.



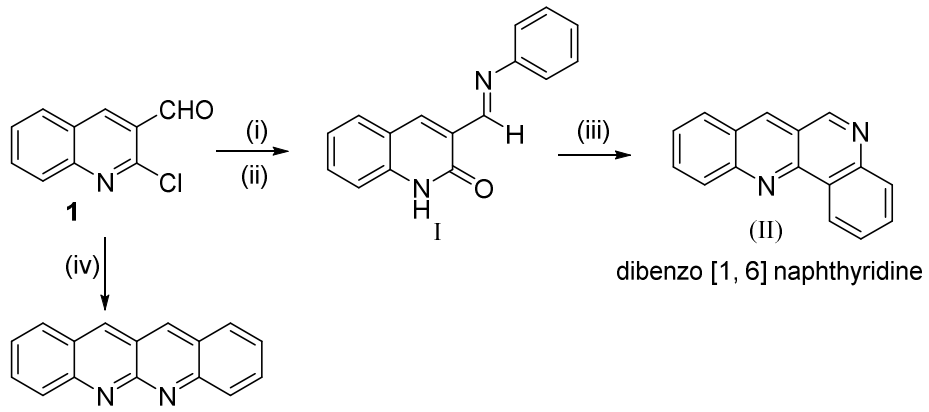
Keywords : 1,8-naphthyridines, 2-chloro-3-formyl quinoline, benzo pyrido naphthyridines

1. INTRODUCTION

1,8-Naphthyridine derivatives are present in many natural and synthetic compounds and show a broad range interesting in anti-inflammatory[1], antitumor[2], trypanocidal, DNA binding [3,4] and antimicrobial[5] studies. Eventhough many synthetic methods have been reported on 1,8-naphthyridine, the great biological importance of these compounds continues the ways to search the methodology. In this view of mind, we add an extra pyridine ring to the quinoline framework for enhancing the biological activity resulting benzo pyrido fused naphthyridines which will be an added advantage. Thus, we introduce nitrogen heterocycles with benzo naphthyridine system which gave positive improvement in the pharmacological activities by using the potential precursor 2-chloro-3-formyl quinolines[6] (**1a-h**).

2. RESULTS AND DISCUSSION

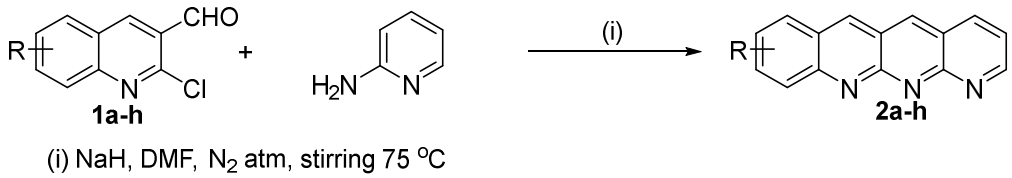
Our group has been actively working on the development of synthetic strategies for the preparation of fused naphthyridines from the potential precursor 2-chloro-3-formyl quinoline. In this connection, we have synthesised linear fused naphthyridine (III) by the reaction of aniline with 2-chloro-3-formyl quinoline in presence of base. We felt that it would result in a Schiff base (I) followed by cyclisation to dibenzo fused [1, 6] naphthyridine (II). But we got unexpected product dibenzo [*b, g*] [1, 8] naphthyridine instead of Schiff base (I).[7]



We extended the same methodology for the synthesis of benzo hetero fused naphthyridines by the use of 2-chloro-3-formyl quinoline (**1**) with 2-aminopyridine. But we didn't achieve positive result even after prolonged stirring and raising the temperature also.

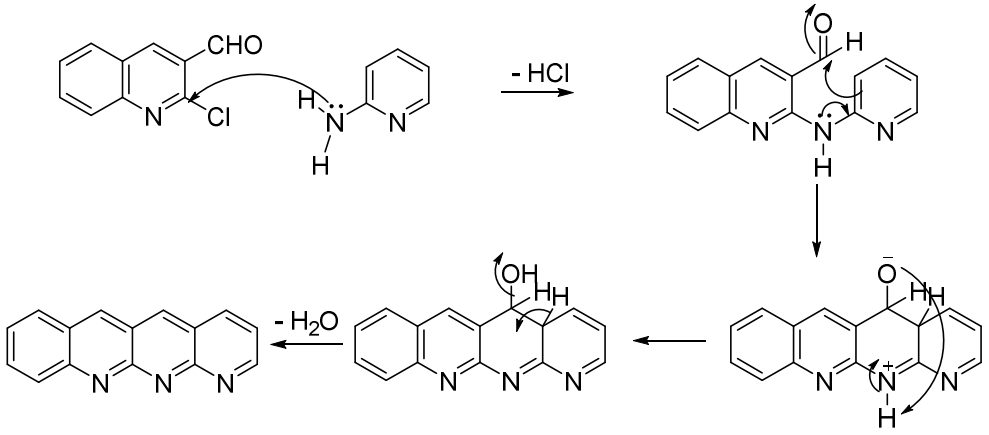
On the other hand, we tried another method. In this method, we increased the effectiveness of amino pyridine by using the base sodium hydride which may induce the nucleophilic substitution reaction on quinoline ring.[8] Then, the reaction mixture was stirred with base at 75 ^{o}C and it was monitored by thin layer chromatography. We observed slight spot change on TLC, but the reactant spot did not disappear completely.

From the above result, in seeking the alternative method to this system we thought that inert atmosphere would promote the reaction. On performing the same reaction under inert atmosphere, a well pronounced new spot developed on TLC after stirring for 48 hrs. Moreover, the reactant spot also disappeared. Then, the reaction 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 39 - 45%.



(i) NaH, DMF, N_2 atm, stirring 75 ^oC

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



3. EXPERIMENTAL

Preparation of benzo[g] pyrido [2,3- b] [1, 8] naphthyridine(2): general procedure

To 1 part of 2-chloro-3-formylquinoline (0.0052 moL) in DMF (16 mL) was added 2-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 [2,3- *b*] [1, 8] naphthyridine.

3.1 Benzo[g] pyrido [2,3- b] [1, 8] naphthyridine (2a)

Yield (41 %); mp: 171 -172 ºC; IR (KBr, υ_{max}) cm^{-1}: 1619 (–C=N); ^1H NMR (DMSO- d_6) [δ ppm]: 7.2 – 8.3 (m, 7H, C_3-H, C_4-H, C_6-H, C_7-H,C_8-H, C_9-H, C_{10}-H), 8.9 (d, 1H, C_2-H, J = 8.0 Hz), 9.3(s, 1H, C_5-H); CHN analysis (%): Calcd. C 77.91, H 3.92, N 18.17; $C_{15}H_9N_3$ (231.25) Found: C 77.84, H 4.02, N 18.13.

3.2 8-methyl benzo[g] pyrido [2,3- b] [1, 8] naphthyridine (2b)

Yield (45 %); mp: 162 -163 ºC; IR (KBr, υ_{max}) cm^{-1}(**Fig.2.1**): 1614 (–C=N); ^1H NMR (DMSO- d_6) [δ ppm] (**Fig.2.2**): 2.6 (s, 3H, C_8-CH_3), 7.1 – 8.1 (m, 6H, C_3-H, C_4-H, C_6-H, C_7-H, C_9-H, C_{10}-H), 9.2(s, 1H, C_5-H), 9.5 (d, 1H, C_2-H, J = 6.5 Hz); ^{13}C NMR (DMSO- d_6) [δ ppm] (**Fig.2.3**): 123, 126, 127, 128, 134, 135, 137, 135, 138, 143; MS (**Fig. 2.3a**) (*m/z*): 245; 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 4.48, N 17.06.

3.3. 9-methyl benzo[g] pyrido [2,3- b] [1, 8] naphthyridine (2c)

Yield (43 %); mp: 160 -162 ºC; IR (KBr, υ_{max}) cm^{-1}: 1610 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 2.8 (s, 3H, C_9-CH_3), 7.2 – 8.2 (m, 6H, C_3-H, C_4-H, C_6-H, C_7-H, C_8-H, C_{10}-H), 9.4 (d,1H, C_2-H), 9.2 (s, 1H, C_5-H); CHN analysis (%): Calcd. C 78.34, H 4.52, N 17.13; $C_{16}H_{11}N_3$ (245.28) Found: C 78.28, H 4.46, N 17.08.

3.4. 10-methyl benzo[g] pyrido [2,3- b] [1, 8] naphthyridine (2d)

Yield (46 %); mp: 154 -155 ºC; IR (KBr, υ_{max}) cm^{-1}: 1614 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 2.7 (s, 3H, C_{10}-CH_3), 7.2 – 8.1 (m, 6H, C_3-H, C_4-H, C_6-H, C_7-H, C_8-H, C_9-H), 9.3 (d,

1H, C_2-H), 9.1 (s, 1H, C_5-H); CHN analysis (%): Calcd. C 78.34, H 4.52, N 17.13; $C_{16}H_{11}N_3$ (245.28) Found: C 78.29, H 4.48, N 17.05.

3.5. 8-methoxy benzo[g] pyrido [2,3- b] [1, 8] naphthyridine (2e)

Yield (48 %); mp: 174 -176 ºC; IR (KBr, υ_{max}) cm^{-1}: 1613 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 3.98 (s, 3H, C_8-OCH_3), 7.1 – 8.3 (m, 6H, C_3-H, C_4-H, C_6-H, C_7-H, C_9-H, C_{10}-H), 9.0(s, 1H, C_5-H), 9.2 (d, 1H, C_2-H, J = 7.0 Hz); CHN analysis (%): Calcd. C 73.55, H 4.24, N 16.08, O 6.13; $C_{16}H_{11}N_3O$ (261.28) Found : C 73.49, H 4.28, N 16. 15.

3.6. 9-methoxy benzo[g] pyrido [2,3- b] [1, 8] naphthyridine (2f)

Yield (41 %); mp: 167 -168 ºC; IR (KBr, υ_{max}) cm^{-1}: 1618 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 3.95 (s, 3H, C_9-OCH_3), 7.2 – 8.1 (m, 6H, C_3-H, C_4-H, C_6-H, C_7-H, C_8-H, C_{10}-H), 8.7 (d, 1H, C_2-H, J=7.5 Hz), 9.1 (s, 1H, C_5-H); CHN analysis (%): Calcd. C 73.55, H 4.24, N 16.08, O 6.13; $C_{16}H_{11}N_3O$ (261.28) Found: C 73.51, H 4.27, N 16.13.

3.7. 10-methoxy benzo[g] pyrido [2,3- b] [1, 8] naphthyridine (2g)

Yield (39 %); mp: 172 -174 ºC; IR (KBr, υ_{max}) cm^{-1}; 1624 (–C=N); ^1H NMR ($CDCl_3$) [δ ppm]: 3.90 (s, 3H, C_{10}-OCH_3), 7.2 – 8.2 (m, 6H, C_3-H, C_4-H, C_6-H, C_7-H, C_8-H, C_9-H), 9.0 (d, 1H, C_2-H), 9.2 (s, 1H, C_5-H); CHN analysis (%): Calcd. C 73.55, H 4.24, N 16.08; $C_{16}H_{11}N_3O$ (261.28) Found: C 73.48, H 4.28, N 16.11.

3.8. 8, 10-Dimethyl benzo[g] pyrido [2,3- b] [1, 8] naphthyridine (2h)

Yield (48 %); mp: 169 -171 ºC; IR (KBr, υ_{max}) cm^{-1}: 1613(–C=N), ^1H NMR ($CDCl_3$) [δ ppm]: 2.8 (s, 3H, C_{10}-CH_3), 2.4 (s, 3H, C_8-CH_3),7.2 – 7.8 (m, 5H, C_3-H, C_4-H, C_6-H, C_7-H, C_9-H), 8.8 (d, 1H, C_2-H, J= 8 Hz), 9.0 (s, 1H, C_5-H); CHN analysis (%): Calcd. C 78.74, H 5.05, N 16.20; $C_{17}H_{13}N_3$ (259.11) Found : C 78.68, H 5.12, N 16.08.

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