Reaction of 1-aminoisindole with methyl 4-chloro-3-oxobutanoate

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Condensation of bifunctional 1-aminoisindole with bis-electrophilic methyl 4-chloro-3-oxobutanoate undergoes regioselectively to afford 2-(chloromethyl)-2-hydroxy-2,6-dihydropyrimido[2,1-*a*]isindol-4(3*H*)-one. The structure of the reaction product was unambiguously established by HMQC and HMBC heteronuclear correlations. The functionalization of the synthesized compound by reactions with a series of aliphatic amines was carried out.

Introduction

Isoindole derivatives are widely used for the development of new drugs [1–7], as dyes, pigments and fluorophores in materials science [1, 8–11], as well as markers in analytical chemistry [1].

The 1-aminoisindole is often used as unsymmetrical 1,3-NCN-binucleophilic building block in the synthesis of various isoindole-based fused heterocyclic systems. Thus, its reaction with ethyl 5-acetyl-3,4-dihydropyridine-1(2*H*)-carboxylate leads to regioselective formation of pyrimido[2,1-*a*]isoindole derivative [12], while condensation of 1-aminoisindole with phthaloyl chloride [13] or *o*-chloromethylbenzonitrile and further treatment with sodium ethanolate [14] results in isoindolo[2,1-*b*][2,4]benzodiazepine derivatives. Reactions of 1-aminoisindole with various α -haloketones, β -diketones and β -keto esters leading to the formation of 5*H*-imidazo[2,1-

a]isoindole and 6*H*-pyrimido[2,1-*a*]isoindole derivatives, respectively, have also been studied [15–17]. To the best of our knowledge, condensation of 1-aminoisindole derivatives with 4-halogen-3-oxobutanoates were not described to date, although the latter are very common reagents in heterocyclization with various amidine-containing substrates. The molecule of 4-halogen-3-oxobutanoate contains several reaction centers and could play a role of 1,3-CCC- as well as 1,2-CC-biselectrophile; that ensures the variability of the reactions and the synthetical diversity of the products obtained. For example, its condensation with different amidines leads to the formation of substituted pyrrolo[2,3-*d*]pyrimidines [18], imidazo[1,2-*a*]pyridines [19], thiazolo[3,2-*b*][1,2,4]triazoles [20], benzo[*d*]imidazo[2,1-*b*]thiazoles [21], imidazo[1,2-*a*]pyrazines [22], pyrido[1,2-*a*]pyrimidines [23] etc.

Results and discussion

Herein, we report our studies on the condensation of 1-aminoisindole hydrobromide with methyl 4-chloro-3-oxobutanoate. The reaction was carried out in dry dioxane in the presence of triethylamine. As a result of heterocyclization, a product was obtained in moderate yield (46%). This product may have one of two alternative regioisomeric structures **3a** or **3b** (Scheme 1). It should be noted that

Scheme 1. Reaction of 1-aminoisindole **1** with methyl-4-chloro-3-oxobutanoate **2**.

Structures **3a** and **3b** have similar spin systems; therefore, they cannot be distinguished on the basis of ^1H and ^{13}C NMR spectra. To solve this problem, we recorded HMQC and HMBC heteronuclear ^{13}C – ^1H correlation spectra of the compound **3** (through one and 2–3 chemical bonds, respectively). The coordinates of the cross-peaks found in the HMQC and HMBC spectra are shown in Table 1.

Correlations through one chemical bond in the HMQC spectrum allowed assigning signals from carbon atoms linked to hydrogen, and quaternary carbon atoms were identified by analysis of correlations through 2–3 chemical bonds in the HMBC spectrum. Here, the most important correlation was the one between the methylene group protons of the isoindoline fragment (δ 4.79 ppm) and the carbon atom C=O group (δ 166.0 ppm). Such

we have not found any literature examples on reaction of amidines with 4-halogeno-3-oxobutanoates, where both chloromethyl fragment and OH group were simultaneously present in the product structure at the same carbon atom. Such type of reactions commonly occurred under rather severe conditions, often upon heating in polyphosphoric acid [24], and were accompanied by water molecule elimination.

correlation indicates that there are no more than three chemical bonds between these atoms.

Table 1. Heteronuclear ^1H – ^{13}C correlations found for compound **3**.

δ , ppm	HMQC	HMBC
7.82	124.0	155.9; 141.2; 133.1; 124.5
7.63	133.1; 124.5	141.2; 135.5; 129.0; 124.0; 48.6
7.47	129.0	141.2; 124.0; 124.5
6.15	-	-
4.79	48.6	166.0; 155.9; 141.2; 135.5; 129.0; 124.5
3.63	52.0	86.2; 39.0
3.68	52.0	86.2; 39.0
2.80	39.0	166.0; 86.2; 52.0
2.62	39.0	166.0; 86.2; 52.0

This allows to assign structure of the reaction product as 2-(chloromethyl)-2-hydroxy-2,6-dihydro-pyrimido[2,1-a]isoindol-4(3H)-one (**3a**). In the alternative molecule **3b**, the carbonyl carbon atom and the methylene group protons are separated by 5

chemical bonds, which does not allow for the spin-spin coupling between them.

Figure 1. Signals assignment of ^1H and ^{13}C NMR spectra for **3a** according to HMQC and HMBC.

Figure 1 shows the chemical shifts of protons and carbon nuclei in the molecule **3a**, as well as the principal correlations in the HMBC spectrum.

To further study chemical properties of pyrimido[2,1-*a*]isoindolone **3a**, we introduced this compound into reactions with a series of aliphatic amines (Scheme 2). The reaction was carried out in dry toluene with large excess of amine, which acted both as a reagent and a base. Derivatives **4** were isolated in good yields using column chromatography.

Scheme 2. Reaction of **3a** with aliphatic amines.

Experimental part

NMR spectra were obtained on Mercury 400 Varian spectrometer at 400 MHz (^1H NMR) or 100 MHz (^{13}C NMR) in $\text{DMSO}-d_6$. All chemical shifts were referenced to the TMS residual peak as an internal standard. The heteronuclear HMQC and HMBC correlation spectra were recorded using a method of indirect detection of carbon signals and gradient selection of useful signals. Melting points were determined with a Boetius microscope hot plate apparatus. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument with chemical ionization.

2-(Chloromethyl)-2-hydroxy-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one (**3a**).

The mixture of 2-aminoisindole hydrobromide (0.43 g, 2 mmol), methyl 4-chloro-3-oxobutanoate (0.38 g, 2.5 mmol) and triethylamine (0.25 g, 2.5 mmol) in dry dioxane (10 ml) were heated under reflux for 40 min. Precipitate formed after cooling was filtered off and purified by column chromatography on silica gel with ethyl acetate–toluene (8:2) as eluent.

Pale yellow powder (Yield 0.23 g, 46 %). M.p. 174–175 °C. ^1H NMR: δ = 2.62 (d, 1H, J = 16 Hz), 2.80 (d, 1H, J = 16 Hz), 3.63 (d, 1H, J = 12 Hz), 3.68 (d, 1H, J = 12 Hz), 4.79 (s, 2H), 6.15 (s, 1H, OH), 7.47 (t, 1H, J = 8 Hz) 7.49–7.63 (m, 2H), 7.82 (d, 1H, J = 8 Hz) ppm. ^{13}C NMR: δ = 39.0, 48.6, 52.0, 86.2, 124.0, 124.5,

129.0, 133.1, 135.5, 141.2, 155.9, 166.0 ppm. $[M+H]^+$ 251.

General procedure for preparation of amino alcohols 4.

The mixture of compound **3a** (0.5 g, 2 mmol) and aliphatic amine (3 mmol) in dry toluene (10 ml) were heated under reflux for 1 h. The solvent was evaporated and the residue was separated by column chromatography on silica gel with hexane-ethyl acetate (9:1) as eluent.

2-Hydroxy-2-(morpholin-4-ylmethyl)-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one (4a).

White powder (Yield 93 %). M.p. 192–193 °C. 1H NMR: δ = 2.50–2.55 (m, 2H), 2.57–2.61 (m, 4H), 3.47 (s, 2H), 3.65–3.71 (m, 4H), 5.05 (s, 1H), 6.37 (s, 1H, OH), 7.59 (t, 1H, $J=7.4$ Hz), 7.67 (t, 1H, $J=8$ Hz), 7.76–7.78 (d, 1H, $J=8$ Hz), 7.99–8.01 (d, 1H, $J=8$ Hz) ppm. ^{13}C NMR δ = 41.0, 49.2, 53.5, 62.8, 65.8, 85.1, 125.2, 125.5, 127.1, 134.4, 136.0, 142.1, 155.5, 166.7 ppm. $[M+H]^+$ 302.

2-Hydroxy-2-[(4-methylpiperazin-1-yl)methyl]-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one (4b)

Pale yellow powder (Yield 74 %). M.p. 187–188 °C. 1H NMR: δ = 2.44 (s, 3H), 2.51–2.55 (m, 2H), 3.35–3.40 (m, 4H), 3.51 (s, 2H), 3.95–4.11 (m, 4H), 5.15 (s, 2H), 6.42 (s, 1H, OH), 7.61 (t, 1H, $J=7.4$ Hz), 7.69 (t, 1H, $J=8$ Hz), 7.72–7.76 (d, 1H, $J=8$ Hz), 7.96–7.98 (d, 1H, $J=8$ Hz) ppm. ^{13}C NMR: δ = 40.2, 46.0, 48.5, 53.1, 54.5, 64.1, 86.5, 123.8, 125.7, 128.3, 133.9, 136.3, 144.0, 157.1, 165.8 ppm. $[M+H]^+$ 315.

4-[(2-Hydroxy-4-oxo-2,3,4,6-tetrahydropyrimido[2,1-a]isoindol-2-yl)methyl]piperazine-1-carbaldehyde (4c)

Pale yellow powder (Yield 76 %). M.p. 190–192 °C. 1H NMR: δ = 2.50–2.53 (m, 2H), 3.32–2.38 (m, 4H), 3.48 (s, 2H), 3.97–3.99 (m, 2H), 4.02–4.04 (m, 2H), 5.18 (s, 2H), 6.40 (s, 1H, OH), 7.62 (t, 1H, $J=7.4$ Hz), 7.65 (t, 1H, $J=8$ Hz), 7.73–7.75 (d, 1H, $J=8$ Hz), 7.91–7.93 (d, 1H, $J=8$ Hz), 8.40 (s, 1H) ppm. ^{13}C NMR δ (DMSO- d_6) 38.1; 42.1; 49.1; 51.8; 62.2; 87.7; 125.2; 125.7; 129.6; 134.1; 135.9; 141.8; 156.9; 160.1; 166.8 ppm. $[M+H]^+$ 329.

2-Hydroxy-2-[(propylamino)methyl]-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one (4d)

Pale yellow powder (Yield 92 %). M.p. 162–163 °C. 1H NMR: δ = 1.04 (t, 3H), 1.70–1.79 (m, 2H), 3.57–3.61 (m, 2H), 3.52 (s, 2H), 5.14 (s, 2H), 6.34 (s, 1H, OH), 7.55 (t, 1H, $J=7.4$ Hz), 7.62 (t, 1H, $J=8$ Hz), 7.70–7.72 (d, 1H, $J=8$ Hz), 7.88–7.90 (d, 1H, $J=8$ Hz) ppm. ^{13}C NMR: δ = 10.8, 21.5, 39.7, 48.2, 50.1, 59.0, 87.0, 125.3, 125.9, 130.3, 134.3, 137.0, 142.4, 157.1, 167.1 ppm. $[M+H]^+$ 274.

2-Hydroxy-2-[(3-methoxypropyl)amino]methyl]-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one (4e)

White powder (Yield 73 %). M.p. 167–168 °C. 1H NMR: δ = 2.54–2.56 (m, 2H), 3.21 (s, 3H, OCH₃), 3.50–3.52 (m, 2H), 3.96–3.98 (m, 2H), 3.48 (s, 2H), 5.04 (s, 2H), 6.29 (s, 1H, OH), 7.53 (t, 1H, $J=7.4$ Hz), 7.65 (t, 1H, $J=8$ Hz), 7.69–7.71 (d, 1H, $J=8$ Hz), 7.92–7.94 (d, 1H, $J=8$ Hz) ppm. ^{13}C NMR: δ = 31.6, 39.5, 47.4, 49.6, 56.2, 57.2, 67.1, 87.7, 126.1,

126.8, 130.2, 134.2, 136.1, 143.1, 156.7, 167.2 ppm. $[M+H]^+$ 304.

2-Hydroxy-2-[(2-phenylethyl)amino]methyl}-2,6-dihydropyrimido[2,1-a]isoindol-4(3H)-one (**4f**)

Pale yellow powder (Yield 92 %). M.p. 191 °C. 1H NMR: δ = 2.79–2.84 (m, 4H), 3.45 (s, 2H), 5.03 (s, 2H), 6.30 (s, 1H, OH), 7.14–7.25 (m, 5H), 7.59 (t, 1H, J = 7.4 Hz), 7.67 (t, 1H, J = 8 Hz), 7.74–7.76 (d, 1H, J = 8 Hz), 7.95–7.97 (d, 1H, J = 8 Hz) ppm. ^{13}C NMR: δ = 34.5, 39.8, 48.5, 48.9, 57.2, 87.0, 124.6, 124.9, 125.9, 126.8, 127.5, 131.1, 134.2, 136.7, 138.1, 143.2, 156.4, 167.7 ppm. $[M+H]^+$ 336.

Conclusions

Reaction of 1-aminoisoindole with methyl-4-chloro-3-oxobutanoate occurs in a regioselective manner to provide 2-(chloromethyl)-2-hydroxy-2,6-dihydropyrimido[2,1-a]-isoindol-4(3H)-one **3a**. A simple approach to novel biologically promising amino alcohols **4** was elaborated, which includes reaction of compound **3a** with aliphatic amines.

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