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Three-Step Synthesis of (*E*)-1-(2-(Pyridin-2-yl)benzo[*d*]thiazol-6-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one as a Potential Ligand for Transition Metals

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Abstract

In the present study, (*E*)-1-(2-(pyridin-2-yl)benzo[*d*]thiazol-6-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**4**) was designed and synthesized via a three-step reaction sequence. Initially, 6-acetylbenzo[*d*]thiazol-2(3*H*)-one (**1**) was hydrolyzed to the corresponding 5-acetyl-2-aminothiophenol **2** and then cyclized with pyridine-2-carbaldehyde. The final product was synthesized by a base-catalyzed aldol condensation of 1-(2-(pyridin-2-yl)benzo[*d*]thiazol-6-yl)ethan-1-one (**3**) and 3,4,5-trimethoxybenzaldehyde and was comprehensively characterized.

Keywords: 2-(pyridin-2-yl)benzothiazol; chalcone; Claisen–Schmidt reaction

1. Introduction

The structure of chalcone is one of the most critical and widely recognized components, and is an integral feature of a range of flavonoids and pharmacological agents [1]. Due to their adaptable structure, chalcones can bind efficiently to various enzymes and receptors, resulting in the diverse biological applications of these compounds [2]. Chalcone is a unique template that is associated with several biological activities such as antioxidant, anticancer, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antimalarial, antileishmanial, antihyperglycemic, tyrosine-inhibitory, and vasorelaxant activity [3].

On the other hand, benzothiazole is a bicyclic heterocycle with N and S as hetero atoms, which possess antitumor, antimicrobial, antimalarial, antitubercular, analgesic, and anti-inflammatory properties. Benzothiazole-derived coordination compounds are of great interest, as they possess a broad spectrum of pharmacological activities [4]. For these reasons, considerable attempts are being made to design molecules integrating diverse pharmacophores. Our research group has experience in the design and synthesis of heterocyclic chalcone, which showed good cytotoxic activity [5,6]. In the present study, we focused on the design and synthesis of a molecule containing a chalcone moiety as a potent cytotoxic pharmacophore, combined with a nitrogen-donor ligand capable of forming coordination complexes with transition metals, analogous to cisplatin, which features amine ligands as non-leaving groups [7].

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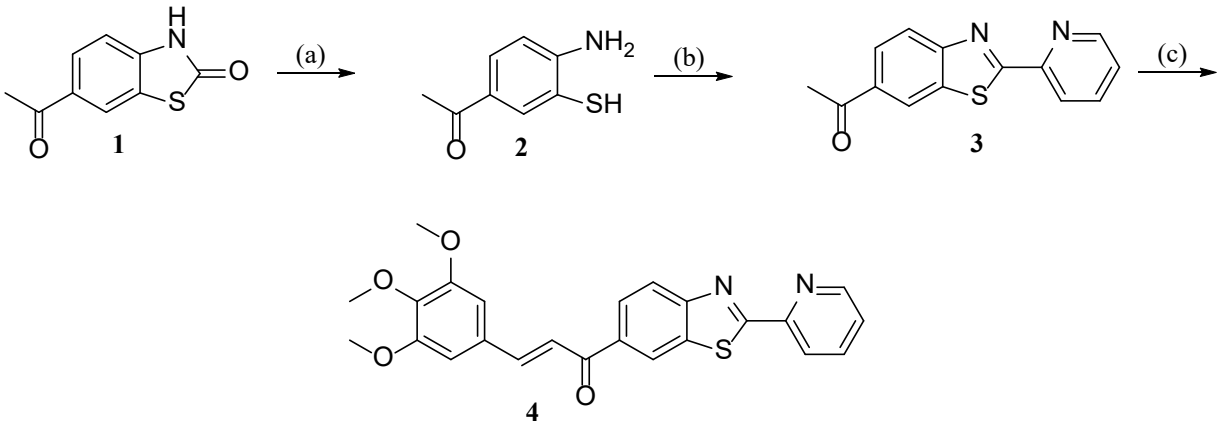
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2. Results and Discussion

To synthesize (*E*)-1-(2-(pyridin-2-yl)benzo[*d*]thiazol-6-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**4**), 6-acetylbenzo[*d*]thiazol-2(3*H*)-one (**1**) was used as a starting material in the reaction of hydrolysis with 50% KOH by heating (Scheme 1). The obtained 2-aminothiophenol **2** was cyclized with pyridine-2-carbaldehyde in DMSO at 160 °C [8]. The final product was synthesized by a base-catalyzed aldol condensation of 1-(2-(pyridin-2-yl)benzo[*d*]thiazol-6-yl)ethan-1-one (**3**) and 3,4,5-trimethoxybenzaldehyde in good yield. The structures of the new compounds **3** and **4** were confirmed by elemental analysis, FTIR spectra, ^{1}H and ^{13}C NMR, and HRMS. In particular, analysis of the ^{1}H NMR spectra revealed that compound **4** is geometrically pure and adopts the *E* configuration, as evidenced by the coupling constant (J = 15.5 Hz) for the vinyl protons, see Supplementary Materials.



a) 50% aq.KOH, reflux, 12h, Ar; b) pyridin-2-carbaldehyde, DMSO, 160°C, yield 64%; c) 3,4,5-trimethoxybenzaldehyde, C_2H_5OH, 10% aq. KOH, r.t., 24h, yield 71%;

Scheme 1. Synthesis of (*E*)-1-(2-(pyridin-2-yl)benzo[*d*]thiazol-6-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**4**).

3. Materials and Methods

3.1. General

All chemicals were purchased from Acros Organics (Geel, Belgium). Reactions and purity of the final compound were monitored by thin-layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}) using toluene/chloroform/ethylacetate (3:1:1 v/v) as the eluent.

Melting points were determined on a Kruss (Hamburg, Germany) KSN I N melting point meter. NMR spectra were recorded in DMSO-d_6 on a Bruker (Billerica, Massachusetts) Avance III HD 500, operating at 500 MHz for ^{1}H and at 125.8 MHz for ^{13}C. Chemical shifts are given in parts per million (δ) relative to the solvent peak. Coupling constants (J) were measured in hertz (Hz). High-resolution mass spectra (HRMS) were obtained with an Orbitrap Exploris 120 Mass Spectrometer, Thermo Fisher Scientific (Waltham, Massachusetts, USA). The elemental analysis was carried on a "VARIO EL III Elemental analyzer (Hesse, Germany)" and the results for C, H, and N were within ±0.4% of the theoretical values. Analytical HPLC was carried out on an Agilent (Santa Clara, California, United States) 1100 HPLC system equipped with a binary pump and diode array detector. The column used was Agilent Eclipse Plus C18 (75 mm × 4.6 mm, 3.5 µm). The mobile phase was AcN:H_2O, using a linear gradient of the binary solvent system (AcN:H_2O from 30:70 to 90:10 v/v% for 7.5 min, with final time 5 min) and a flow rate of 0.500 mL/min.

3.2. Synthesis

3.2.1. 1-(2-(Pyridin-2-yl)benzo[*d*]thiazol-6-yl)ethan-1-one (**3**)

6-Acetylbenzo[*d*]thiazol-2(*3H*)-one (**1**, 2.5 g, 13 mmol) was refluxed in 50% aq. KOH (15 mL) for 12 h under argon. The mixture was then diluted with water (50 mL) and filtered. To the filtrate, acetic acid was added with vigorous stirring and cooling until it was just acidic. The obtained product was filtered, washed with water, and used without purification in the next step. A mixture of 2-amino-5-acetylthiophenol (**2**, 0.50 g, 3 mmol) and pyridine-2-carbaldehyde (0.32 g, 3 mmol) in DMSO (6 mL) was heated to 160 °C for 10 min. After cooling to 100 °C, water (1 mL) was added. The crystalline product was filtered and recrystallized. Yield: 64% (0.48 g).

Light yellow crystals, m.p.: 184–185° C (C_2H_5OH). IR (nujol): 1669, 1587, 1329, 991, 823, 783 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 2.66 (s, 3H, CH_3), 7.61 (dd, 1H, pyridine. H, *J* = 4.9 Hz, *J* = 7.3 Hz), 8.03–8.08 (m, 2H, pyridine-H,), 8.14 (d, 1H, ArH, *J* = 8.6 Hz), 8.32 (d, 1H, ArH, *J* = 7.8 Hz), 8.73 (d, 1H, pyridine-H, *J* = 4.5 Hz), 8.82 (s, 1H, pyridine-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 27.4, 121.1, 123.6, 124.5, 126.6, 127.1, 134.5, 136.1, 138.5, 150.4, 150.6, 156.9, 173.3, 197.6. HRMS (ESI): Found 255.0583. Calcd. for $C_{24}H_{20}N_2O_4S$: 255.0592 $[M + H]^+$. Anal. calcd. for $C_{14}H_{10}N_2OS$ (254.31): C, 66.12; H, 3.96; N 11.02. Found: C, 66.31; H, 3.84; N, 10.98.

3.2.2. (*E*)-1-(2-(Pyridin-2-yl)benzo[*d*]thiazol-6-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**4**)

To a mixture of 1-(2-(pyridin-2-yl)benzo[*d*]thiazol-6-yl)ethan-1-one (**3**, 153 mg, 0.6 mmol) and 3,4,5-trimethoxybenzaldehyde (137 mg, 0.7 mmol) in ethanol (6 mL), 10% aq. KOH (2 mL) was added. The obtained yellow mixture was stirred for 24 h at room temperature. The mixture was poured into 20 mL water. The crystalline product was filtered and dried. Yield: 71% (185 mg).

Light yellow crystals, m.p.: 204–206° C (CH_3CN). IR (nujol): 1656, 1590, 1124, 1001, 819 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 3.73 (s, 3H, OCH_3), 3.89 (s, 6H, OCH_3), 7.28 (s, 2H, arom. H), 7.63–7.66 (m, 1H, pyridine H), 7.77 (d, 1H, CH=CH, *J* = 15.5 Hz), 8.04 (d, 1H, CH=CH, *J* = 15.5 Hz), 8.06–810 (m, 1H, pyridine-H), 8.25 (d, 1H, ArH, *J* = 8.6 Hz), 8.31 (dd, 1H, ArH, *J* = 8.6 Hz, *J* = 1.3 Hz), 8.38 (d, 1H, ArH, *J* = 7.8 Hz), 8.77 (d, 1H, pyridine-H, *J* = 4.5 Hz), 9.07 (s, 1H, pyridine-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 56.2, 60.2, 106.7, 120.7, 121.1, 123.4, 124.0, 126.7, 126.8, 130.2, 135.0, 135.8, 138.1, 139.9, 144.9, 150.0, 150.2, 153.1, 156.5, 172.8, 188.1. HRMS (ESI): Found 433.1208. Calcd. for $C_{24}H_{20}N_2O_4S$: 433.1222 $[M + H]^+$. Anal. calcd. for $C_{24}H_{20}N_2O_4S$ (432.49): C, 66.65; H, 4.66; N 6.48. Found: C, 66.81; H, 4.37; N, 6.29.

4. Conclusions

The three-step synthetic procedure developed in this study for the preparation of 2-pyridylbenzothiazole derivatives is efficient, reproducible, and affords pure compounds without the need for further purification. The present work provides an experimental foundation for the design of analogous derivatives and the development of novel drug candidates.

Supplementary Materials: FT-IR, ^1H- and ^{13}C-NMR, and HRMS results for compounds **3** and **4** are available online; Figure S1: FT-IR spectrum of compound **3**; Figure S2: FT-IR spectrum of compound **4**; Figure S3: ^1H-NMR spectrum of compound **3**; Figure S4: ^{13}C-NMR spectrum of compound **3**; Figure S5: ^1H-NMR spectrum of compound **4**; Figure S6: ^{13}C-NMR spectrum of compound **4**; Figure S7: HRMS of compound **3**; Figure S8: HRMS of compound **4**; Figure S9: HPLC of compound **3**; Figure S10: HPLC of compound **4**.

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