Application of pfitzinger reaction in the synthesis of quinoline-4-carboxylic acid derivatives of carbazolo and azacarbazolo fused indophenazine

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ABSTRACT

Application of the Pfitzinger reaction on indophenazine fused carbazole 4a and azacarbazoles 4(b-e) with isatin (5) yielded the corresponding indophenazine fused quinoline-4-carboxylic acid derivatives 6(a-e) in moderate to good yield. All quinoline-4-carboxylic acid derivatives were characterized on the basis of their microanalysis IR, $^1$HNMR and MS spectral data.

Keywords: Indophenazine, carbazoles, azacarbazoles, Pfitzinger reaction.

INTRODUCTION

Indophenazine (indoloquinoxaline) exhibits impressive biological activity and has been used as antimicrobial agent against herpus virus along with potent anticancer effects [1]. The proven record of the cytotoxicity of carbazoles and azacarbazoles [2] reveal that these materials form interesting targets in synthesis, since such structures have potential for development of compounds with antitumor activity that could mimic to the activity of ellipticene. Ellipticene exhibits significant antitumor activity due to its DNA intercalating properties [3]. Quinoline carboxylic acid and their analogues show wide variety of medicinal properties including antitumour [4], antiviral [5] and antibacterial [6] activities. It has been shown [7] that quinolines exhibit antitumor activity due to the formation of stable complex with DNA. Recent demonstrations [8-11] that quinoline carboxylic acid can be used as potential anti-HIV agents has stimulated further interest on these molecules with yet another perspective.

It has been observed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exert a profound influence on the biological activity of the parent molecules, it was thought of interest to incorporate active pharmacophore like quinoline in indophenazo fused carbazole framework [12] with the hope that it could produce interesting series of compounds with enhanced biological activities. In the present work, we describe the application of Pfitzinger reaction for the synthesis of indophenazo fused quinoline-4-carboxylic acid derivatives 6(a-e) from isatin (5) and appropriate carbonyl compounds 4(a-e).

EXPERIMENTAL SECTION

Melting points were determined on an open capillary and are uncorrected. The IR spectra were recorded on Schimadzu FTIR-8400S. $^1$H NMR spectra were recorded in DMSO-d$_6$ and CDCl$_3$ on Bruker DRX-300 spectrometer using TMS as internal reference and values are expressed in δ ppm. $^{13}$C NMR spectra were measured on a Joel 68.5 MHz instrument. Mass spectra were taken on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV.

Preparation of quinoline-4-carboxylic acid derivatives 6(a-e) from the ketones 4(a-e):
A solution of ketone 4a (0.07 mol), isatin (5) (0.07 mol) and of potassium hydroxide (0.2 mol) in ethanol (25 ml) was refluxed for 24 hrs. After the distillation of most of the solvent, water was added. The neutral impurities were removed by ether extraction, and the aqueous layer was acidified with acetic acid till neutralization. The brown
coloured precipitate of compound 6a was collected and recrystallized from ethanol. Compounds 6(b-e) were prepared by using similar procedure.

6a. Yield: 73%; IR (KBr) cm⁻¹: 3500, 3300, 2900, 1810, 1750, 1480, 1030; ¹H NMR (300 MHz, CDCl₃ + DMSO-d₆) δ ppm: 11.0 (1H, s, COOH), 10.1 (2H, s, NH), 9.08(1H,d,CH), 8.30(1H,d,CH), 8.07(2H,s,CH), 7.82(2H,t,CH₂ J-8.9Hz), 2.92(2H,t,CH₂ J-8.9Hz), 13C NMR : 172 (C of COOH), 127.1, 128.6, 126.7, 121.6, 120.5, 119.6, 111.0 (9C of Ar-Benzene), 144.8, 137.0, 103.0 (4C of pyrrole), 142.8, 129.6, 129.4 (4C of quinoxaline); MS: m/z 455 [M⁺]; Anal. Calcd. / found for C₂₈H₁₇N₅O₂: C, 73.84/73.81, H, 3.76/3.72, N, 15.38 / 15.33.

6b. Yield: 65%; IR (KBr) cm⁻¹: 3500, 3300, 2920, 1840, 1750, 1460, 1010; ¹H NMR (300 MHz, CDCl₃ + DMSO-d₆) δ ppm: 11.0 (1H, s, COOH), 10.1 (2H, s, NH), 9.08(1H,d,CH), 8.30(1H,d,CH), 8.07(2H,s,CH), 7.82(1H,t,CH₂, J-8.9Hz), 7.76(1H,t,CH₂, J-8.9Hz), 7.55-7.00(9H,m,Ar-H), 4.32(4H,t,CH₂); ¹C NMR; 172.0 (1C of COOH), 137.2, 128.3, 128.1, 126.8, 126.7, 128.1, 128.1, 126.8, 126.7, 128.1, 123.8, 147.1, 121.6, 111.0, 120.5, 119.0 ( 14C of Ar-Benzene), 127.6, 135.5, 129.4 (4C of pyrrole), 144.8, 134.1, 132.5, 137.2, 121.6 (6C of quinoxaline), 124.0, 102.0 (2C of piperidine), 62.1 (1C of benzyl CH₂); MS: m/z 546 [M⁺]; Anal. Calcd. / found for C₃₄H₂₄N₆O₂: C, 74.71/74.69, H, 4.06/4.01, N, 15.38 / 15.33.

6c. Yield: 62%; IR (KBr) cm⁻¹: 3500, 3300, 2900, 1820, 1750, 1460, 1040; ¹H NMR (300 MHz, CDCl₃ + DMSO-d₆) δ ppm: 11.0 (1H, s, COOH), 10.1 (2H, s, NH), 9.08(1H,d,CH), 8.30(1H,d,CH), 8.07(2H,s,CH), 7.82(1H,t,CH₂, J-8.9Hz), 7.76(1H,t,CH₂, J-8.9Hz), 7.55-7.00(4H,m,Ar-H), 4.32(4H,t,CH₂); ¹C NMR; 172.0 (1C of COOH), 137.2, 128.3, 128.1, 126.8, 126.7, 128.1, 128.1, 126.8, 126.7, 128.1, 123.8, 147.1, 121.6, 111.0, 120.5, 119.0 ( 11C of Ar-Benzene), 127.6, 135.5, 129.4 (4C of pyrrole), 144.8, 134.1, 132.5, 147.2, 121.7, 120.5, 119.6, 111.0 (9C of Ar-Benzene), 144.8, 137.0, 103.0 (4C of pyrrole), 142.8, 129.6, 129.4 (4C of quinoxaline), 144.8, 134.1, 132.5, 137.2, 121.6 (6C of quinoxaline), 124.0, 102.0 (2C of piperidine), 62.1 (1C of benzyl CH₂); MS: m/z 546 [M⁺]; Anal. Calcd. / found for C₃₄H₂₄N₆O₂: C, 74.71/74.69, H, 4.06/4.01, N, 15.38 / 15.33.

Scheme:1

6a, X= CH₂
6b, X= N-CH₂CH₃
6c, X= N-CH(Me)₂
6d, X= N-COMe
6e, X= N-COOME
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137.2, 121.6 (6C of quinoxaline), 124.0, 102.0 (2C of piperidine), 52.5 (C of CH), 21.6 (2C of CH$_3$); MS: $m/z$ 498 $[M^+]$; Anal. Calcd. / found for C$_{30}$H$_{22}$N$_6$O$_2$: C, 72.28/ 72.24, H, 4.45/ 4.41, N, 16.86 / 16.82.

**Scheme: 2 Mechanism of formation of 6(a-e) from 4(a-e)**

6d. Yield: 70%; IR (KBr) cm$^{-1}$: 3500, 3300, 2900, 1820, 1750, 1450, 1040; $^1$H NMR (300 MHz, CDCl$_3$ + DMSO-d$_6$) $\delta$ ppm: 11.0 (1H, s, COOH), 10.1 (2H, s, NH), 9.08 (1H,d,CH), 8.30 (1H,d,CH), 8.07 (2H,s,CH), 7.82 (1H,t,CH$_2$ J=8.9Hz), 7.76 (1H,t,CH$_2$ J=8.9Hz), 7.55-7.00 (4H,m,Ar-H), 4.64 (2H,t,CH$_2$), 2.02 (3H,s,CH$_3$); $^{13}$C NMR; 172.0 (1C of COOH), 166.7 (C of COMe), 137.2, 128.3, 128.1, 126.8, 126.7, 128.1, 128.3, 128.1, 126.8, 126.7, 128.1, 123.8, 147.1, 121.6, 111.0, 120.5, 119.0 (11C of Ar-Benzene),127.6, 135.5, 129.4 (4C of pyrrole), 144.8, 134.1, 132.5, 137.2, 121.6 (6C of quinoxaline), 124.0, 102.0 (2C of piperidine), 15.4 (C of CH$_3$); MS: $m/z$ 498 $[M^+]$; Anal. Calcd. / found for C$_{30}$H$_{22}$N$_6$O$_2$: C, 69.87/69.84, H, 3.64/3.61, N, 16.86 / 16.82.

6e. Yield: 70%; IR (KBr) cm$^{-1}$: 3500, 3300, 2900, 1820, 1750, 1450, 1040; $^1$H NMR (300 MHz, CDCl$_3$ + DMSO-d$_6$) $\delta$ ppm: 11.0 (1H, s, COOH), 10.1 (2H, s, NH), 9.08 (1H,d,CH), 8.30 (1H,d,CH), 8.07 (2H,s,CH), 7.82 (1H,t,CH$_2$ J=8.9Hz), 7.76 (1H,t,CH$_2$ J=8.9Hz), 7.55-7.00 (4H,m,Ar-H), 4.22 (2H,t,CH$_2$), 3.67 (3H,s,CH$_3$); $^{13}$C NMR; 196.5 (C of COOMe), 172.0 (1C of COOH), 156.0 (C of CO), 137.2, 128.3, 128.1, 126.8, 126.7, 128.1, 128.3, 128.1, 126.8, 126.7, 128.1, 123.8, 147.1, 121.6, 111.0, 120.5, 119.0 (11C of Ar-Benzene),127.6, 135.5, 129.4 (4C of pyrrole), 144.8, 134.1, 132.5, 137.2, 121.6 (6C of quinoxaline), 124.0, 102.0 (2C of piperidine), 15.4 (C of CH$_3$); MS: $m/z$ 514 $[M^+]$; Anal. Calcd. / found for C$_{29}$H$_{18}$N$_6$O$_3$: C, 68.44/68.41, H, 3.45/3.41, N, 16.33 / 16.29.

**RESULTS AND DISCUSSION**

The synthetic plan that was conceived to the preparation of the materials 6(a-e) (scheme-1) required it to be accomplished in two stages. The first stage of this strategy involved the conversion of diazotised indophenazine to the indophenazino fused oxocarbazole and oxoazacarbazole derivatives [12] 4(a-e) respectively. These were realized by the interaction of diazotised indophenazine with 2-hydroxymethylidene cyclohexanone (3a) and various N-substituted piperidones 3(b-e) respectively under the conditions of Japp-Klingemann reaction, followed by the Fischer indolization of the resulting hydrazones with Kent’s acid (HCl:AcOH; 1:4 v/v). The compounds 3(a-e) were inturn obtained, following the reported procedure [15] which consisted of treating cyclohexanone and various N-substituted piperidone with ethyl formate in presence of sodium ethoxide. The second stage of the strategy required
the conversion of 4(a-e) to the corresponding carbazolo fused quinoline-4-carboxylic acid derivatives 6(a-e). The Pfitzinger reaction of isatin on compounds containing the COCH₂ group is known to provide a very convenient one-pot synthetic entry to quinoline-4-carboxylic acid [13] derivatives. It is reported [14] that enolizable ketones show great facility to condense with isatin in strongly alkaline medium to subsequently cyclize to give quinoline products. The procedure developed by Pfitzinger reaction for the preparation of carbazolo and azacarbazolo fused quinoline-4-carboxylic acid derivatives 6(a-e) from isatin and the carbonyl compounds containing an adjacent methylene group (Scheme:1). The mechanism outlined in scheme:2 for this reaction is believed to follow the same process previously described in the literature. The data shown in experimental section were found in good agreement to the assigned structures. The nitrogen analysis and all the spectral data shown in experimental section were found in good agreement to the assigned structures. The IR spectrum of all the compounds showed the presence of a strong absorption band near 1750 cm⁻¹ for CO group. The presence of carboxylic acid group in 6(a-e) was ascertained by the appearance of a broad band of OH group in the region of 3500-3400 cm⁻¹. The ¹H NMR spectrum displayed the corresponding peak for OH proton of carboxylic acid in the region of δ 11.0 ppm. The appearance of the M⁺ peaks corresponding to their molecular formula in MS spectrum substantiated further the formation of the compounds and unequivocally established their structures.

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REFERENCES