SYNTHESIS OF SOME NOVEL 1, 2, 4-TRIAZOLO [4, 3-a] 2H-PYRANO [3, 2-e] PYRIDINE DERIVATIVES

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Abstract : New 1, 2, 4 triazoles containing 2H-pyrano [2, 3-b] pyridine moiety **3a-f** and **4a-b** have been synthesized. Ethyl-5-methyl-6-cyano-7-chloro-2-oxo-2H-pyrano [2, 3-b] pyridine-3-carboxylate was converted into 5-methyl-6-cyano-7-hydrazino-2-oxo-2H-pyrano [2, 3-b] pyridine-3-carboxylic acid by reacting with hydrazine hydrate, followed by cyclization with aliphatic acids and aromatic acid chlorides to afford 1, 2, 4 triazoles. The structures of all compounds synthesized were assigned on the basis of elemental analysis, IR and ^{1}H NMR spectral data.

Keywords: 1, 2, 4 triazoles, 2H-pyrano [2, 3-b] pyridine, Hypertension

Introduction

Pyranopyridines[1-5] are an important compounds[6-10] in the synthesis of biological active, and chemically interesting molecules[11-12] due to their structurally similarity to quinolines, substituted pyridines and benzopyrans. 2-H-pyranopyridine-2-one nucleus is a very important system in the field of new drug discovery especially in the area of blood pressure lowering activity, useful in the treatment of hypertension[13-15].Along with Pyranopyridines a wide spectrum of biological activities are associated with 1,2,4-triazole nucleus. It has been found that incorporation of various fused heterocycles in Pyranopyridines moiety enhances the biological activities. In view of the above findings and in continuation of our interest in the chemistry of Pyranopyridines, we report herein the synthesis of 1, 2, 4-triazolo [4, 3-a] 2H-pyrano [3, 2-e] pyridine derivatives.

Results and Discussion

Continuation of our interest to synthesize new heterocyclic compound containing 2H-pyrano [2, 3-b] pyridine-2-one moiety[16], we report herein the synthesis of 1, 2, 4-triazolo [4, 3-a] 2H-pyrano [3, 2-e] pyridine. The reaction sequence is outlined in Scheme I. The starting compound ethyl 5-methyl-6-cyano-7-chloro-2-oxo-2H-pyrano [2, 3-b] pyridine-3-carboxylate **1** which was previously prepared by us[17], **1** is reacted with hydrazine hydrate at room temperature furnished 5-methyl-6-cyano-7-hydrazino-2-oxo-2H-pyrano [2, 3-b] pyridine-3-carboxylic acid **2** with good yield. Structure of the compounds **2** was confirmed by using IR and ^{1}HNMR spectral data and elemental analysis. The IR spectrum of compound **2** displayed no absorption derived from ester at 1752; instead, a new signal representing the carboxyl group was observed at 1626 cm^{-1}. In the ^{1}H-NMR spectra of compound **2** the signal corresponds to ester protons at δ 1.22-1.29 (t, 3H, -CH_2-CH_3), 4.1-4.2 (q, 2H, -CH_2-CH_3) were disappeared, observed new peak at δ 7.2-7.5 (D_2O exchangeable).Condensation of **2** with aliphatic acids resulted in the formation of 1-substituted 2H-pyrano [3, 2-e][1,2,4]triazolo[4,3-a]pyridine **3a-f**. further the hydrazine derivative **2** was transformed to 1-aryl- 2H-pyrano [3, 2-e][1,2,4]triazolo[4,3-a]pyridine **4a-b**, by reacting with aromatic acid chlorides.

Experimental

Melting points were determined on Buchi 545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 1650 Spectrometer, ^{1}H NMR was recorded in $DMSOd_6$ using 200 MHz Bruker spectrometer (chemical shifts in δ ppm) with TMS as internal standard and mass spectra on a HP-5989A spectrometer. All the organic extracts were dried over sodium sulfate after work-up.

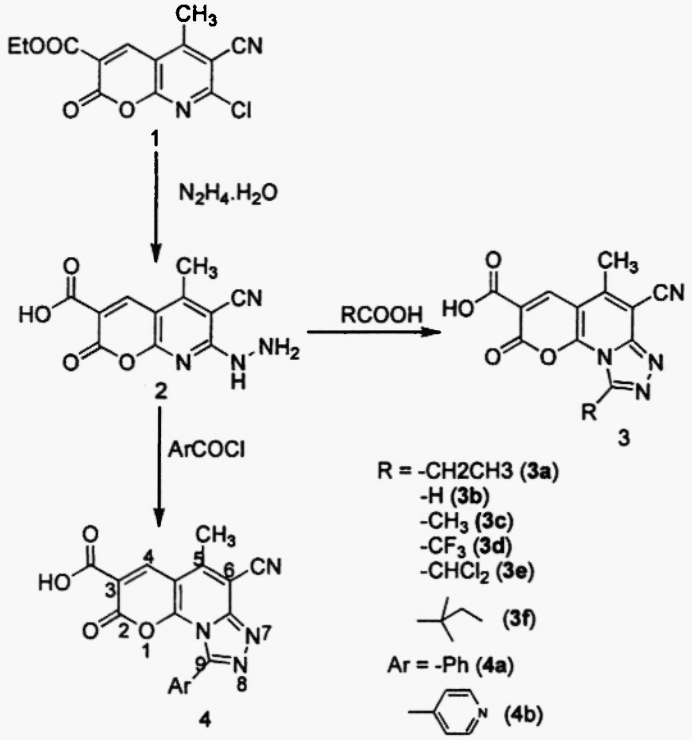
The dry reactions were carried out under nitrogen with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light.

Preparation of 2

To the solution of 2 (0.01 mole) in ethanol (50 mL) was added hydrazine hydrate (0.015 mole). The resulting mixture was stirred at room temperature for 3-4 hr. After completion of the reaction, cooled the reaction mass to 0-5°C and solid which precipitated was collected by filtration, washed with ethanol, and then dried under reduced pressure. The solid so obtained was recrystallized from ethanol to give compound afford 2 as a white solid, yield 80%, mp: 289-291°C; IR (KBr) (cm^{-1}): 3353 (-NH_2), 2208 (-CN), 1718 (-C=O, lactone), 1626 (-C=O, acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 2.30 (s, 3H, -CH_3), δ 7.2-7.5 (b, D_2O exchangeable), 7.90 (s, 1H, C_4-H). Anal. Found: C, 50.98; H, 3.08; N, 21.61%, Calcd for $C_{11}H_8N_4O_4$: C, 50.78; H, 3.10; N, 21.53%.

Preparation of 3a-f

A mixture of compound 2 (0.01 mole) and appropriate acid (10 mL) was heated to refluxed 4-6 hr. After completion of the reaction, the excess reagent was removed under vacuum and water was added to the crude mass. The solid thus separated was filtered, washed with water and crystallized from ethanol-water to give 3a-f. (Scheme-1)



Scheme - I

3a: yield 80%, mp: 398-400°C; IR (KBr) (cm^{-1}): 3122.9 (-NH_2), 2216.8 (-CN), 1705 (-C=O, lactone), 1615.3 (-C=O, acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 0.92-0.99 (t, 3H -CH_2**CH_3**), 2.3 (s, 3H -CH_3), 3.5-3.58 (q, -**CH_2**CH_3), , 8.14 (s, 1H, C_4-H). Anal. Found: C, 56.41; H, 3.42; N, 18. 81%, Calcd for $C_{14}H_{10}N_4O_4$: C, 56.38; H, 3.38 N, 18.78%.

3b: yield 75%, mp: 412-415°C; IR (KBr) (cm^{-1}): 2221 (-CN), 1725 (-C=O, lactone), 1652 (-C=O acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 2.4 (s, 3H -CH_3), 8.4 (s, 1H, C_4-H), 9.75 (s, 1H). Anal. Found: C, 53.39; H, 2.28; N, 20.71%, Calcd for $C_{12}H_6N_4O_4$: C, 53.34; H, 2.24 N, 20.74%.

3c: yield 88%, mp: 383-385°C; IR (KBr) (cm^{-1}): 2209 (-CN), 1715 (-C=O, lactone), 1635 (-C=O acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 2.1 (s, 3H, -**CH_3**), 2.49 (s, 3H, -**CH_3**), 8.4 (s, 1H, C4-H). Anal. Found: C, 54.99; H, 2.9; N, 19.78%, Calcd for $C_{13}H_8N_4O_4$: C, 54.94; H, 2.84; N, 19.71%.

3d: yield 72%, mp: 324-326°C; IR (KBr) (cm^{-1}): 2232 (-CN), 1720 (-C=O, lactone), 1642 (-C=O acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 2.3 (s, 3H, -CH_3), 8.4 (s, 1H, C4-H). Anal. Found: C, 46.21; H, 1.53; N, 16.62; F, 16.89%, Calcd for $C_{13}H_5F_3N_4O_4$: C, 46.17; H, 1.49; N, 16.57; F, 16.85%.

3e: yield 65%, mp: 352-354°C; IR (KBr) (cm^{-1}): 2217 (-CN), 1708 (-C=O, lactone), 1645 (-C=O acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 2.3 (s, 3H, -**CH_3**), 6.5 (s, 1H,), 8.3(S, 1H, C4-H). Anal. Found: C, 44.27; H, 1.76; N, 15.92; Cl, 20.12%, Calcd for $C_{13}H_6Cl_2N_4O_4$: C, 44.22; H, 1.71; N, 15.87; Cl, 20.08%.

3f: yield 85%, mp: 408-410°C; IR (KBr) (cm^{-1}): 2205 (-CN), 1710 (-C=O, lactone), 1636 (-C=O, acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 0.7-0.8 (t, 3H,-CH_2-**CH_3**), 1.0 (s, 6H, C(**CH_3**)$_2$), 1.4 (q, 2H, -**CH_2**-CH_3), 2.3 (s, 3H, -**CH_3**),8.5 (s, 1H, C_4-H). Anal. Found: C, 60.06; H, 4.69; N, 16.49%, Calcd for $C_{17}H_{16}N_4O_4$: C, 60.0; H, 4.74; N, 16.46%.

Preparation of 4a-b

A mixture of compound **2** (0.01 mole) and appropriate acid chloride (10 mL) was heated to refluxed 4-6 hr. After completion of the reaction, the excess reagent was removed under vacuum and water was added to the crude mass. The solid thus separated was filtered, washed with water and crystallized from ethanol-water to give **4a-b**.

4a: yield 78%, mp: 338-340°C; IR (KBr) (cm^{-1}): 2228.5 (-CN), 1715 (-C=O, lactone), 1644.1 (-C=O acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 2.3 (s, 3H, -**CH_3**), 7.4-7.9 (m, 5H, Ar), 8.3(S, 1H, C4-H). Anal. Found: C, 62.47; H, 2.97; N, 16.23%, Calcd for $C_{18}H_{10}N_4O_4$: C, 62.43; H, 2.91; N, 16.18%.

4b: yield 76%, mp: 362-365°C; IR (KBr) (cm^{-1}): 2215 (-CN), 1706 (-C=O, lactone), 1625 (-C=O acid); ^{1}H NMR (200 MHz, DMSO d_6): δ 2.3 (s, 3H, -**CH_3**), 7.4-7.6 (m, 5H, Ar), 8.3(S, 1H, C4-H). Anal. Found: C, 58.73; H, 2.68; N, 20.22%, Calcd for $C_{17}H_9N_5O_4$: C, 58.79; H, 2.61; N, 20.17%.

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Received on April 18, 2007