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Short Note

N-[3-(Chloromethyl)-1,2-benzisoxazol-5-yl]acetamide

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Abstract: Functionally substituted 1,2-benzisoxazoles are very important and promising heterocycles with various pharmacological activities. Benzoxazoles containing reactive 3-chloromethyl and 5-amino groups are practically unexplored derivatives in this series. In this communication, the simple method for the synthesis of *N*-[3-(chloromethyl)-1,2-benzisoxazol-5-yl]acetamide which is an interesting precursor for the preparation of a series of 3,5-disubstituted benzoxazoles was described. The structure of the synthesized compound was established by elemental analysis, high-resolution mass spectrometry, ^{1}H, ^{13}C NMR and IR spectroscopy, and mass spectrometry.

Keywords: 1,2-benzisoxazoles; synthesis; *N*-[3-(chloromethyl)-1,2-benzisoxazol-5-yl]acetamide; ring closure

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1. Introduction

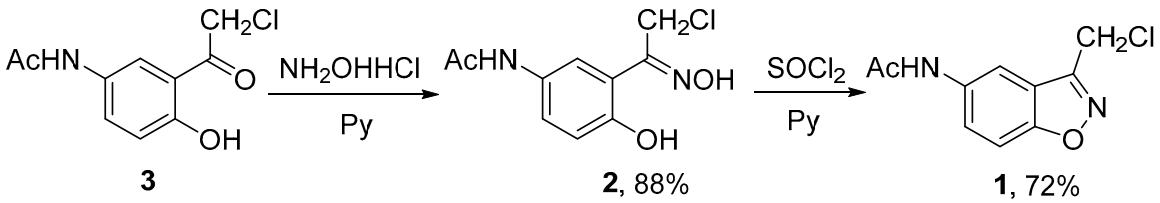
1,2-Benzisoxazole derivatives are oxygen- and nitrogen-containing heterocycles with a wide range of synthetic and pharmaceutical applications. They possess significant pharmacological and biological activities such as analgesics [1], anticonvulsant [2,3], antipscychotic [4], anticancer [5], and antimicrobial [6], and also showed affinity for serotonergic and dopaminergic receptors [7]. New functional derivatives of this class can be considered as compounds with great potential for biological activity. 5-Amino derivatives of 1,2-benzisoxazoles are actively investigated as biologically active compounds [3,8–10]. There is information about the synthesis of 3-chloromethyl 1,2-benzisoxazoles [11]. To expand the range of functionally substituted 1,2-benzisoxazoles, we aimed to combine in one molecule a protected amino group in the fifth position and a functionally active chloromethyl group in the third position of the heterocycle. Herein, we report the synthesis of *N*-[3-(chloromethyl)-1,2-benzisoxazol-5-yl]acetamide **1**, which can be considered as an important intermediate for the preparation of previously inaccessible 3,5-disubstituted 1,2-benzisoxazoles.

2. Results and Discussion

There are several synthetic protocols for the synthesis of 3-substituted 1,2-benzisoxazoles [12]. We chose the method of base-catalyzed cyclization of *o*-hydroxyphenylketoximes [13]. It was found that the treatment of *N*-[4-(chloroacetyl)-3-hydroxyphenyl]acetamide **3** [14] with hydroxylamine hydrochloride and pyridine in EtOH gave oxime **2** in high yield. The reaction of oxime **2** with thionyl chloride in the presence of pyridine in anhydrous THF yielded the target *N*-[3-(chloromethyl)-1,2-benzisoxazol-5-yl]acetamide **1** (Scheme 1).

The structure of *N*-[3-(chloromethyl)-1,2-benzisoxazol-5-yl]acetamide **1** was fully confirmed by elemental analysis, high-resolution mass spectrometry, ^{1}H, ^{13}C NMR and IR spectroscopy, and mass spectrometry. HRMS and elemental analysis confirm the brutto formula of compound **1**. The mass spectrum of the compound **1** contains two molecular ion peaks (244 and 242) with intensities characteristic of compounds containing one chlorine atom. The ^{1}H NMR spectrum of **1** showed characteristic singlets of Me (2.11 ppm), $ClCH_2$ (5.22 ppm) groups and C-H signals of the benzene ring (7.74 and 8.34 ppm). The IR

spectrum contains signals characteristic of the acetamide group: NH (3300 cm^{-1}) and C=O (1611 cm^{-1}).



3 **2**, 88% **1**, 72%

Scheme 1. Synthesis of *N*-[3-(chloromethyl)-1,2-benzisoxazol-5-yl]acetamide **1**.

In conclusion, we synthesized *N*-[3-(chloromethyl)-1,2-benzisoxazol-5-yl]acetamide **1**, which is a convenient precursor of various functionally disubstituted 1,2-benzisoxazoles, compounds with useful pharmacological properties.

3. Materials and Methods

N-(3-(2-Chloroacetyl)-4-hydroxyphenyl)acetamide **3** was prepared according to the published method [14]. The solvents and reagents were purchased from commercial sources and used as received. Elemental analysis was performed on a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA). Melting point was determined on a Kofler hot-stage apparatus and is uncorrected. ^{1}H and ^{13}C NMR spectra were taken with a Bruker AM-300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA), at frequencies of 300 and 75 MHz, in DMSO-d_6 solution, with TMS as the standard. J values are given in Hz. MS spectrum (EI, 70 eV) was obtained with a Finnigan MAT INCOS 50 instrument (Hazlet, NJ, USA). IR spectrum was measured with a Bruker "Alpha-T" instrument (Santa Barbara, CA 93117, USA) in KBr pellet. High-resolution MS spectrum was measured on a Bruker micrOTOF II instrument (Bruker Daltonik Gmbh, Bremen, Germany) using electrospray ionization (ESI).

Synthesis of *N*-(3-(2-chloro-1-(hydroxyimino)ethyl)-4-hydroxyphenyl)acetamide **2** (Supplementary Materials).

Hydroxylamine hydrochloride (29.2 g, 0.42 mol) was added to a suspension of *N*-[4-(chloroacetyl)-3-hydroxyphenyl]acetamide (71.5 g, 0.31 mol) in EtOH (1200 mL). After stirring for 40 min at room temperature, pyridine (26.7 mL, 0.33 mol) was added dropwise within 30 min. The reaction mixture was stirred at room temperature until consumption of the starting compound **3** (TLC) for 5 h. The solvent was distilled off in vacuo; the residue was treated with water and hydrochloric acid to pH 4-5. The precipitate formed was filtered off, washed with water and dried. Yield 66.7 g (88%), white crystals, mp. 172–173 °C. IR spectrum (KBr), ν, cm^{-1}: 3339 and 3165 (NH, OH), 2862 (CH), 1611 (C=O), 1553, 1394, 1273, 1008, 735. ^{1}H-NMR (DMSO-d_6, ppm): 2.02 (s, 3H), 4.70 (s, 2H), 6.85 (d, J = 8.8, 1H), 7.49 (d, J = 8.8, 1H), 7.64 (s, 1H), 9.82 (s, 1H), 10.30 (s, 1H), 12.12 (s, 1H). ^{13}C-NMR (DMSO-d_6, ppm): 23.8 (CH_3), 32.8 (CH_2), 116.3, 118.6, 119.9, 122.0, 131.3, 152.1, 154.2, 167.8. MS (EI, 70 Ev), m/z (I, %): 244 (M + 2, 7), 242 (M+, 25), 182 (22), 147 (48), 43 (100). HRMS (ESI-TOF): calcd for $C_{10}H_{12}ClN_2O_3$ $[M + H]^-$ 243.0531; found m/z 243.0539. Anal. calcd for $C_{10}H_{11}ClN_2O_3$: C, 49.50; H, 4.57; N, 11.54; found: C, 49.75; H, 4.62; N, 11.69%.

Synthesis of *N*-[3-(chloromethyl)-1,2-benzisoxazol-5-yl]acetamide **1** (Supplementary Materials).

A solution of thionyl chloride (5.5 mL, 75 mmol) in dry THF (50 mL) was added dropwise to a solution of oxime **2** (19.19 g, 75 mmol) and pyridine (20 mL) in dry THF (300 mL), at such a rate that the temperature did not rise above 0 °C. The reaction mixture was stirred at room temperature for 8 h, poured to cold water (500 mL) and acidified to pH~3; the THF was distilled off and residue was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with water and dried over $MgSO_4$. The solvent was partially distilled off in vacuo; the residue was filtered off and crystallized from a mixture of ethyl acetate–*tert*-butyl methyl ether. Yield 13.2 g (72%), white crystals, mp. 198–199 °C. IR spectrum (KBr), ν, cm^{-1}: 3300 (NH), 2983 (CH), 1662 (C=O), 1565, 1519, 1476, 1338, 1265,

818, 738. ^{1}H-NMR (DMSO-d_6, ppm): 2.11 (s, 3H), 5.22 (s, 2H), 7.74 (m, 2H), 8.34 (s, 1H), 10.26 (s, 1H). ^{13}C-NMR (DMSO-d_6, ppm): 23.9 (CH_3), 34.9 (CH_2), 110.1, 110.5, 119.8, 123.5, 135.9, 155.7, 159.3, 168.5. MS (EI, 70 Ev), m/z (I, %): 226 (M + 2, 3), 224 (M+, 10), 182 (25), 147 (38), 43 (100). HRMS (ESI-TOF): calcd for $C_{10}H_{10}ClN_2O_2$ $[M + 1]^-$ 225.0425; found m/z 225.0432. Anal. calcd for $C_{10}H_9ClN_2O_2$: C, 53.47; H, 4.04; N, 12.47; found: C, 53.62; H, 4.15; N, 12.62%.

Supplementary Materials: The following are available online: copies of ^{1}H and ^{13}C NMR, IR, HRMS and mass-spectra for the compounds **1** and **2**.

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Sample Availability: Samples of the compounds **1** and **2** are available from the authors.

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