

Green and Environmentally Friendly Synthesis of Quinolinylnyl 1, 2, 4-S-Triazolo [4, 3-a] Quinoxalines from 2-Chloroquinoline-3-Carboxaldehyde

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Abstract—A simple and efficient protocol for microwave-assisted solvent-free, green and environmentally friendly synthesis of quinolinylnyl-1, 2, 4-s-triazolo [4, 3-a]quinoxalines 4 Using iodobenzene diacetate is reported.

Index Terms—Quinolinylnyl-1, 2, 4-s-triazolo [4, 3-a] quinoxalines, iodobenzene diacetate, $\text{PhI}(\text{OAc})_2$, solvent-free conditions

I. INTRODUCTION

In recent years, organic transformations accelerated under microwave conditions have gained wide popularity due to many practical advantages associated with them such as enhanced reaction rates, high yields, improved selectivity and environment-friendly reaction conditions¹⁻⁴. The upcoming area of Green Chemistry, which involves carrying out reactions under solvent-free conditions and using microwaves for synthesis aims at reducing the use of toxic solvents thereby preventing pollution in organic synthesis at source. Literature survey reveals that various fused quinolines have attracted considerable attention as they possess antihypertensive and antibacterial properties^{5,6}. Some of their fused analogues have been found to possess anti-cancer activity such as the well known Camptothecin⁷. 2-Chloroquinoline-3-carboxaldehydes have been investigated during the last few years and a number of their derivatives have been prepared possessing different types of biological activities. Fused 1,2,4-triazoles generate a widespread interest due to diverse biological activities⁴. In view of their importance as potential pharmacological compounds, we intended to develop an efficient and green method for the synthesis of quinolinylnyl-1,2,4-s-triazolo[4,3-a]quinoxalines under solvent free conditions by using hypervalent iodine reagents like iodobenzene diacetate [$\text{PhI}(\text{OAc})_2$].

We report herein the application of solvent free and neat technique to the reaction between 2-chloroquinoline-3-carboxaldehyde 1 and 2-chloro-3-hydrazinoquinoxaline 2 and resulting in N-(2-chloro-4a,8a-dihydroquinoline-3yl-methyl)-N-3-chloro-quinoxalin-2-yl)hydrazine 3. Further subsequent reaction with iodobenzene diacetate [$\text{PhI}(\text{OAc})_2$] using microwave

technique resulted in the formation of quinolinylnyl-1,2,4-s-triazolo[4,3-a]quinoxalines 4. The products are obtained in good yields and in a state of high purity. The structures of the synthesized compounds have been established on the basis of spectral and analytical data. Results of these studies will be presented.

II. RESULTS AND DISCUSSION

Condensation of 2-chloroquinoline-3-carboxaldehyde⁸ (1) with 2-Chloro-3-hydrazinoquinoxaline (2) at 160°C–180°C under solvent free conditions afforded the corresponding N-(2-chloro-4a,8a-dihydroquinoline-3yl-methyl)-N-3-chloro-quinoxalin-2yl) hydrazones 3 in good yields. Cyclization of hydrazones 3 with iodobenzene diacetate under microwave irradiation technique furnished the respective 4-chloro-1-(2-chloroquinoline-3yl)-1, 2, 4-s-triazolo [4, 3-a]quinolines 4. Alternatively, 4 was also obtained by refluxing 3 in methanol using IBD for 1 hr. It may be mentioned here that synthesis of 4 has been reported by G. J. Reddy *et. al* using DDQ in refluxing toluene for 1hr.

In the present communication, we have reported a new method for the preparation of 3 from 1 and 2, and subsequent cyclization of 3 to 4 under microwave technique using iodobenzene diacetate as cyclodehydrogenation agent, requiring hardly 5 min of reaction time to synthesize (Fig. 1). The reaction conditions and work-up procedure are mild, simple and convenient. The process is environmentally benign. The reaction involving dehydrogenative cyclisation of 3 to 4 probably follows the mechanism depicted in Fig. 2. Electrophilic attack of iodobenzene diacetate generates the nitrile imine (I) by loss of iodobenzene and acetic acid, finally ring closure occurs through quinoxaline ring nitrogen and leads to the formation of product. The structural assignments of the compounds 3a-d to 4a-d were based on their spectral data (IR, ¹H NMR).

A. Experimental

Melting points are uncorrected and were obtained in open capillary tubes in sulphuric acid bath. TLC checking was done on plastic sheets coated with silica gel GF-254, supplied by Merck & Co., and spotting was done using Iodine or UV lamp. IR spectra were recorded using Perkin-Elmer model 1000 instrument in KBr phase. ¹H NMR spectra were recorded on a Gemini-200 and AU-400 operating at 200MHz and 400 MHz respectively.

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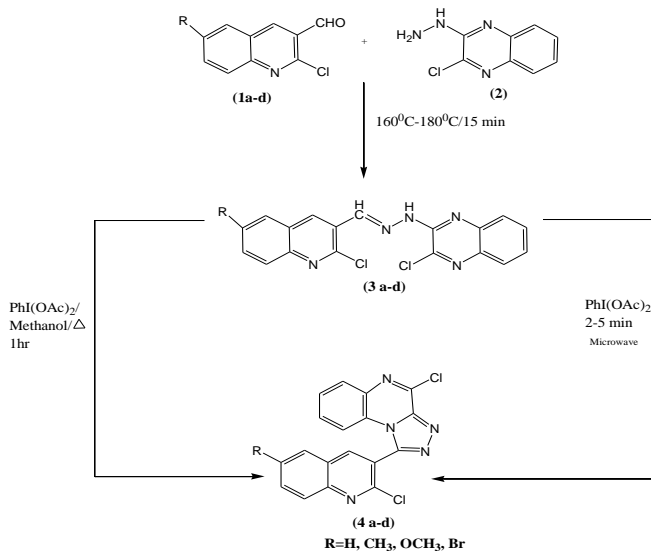


Fig. 1

The reaction involving dehydrogenative cyclisation of 3 to 4 probably follows the mechanism shown in Fig. 2:

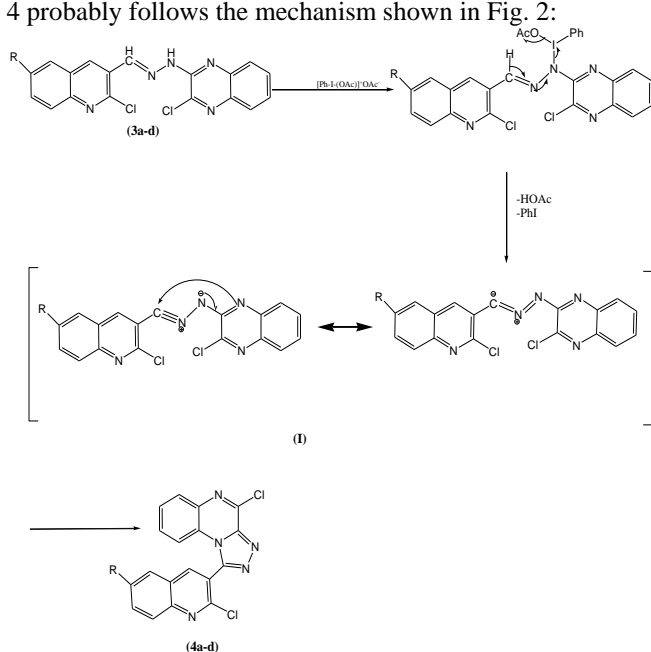


Fig. 2

B. General Procedure for the Preparation of 3

An intimate mixture of 1 (0.97gm, 5mM) and 2 (0.96gm, 5mM) was heated at 160°C–180°C for 15 minutes. On completion of the reaction, as monitored by TLC, the residue (crude 3) was recrystallised from ethanol to obtain pure 3.

3a: Yield= 1.6g (90%); M.P. 218°C - 220°C (Lit. M.P.220°C); IR (KBr): 3015-2855 cm⁻¹ (broad,-NH); ¹H NMR (400 MHz, CDCl₃/TMS): δ 7.48-8.12 (m, 8H, four quinoline aryl protons, four quinoxaline aryl protons), 8.62 (s, 1H, quinoline proton), 9.10 (s, 1H, N=CH* - proton), 9.32(s, 1H, NH, D₂O exchangeable) ; MS: *m/z* 369 (M⁺+1).

3b: Yield=1.6g (89%); M.P. 221°C - 224°C; IR (KBr): 3015-2855 cm⁻¹ (broad,-NH); ¹H NMR (400 MHz, CDCl₃/TMS): 2.5 (s, 3H, CH₃), 7.46-8.10 (m, 7H, three quinoline aryl protons & four quinoxaline aryl protons), 8.61 (s, 1H, quinoline periproton), 9.11 (s, 1H, N=CH), 9.32 (s,

1H, D₂O exchangeable-NH-); MS: *m/z* 383 (M⁺+1).

3c: Yield= 1.7g (87%); M.P > 250°C; IR (KBr): 3015-2855 cm⁻¹ (broad,-NH); ¹H NMR (400 MHz, CDCl₃/TMS): 3.5 (s, 3H, -OCH₃), 7.48-8.12 (m, 7H, three quinoline aryl protons & four quinoxaline aryl protons), 8.63 (s, 1H, quinoline periproton), 9.13 (s, 1H, N=CH), 9.36 (s, 1H, D₂O exchangeable-NH-); MS: *m/z* 399 (M⁺+1).

3d: Yield= 1.9g (90%); M.P > 250°C; IR (KBr): 3015-2855 cm⁻¹ (broad,-NH), ¹H NMR (400 MHz, CDCl₃/TMS): 7.49-8.15 (m, 7H, three quinoline aryl protons & four quinoxaline aryl protons), 8.69 (s, 1H, quinoline periproton), 9.20 (s, 1H, N=CH), 9.45 (s, 1H, D₂O exchangeable-NH-); MS: *m/z* 448 (M⁺+1).

C. General Procedure for the Preparation of 4

An intimate mixture of 3 (1.83gm, 5mM) and iodobenzene diacetate (1.67gm, 5.2mM) was taken in a 50ml of borosil conical flask and subjected to microwave-irradiation at 100% exposure intermittently at 30sec intervals for 5 minutes. On completion of reaction, as monitored by TLC, the residue (crude 4) was recrystallised from ethanol to obtain pure 4.

4a: Yield= 1.6g (87%); M.P. > 250°C (Lit. M.P.300°C); IR (KBr): 1620 -1600 cm⁻¹ (C=N); ¹H NMR (400 MHz, CDCl₃/TMS): 7.42-8.62 (m, 8H, four quinoline aryl protons, four quinoxaline aryl protons), 9.10 (s, 1H, quinoline proton); MS: *m/z* 367 (M⁺+1).

4b: Yield= 1.6g (86%); M.P.> 250°C (Lit. M.P.300°C); IR (KBr): 1615-1600 cm⁻¹, (C=N); ¹H NMR (400 MHz, CDCl₃/TMS): 2.5 (s, 3H, CH₃), 7.41-8.60 (m, 7H, three quinoline aryl protons, four quinoxaline aryl protons), 9.10 (s, 1H, quinoline proton); MS: *m/z* 381 (M⁺+1).

4c: Yield= 1.6g (85%); M.P. > 250°C (Lit. M.P.300°C); IR (KBr): 1620-1600 cm⁻¹ (C=N); ¹H NMR (400 MHz, CDCl₃/TMS): 3.8 (s, 3H, -OCH₃), 7.44-8.63 (m, 7H, three quinoline aryl protons, four quinoxaline aryl protons), 9.13 (s, 1H, quinoline proton); MS: *m/z* 397 (M⁺+1).

4d: Yield= 1.6g (85%); M.P. > 250°C (Lit. M.P.300°C); IR (KBr): 1615-1600 cm⁻¹ (C=N); ¹H NMR (400 MHz, CDCl₃/TMS): 7.46-8.68 (m, 7H, three quinoline aryl protons, four quinoxaline aryl protons), 9.15 (s, 1H, quinoline proton); MS: *m/z* 446 (M⁺+1).

D. Alternate Procedure for Preparation of 4

A mixture of 3 (1.83 gm, 5mM) and iodobenzene diacetate (1.67gm; 5.2mM) in methanol was refluxed for 1hr. The reaction was monitored by TLC. After completion of the reaction, it was filtered, washed with methanol and dried to obtain crude 4. The crude 4 were recrystallised from ethanol to obtain pure 4.

Yield of 4a=1.4gm (81%), yield of 4b=1.52gm (80%), Yield of 4c=1.5gm (80%), yield of 4d=1.7gm (80%)

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