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Cyanoacetanilide intermediates in heterocyclic synthesis. Part 7: preparation of some spiro[indoline-3,4′-pyridine] and chromeno[3,4-c]pyridine derivatives

Abstract: The reaction of cyanoacetanilide derivative 1 with some electrophiles was investigated. Treatment of compound 1 with 2-(2-oxoindol-3-ylidene)malononitrile (2a) under reflux in ethanol in the presence of piperidine afforded the spiro[indoline-3,4′-pyridine] derivative 3. Under similar conditions, condensation of compound 1 with the analog 2b yielded a spiroindole 4. Chromeno[3,4-c]pyridine derivative 6 was obtained by cyclization of chromene derivative 5 with ethyl cyanoacetate. In a similar manner, condensation of compound 5 with cyclohexanone under reflux in ethanol in the presence of sodium acetate furnished chromeno[3,4-c]quinoline derivative 7. Compound 1 was condensed with 2-hydroxy-1-naphthaldehyde to yield the benzo[f]chromeno derivative 8. Refluxing of benzochromene derivative 8 with ethyl cyanoacetate in ethanol in the presence of catalytic amount of piperidine produced benzo[f]chromeno[3,4-c]pyridine derivative 9. The structures of the newly synthesized compounds were confirmed on the basis of analytical and spectral data.

Keywords: chromene; chromeno[3,4-c]-pyridine; chromeno[3,4-c]quinolone; cyanoacetanilide; 2-oxoindoline; spiroindole.

Introduction

The spirooxindole is one of the most important classes of naturally occurring substances, characterized by highly pronounced biological properties. It is also the core structure of many synthetic pharmaceuticals [1, 2]. The various biological activities of spirooxindole derivatives have attracted much attention of organic chemists and, as a consequence, a number of methods have been reported for the preparation of spirooxindole-fused heterocycles [3–7]. Chromenes and their benzo derivatives constitute an important class of oxygenated heterocycles, representing a key structural motif of many natural products such as alkaloids, flavonoids, tocopherols and anthocyanins. They have been used as valuable leads for the design and synthesis of new pharmacophores for medicinal chemistry and drug development due to their discernible biological activities. Substituted chromenes are endowed with a broad spectrum of pharmacological properties such as anti-HIV [8], antibacterial [9], antifungal [10] and anti-trypanosominal properties [11]. In addition, benzo[f]chromenes (naphthopyrans) are of special interest as photochromic compounds [12, 13], which have a wide variety of applications in ophthalmic glasses, electronic display systems, optical switches and temporary or permanent memories. Cyanoacetanilide derivatives are important and versatile reagents, which have especially been used for the synthesis of polyfunctionalized three-, five- and six-membered rings and condensed heterocycles [14, 15].

Figure 1 Reactivity of cyanoacetanilides 1.
Cyanoacetanilides are polyfunctional compounds that possess both electrophilic and nucleophilic properties [16]. Two nucleophilic centers in cyanoacetanilides are localized on NH and C-2. Also, cyanoacetanilides possess two electrophilic positions [15], which are associated with C-1 and C-3 (Figure 1). In view of the above-mentioned benefits and in continuation of our previous work on the chemistry of cyanoacetanilides [17–22], here we report the synthesis of versatile hitherto unknown spiro[indoline-3,4′-pyridine], chromeno[3,4-c]pyridine, chromeno[3,4-c]quinoline, benzo[f]chromene and benzo[f]chromeno[3,4-c]pyridine derivatives utilizing inexpensive cyanoacetanilide intermediate 1 as the starting material.

Results and discussion

The key intermediate was methyl 2-(2-cyanoacetamido) benzoate (1) [23] obtained by the solvent free reaction of ethyl cyanoacetate with methyl anthranilate (Scheme 1).

The reactivity of compound 1 towards some electrophiles was investigated. The reaction of 1 with 2-(2-oxoindolin-3-ylidene)malononitrile (2a) in refluxing ethanol in the presence of catalytic amounts of piperidine yielded the spiro[indoline-3,4′-pyridine] derivative 3 (Scheme 2). Evidence of the structure of compound 3 includes the infrared spectrum which reveals strong absorption bands at 3272 and 3176 cm⁻¹ for the NH₂ group and contains the characteristic absorption band at 2224 cm⁻¹ for the cyano group. The ¹H NMR spectrum of the reaction product taken in DMSO-d₆ shows a singlet at 3.93 ppm assigned for the methoxy protons, 6.48 ppm assigned for the amino protons (D₂O exchangeable), 7.26 ppm assigned to the pyridine-H, a multiplet at 7.52–7.99 ppm assigned to the aromatic protons and a downfield singlet at 10.56 ppm
for the NH proton ($D_2O$ exchangeable). The formation of spiro derivative $3$ is assumed to proceed via Michael addition of the ionized methylene group of $1$ to the activated double bond of $2a$ to give the intermediate Michael adduct $A$ followed by intramolecular cyclization through nucleophilic addition of the amino group to the cyano group and tautomerization to afford $3$. Under similar reaction conditions, the treatment of compound $1$ with the ester analog $2b$ afforded product $4$ but not compound $C$ (Scheme 2). The infrared spectrum of the reaction product shows the characteristic absorption bands at 3370 and 3200 cm$^{-1}$ for the NH$_2$ group and at 1720, 1616 cm$^{-1}$ for the carbonyl groups of esters and amide, respectively. In addition, the $^1H$ NMR spectrum of compound $4$ reveals a triplet at 1.41 ppm and a quartet at 4.45 ppm assigned to the ethyl group, a singlet at $\delta 3.81$ ppm assigned to the methoxy protons, a broad singlet at $\delta 10.22$ ppm assigned to the NH proton (exchangeable with $D_2O$) and a multiplet at $\delta 6.86–8.22$ ppm assigned to the aromatic and amino protons (exchangeable with $D_2O$).

Treatment of chromene derivative $5$ [24] with ethyl cyanoacetate in ethanol in the presence of catalytic amount of piperidine furnished the chromeno[3,4-$c$]pyridine derivative $6$ (Scheme 3) instead of compound $F$, as evidenced by analytical and spectral data. The infrared spectrum of the reaction product shows the characteristic absorption bands at 3410, 3278 cm$^{-1}$ for the NH/OH groups and at 2206 cm$^{-1}$ for the cyano group. The $^1H$ NMR spectrum indicates the absence of the ethyl group and displays signals at $\delta 3.72$ ppm assigned to the methoxy protons, at $7.18–8.09$ ppm assigned to aromatic protons, in addition to the presence of two downfield singlets at $\delta 9.18$ and $11.40$ ppm assigned to NH and hydroxyl protons (exchangeable with $D_2O$). The formation of $6$ is assumed to proceed via the intramolecular cyclization of the Michael adduct $B$ via loss of ethanol and subsequent tautomerization and oxidation under the reaction conditions [25] (Scheme 3).

The reaction of compound $5$ with cyclohexanone in refluxing ethanol in the presence of sodium acetate gave 6-imino-8-(2-methoxycarbonylphenyl)-9,10,11,12-tetrahydro-6$H$-chromeno[3,4-$c$]quinoline-7$(8H)$-one ($7$, Scheme 4). The infrared spectrum of the reaction product shows the characteristic bands at 3230 cm$^{-1}$ for the NH group and at 1698 cm$^{-1}$ for the carbonyl group. Also, the $^1H$ NMR spectrum shows a downfield singlet at $\delta 10.56$ ppm assigned to the NH proton (exchangeable with $D_2O$) and
two signals at δ 1.50, 1.87 ppm assigned to aliphatic protons, in addition to the presence of the expected signals at 3.87 and 7.19–7.85 ppm for the methoxy and aromatic protons, respectively. The formation of 7 is assumed to proceed through the formation of the Michael adduct G followed by intramolecular cyclization via loss of water and subsequent tautomerization and oxidation under the reaction conditions.

Condensation of compound 1 with 2-hydroxy-2-naphthaldehyde in refluxing ethanol in the presence of a catalytic amount of piperidine afforded product 8, apparently through the intermediaries of J and K (Scheme 5). The infrared spectrum of compound 8 shows the absence of the cyano group. The 1H NMR spectrum reveals a singlet at δ 3.89 for the methyl protons, a multiplet at δ 7.11–8.06 ppm for the aromatic protons and two downfield singlets at 9.06 and 9.27 ppm assigned to the NH and OH protons (D2O exchangeable), respectively.

Experimental

Melting points were determined on a digital Gallen-Kamp MFB-595 instrument and are uncorrected. IR spectra were measured in KBr pellets on a Shimadzu 440 spectrometer. 1H NMR (300 MHz) and 13C NMR (75 MHz) spectra were recorded in DMSO-d6 on a Varian Gemini 300 spectrometer using tetramethylsilane (TMS) as an internal standard. Elemental analyses were carried out at the Microanalytical Center, Cairo University.

General procedure for synthesis of spiropyridine derivatives 3 and 4

A mixture of cyanoacetanilide 1 (0.01 mol), 2-(2-oxoindolin-3-ylidine) malononitrile  (2a, 0.01 mol), or ethyl 2-cyano-2-(2-oxoindolin-3-ylidine)acetate  (2b, 0.01 mol), piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 4 h. The resultant solid product was collected and crystallized to give 3 or 4.

Methyl 2-(6′-amino-3′,5′-dicyano-1,2′,2′-dioxo-1,2,2′,3′-tetrahydro-1′H-spiro[indole-3,4′-pyridin]-1′-yl)benzoate (3)

This compound was obtained in 83% yield as brown crystals (from EtOH/DMF); mp 230–231°C; IR: 3272, 3176, 3118 (NH/NH2), 3058 (CH-aromatic), 2950 (CH-aliph), 2224 (C=O), 1688, 1628, 1610 cm−1 (2C=O); 1H NMR: δ 3.93 (s, 3H, OCH3), 6.48 (s, 2H, NH2, exchangeable with D2O), 7.26 (s, 1H, pyridine-H), 7.52–7.99 (m, 8H, Ar-H), 10.56 (s, 1H, NH, exchangeable with D2O); 13C NMR: δ 168.3, 165.5, 157.3, 154.6, 141.7, 137.2, 133.8, 132.3, 131.1, 130.2, 127.9, 127.1, 125.4, 124.8, 115.6, 115.4, 113.2, 64.1, 52.7, 49.5, 38.3. Anal. Calcd for C22H15N5O4: C, 63.92; H, 3.66; N, 16.94. Found: C, 63.77; H, 3.53; N, 16.82.

Ethyl 2′-amino-1′-(2-(methoxycarbonylphenyl)-5′-cyano-2′,6′-dioxo-1,2′,5′,6′-tetrahydro-1′H-spiro[indole-3,4′-pyridin]-3′-carboxylate (4)

This compound was obtained in 74% yield as brown crystals (from EtOH/DMF); mp 245–246°C; IR: 3370, 3200, 3150 (NH/NH2), 2216 (C=O), 1720, 1670, 1616 cm−1 (3C=O); 1H NMR: δ 1.41 (t, J = 7 Hz, 3H, CH3), 3.81 (s, 3H, OCH3), 4.45 (q, J = 7 Hz, 2H, CH2) 6.65 (s, 1H, pyridine-H), 6.86–8.22 (m, 10H, Ar-H + D2O), 10.22 (s, 1H, NH exchangeable with D2O); 13C NMR: δ 167.6, 164.9, 164.1, 159.8, 158.7, 142.5, 137.4, 134.3, 131.4, 130.2, 129.8, 129.3, 128.1, 126.7, 125.4, 124.4, 115.1, 114.7, 87.3, 62.6, 52.7, 50.1, 38.4, 15.6. Anal. Calcd for C24H19N7O4: C, 62.61; H, 3.48; N, 12.17. Found: C, 62.68; H, 4.24; N, 12.21.

Methyl 2-(3-imino-3H-benzo[3,4-c]pyridine-2-carboxamido)-benzoate (8)

A mixture of cyanoacetanilide 1 (0.01 mol), 2-hydroxy-1-naphthaldehyde (0.01 mol) and ammonium acetate (0.01 mol) was refluxed in ethanol (30 mL) for 1 h. The resultant solid product was collected.

Scheme 5
by filtration, washed with water, dried, and crystallized from ETOH/DMF to afford 8. This compound was obtained in 65% yield as brown crystals, mp 270–271°C; IR: 3310, 3170 (2NH), 3016 (CH-arom), 1698, 1648 cm⁻¹ (C=O); 1H NMR: δ 3.89 (s, 3H, OCH₃), 7.11–8.06 (m, 10H, Ar-H); 8.33 (s, 1H, chromene-H); 13.11, 11.46 (2s, 2H, 2NH-exchangeable with D₂O); 13 C NMR: δ 171.4, 164.3, 162.6, 153.1, 141.0, 137.4, 131.2, 130.6, 129.9, 129.2, 128.7, 127.2, 126.1, 125.0, 124.2, 123.0, 121.5, 115.8, 116.9, 116.3, 115.8, 53.0. Anal. Calcd for C₂₅H₁₅N₃O₅: C, 68.65; H, 3.50; N, 9.47.

Methyl 2-(1-cyano-2-hydroxy-5-imino-4-oxo-4H-chromeno[3,4-c]pyridin-3(5H)-yl)benzoate (6) This compound was obtained in 63% yield as brown crystals, mp >300°C; IR: 3378, 3250 (NH/OH), 2202 (C≡O); 1H NMR: δ 3.74 (s, 3H, OCH₃), 7.65–8.64 (m, 10H, Ar-H); 9.06 (s, 1H, NH-exchangeable with D₂O); 13 C NMR: δ 176.1, 172.5, 168.4, 160.2, 156.7, 150.5, 134.2, 133.2, 132.1, 131.1, 130.7, 129.8, 128.5, 127.3, 124.7, 123.8, 117.6, 116.5, 115.1, 113.7, 108.3, 57.5, 55.3. Anal. Calcd for C₁₅H₁₃N₂O₇: C, 68.65; H, 3.46; N, 9.61. Found: C, 68.52; H, 3.50; N, 9.47.

General procedure for the preparation of chromeno[3,4-c]pyridine and benzo[f]chromeno[3,4-c]pyridine derivatives 6 and 9

A mixture of 5 or 8 (0.01 mol), ethyl cyanoacetate (0.01 mol) and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 3 h. The resultant solid product was collected by filtration and crystallized to afford products 6 and 9, respectively.

References


Methyl 2-(1-cyano-2-hydroxy-5-imino-4-oxo-4H-benzo[5,6]chromeno[3,4-c]pyridin-3(5H)-yl)benzoate (9) This compound was obtained in 63% yield as brown crystals (from ETOH/DMF); mp >300°C; IR: 3378, 3250 (NH/OH), 1720, 1610 cm⁻¹ (C=O); 1H NMR: δ 3.74 (s, 3H, OCH₃), 7.65–8.64 (m, 10H, Ar-H); 9.06 (s, 1H, NH-exchangeable with D₂O); 13 C NMR: δ 176.1, 172.5, 168.4, 160.2, 156.7, 150.5, 134.2, 133.2, 132.1, 131.1, 130.7, 129.8, 128.5, 127.3, 124.7, 123.8, 122.5, 117.6, 116.5, 115.1, 113.7, 108.3, 57.5, 55.3. Anal. Calcd for C₂₅H₁₅N₃O₇: C, 68.65; H, 3.46; N, 9.61. Found: C, 68.52; H, 3.50; N, 9.47.

6-Imino-8-(2-methoxycarbonylphenyl)-9,10,11,12-tetrahydro-6H-chromeno-[3,4-c]quinoline-7(8H)-one (7)

A mixture of chromene derivative 5 (0.01 mol), cyclohexane (0.01 mol) and sodium acetate (0.5 g) in ethanol (30 mL) was heated under reflux for 6 h and then cooled. The resultant solid was collected by filtration, washed with water, dried, and crystallized from ethanol to give 7. This compound was obtained in 60% yield as brown crystals, mp 285–286°C; IR: 3230 (NH), 2950(CH-aliph), 1698, 1660 cm⁻¹ (C=O); 1H NMR: δ 1.50 (m, 4H), 1.87 (m, 4H), 3.87 (s, 3H, OCH₃), 7.19–7.85 (m, 8H, Ar-H); 10.56 (s, 1H, NH-exchangeable with D₂O); 13 C NMR: δ 169.9, 163.1, 159.8, 157.2, 152.7, 150.8, 140.8, 136.5, 134.1, 131.4, 125.0, 124.1, 122.1, 121.4, 115.7, 114.5, 110.1, 108.4, 55.7, 57.1, 25.3, 23.1, 22.2. Anal. Calcd for C₂₅H₁₅N₃O₇: C, 71.99; H, 5.03; N, 10.85. Found: C, 65.02; H, 3.72; N, 10.72.

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