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Short Note

(*E*)-3-Methyl-6-(3-oxo-3-(thiophen-2-yl)-1-propenyl)-2(3*H*)-benzothiazolone

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Abstract: The title compound, (*E*)-3-methyl-6-(3-oxo-3-(thiophen-2-yl)-1-propenyl)-2(3*H*)-benzothiazolone, was synthesized by Claisen-Schmidt condensation of 3-methyl-2(3*H*)-benzothiazolone-6-carbaldehyde with 2-acetylthiophene in 94% yield. The structure of the target compound was confirmed using ^{1}H-NMR, ^{13}C-NMR, IR, MS, and elemental analysis.

Keywords: chalcone; 2(3*H*)-benzothiazolone; thiophene

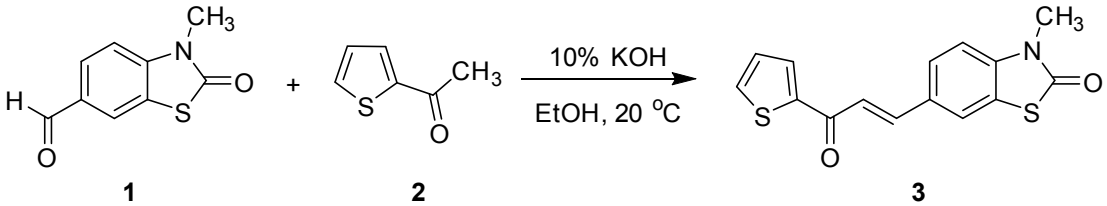
1. Introduction

Chalcones, being quite good pharmacophores for the design of new bioactive molecules, have received increasing attention from medicinal chemists during the past decade. Compounds with chalcone fragments can be found in some natural products as well as in synthetic derivatives with antitumour [1], antibacterial [2], antioxidant [3] and antiulcer [4] activities.

In continuation of our previous studies on the synthesis of heterocyclic chalcone derivatives with benzoxazolone [5] or benzothiazolone ring [6–8], in this work we report the preparation of a novel (*E*)-3-methyl-6-(3-oxo-3-(thiophen-2-yl)-1-propenyl)-2(3*H*)-benzothiazolone. The compound consists of thiophene and benzothiazolone heterocycles, connected via α,β-unsaturated carbonyl system, a key framework of chalcones.

2. Results

The synthesis of (*E*)-3-methyl-6-(3-oxo-3-(thiophen-2-yl)-1-propenyl)-2(3*H*)-benzothiazolone (**3**) (Scheme 1) was performed by a Claisen-Schmidt condensation of 3-methyl-2(3*H*)-benzothiazolone-6-carbaldehyde (**1**) with 2-acetylthiophene (**2**). The reaction was carried out in ethanol in the presence of aqueous KOH and led to only one product with nearly quantitative yield.



1 **2** **3**

Scheme 1. Synthesis of (*E*)-3-methyl-6-(3-oxo-3-(thiophen-2-yl)-1-propenyl)-2(3*H*)-benzothiazolone (**3**).

The structure of compound **3** was confirmed by ^{1}H- and ^{13}C-NMR, IR, MS and elemental analysis and all data are in accordance with the assumed structure. The lactam and ketone C=O stretching bands in IR spectra were seen at about 1640 cm^{-1} and 1670 cm^{-1}. In particular, analysis of ^{1}H-NMR spectra revealed that the structure is geometrically pure with the *E* configuration, as derived from coupling constant *J* = 15.4 Hz for vinyl protons (Figure S1).

3. Experimental Section

3.1. General Information

All chemicals were purchased from Acros Organics (Geel, Belgium). 3-Methyl-2(3*H*)-benzothiazolone-6-carbaldehyde (**1**) was synthesized as described previously [9]. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}) using hexane/acetone (2:1 *v*/*v*) as eluent. The purity of the final compound was determined by GC-MS on an Agilent 6890 system with MSD 5973 (single quadrupol and EI at 70 eV ionization), (Wilmington, DE, USA), using a capillary column HP-5/MS (30 m × 0.250 mm × 0.25 μm). Carrier gas He was used at 0.8 mL/min. The temperature programmed mode was used (from 60 °C for 2 min, then with 10 °C/min to 300 °C for 10 min). The sample was introduced in splitless injection mode.

Melting point was determined on a Boetius hot-stage microscope (Carl Zeiss Jena, Germany) and was uncorrected. IR spectrum (nujol) was recorded on a Specord 71 spectrometer (Carl Zeiss Jena, Germany). NMR spectra were recorded in DMSO-d_6 on a Bruker Avance III HD 500 (Bruker BioSpin GmbH, Rheinstetten, Germany), 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). The elemental analyses was carried on a VARIO EL III Elemental analyzer (Elementar Analysensysteme GmbH, Hanau, Germany) and the results for C, H, and N were within ±0.4% of the theoretical values.

3.2. Synthesis of (E)-3-Methyl-6-(3-oxo-3-(thiophen-2-yl)-1-propenyl)-2(3H)-benzothiazolone (**3**)

To a slightly heated solution of 3-methyl-2(3*H*)-benzothiazolone-6-carbaldehyde (**1**, 386 mg, 2 mmol) in ethanol (5 mL), 2-acetylthiophene (**2**, 278 mg, 2.2 mmol) was added, followed by 10% aq. KOH (1 mL). The obtained mixture was stirred for 24 h at room temperature to afford a precipitate. The crystalline product was filtered, washed with cold ethanol, water to neutrality and dried.

Yellow crystals. Yield: 94% (566 mg), m.p.: 205–207 °C (2-methoxyethanol). IR (nujol): 1643, 1671 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) 3.42 (s, 3H, CH_3), 7.31 (dd, 1H, thiophene-H, *J* = 3.8 Hz, *J* = 4.9 Hz), 7.37 (d, 1H, arom. H, *J* = 8.4 Hz), 7.71 (d, 1H, =CHCO, *J* = 15.5 Hz), 7.84 (d, 1H, ArCH=, *J* = 15.5 Hz), 7.88 (dd, 1H, arom. H, *J* = 8.4 Hz, *J* = 1.6 Hz), 8.05 (dd, 1H, thiophene-H, *J* = 4.9 Hz, *J* = 0.9 Hz), 8.21 (d, 1H, arom. H, *J* = 1.5 Hz), 8.29 (dd, 1H, thiophene-H, *J* = 3.8 Hz, *J* = 0.9 Hz). ^{13}C-NMR (125.8 MHz, DMSO-d_6): δ (ppm) 29.2, 111.6, 120.8, 122.1, 122.6, 128.2, 128.9, 129.9, 133.4, 135.4, 139.4, 142.5, 145.6, 168.7, 181.3. Anal. calcd. for $C_{15}H_{11}NO_2S_2$ (301.36): C, 59.78; H, 3.68; N 4.65. Found: C, 59.41; H, 3.79; N, 4.72. MS (EI): $[M]^+$ *m*/*z* = 301(100), $[M + 2]^+$ *m*/*z* = 303(11), 272(19), 240(18), 218(11), 165(17), 160(16), 111(52).

Supplementary Materials: Copies of the ^{1}H-, ^{13}C-NMR and MS spectra for compound **3** are available online at http://www.mdpi.com/1422-8599/2016/2/M897.

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Author Contributions: O.P. designed the whole experiments; Y.I. and M.G. performed the experiments and contributed to manuscript; O.P. and Y.I. analyzed the NMR spectral data and wrote the manuscript; C.C. provided the mass spectra. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Reddy, M.; Su, C.; Chiou, W.; Liu, Y.; Chen, R.; Bastow, K.; Lee, K.; Wua, T. Design, synthesis, and biological evaluation of Mannich bases of heterocyclic chalcone analogs as cytotoxic agents. *Bioorg. Med. Chem.* **2008**, *16*, 7358–7370. [CrossRef] [PubMed]
2. Alvarez, M.; Zarelli, V.E.P.; Pappano, N.B.; Debattista, N.B. Bacteriostatic action of synthetic polyhydroxylated chalcones against *Escherichia coli*. *Biocell* **2004**, *28*, 31–34.
3. Aoki, N.; Muko, M.; Ohta, E.; Ohta, S. C-Geranylate chalcones from the stems of *Angelica keiskei* with superoxide-scavenging activity. *J. Nat. Prod.* **2008**, *71*, 1308–1310. [CrossRef] [PubMed]
4. Dimmock, J.; Elias, D.; Beazely, M.; Kandepu, N. Bioactivities of chalcones. *Curr. Med. Chem.* **1999**, *6*, 1125–1149. [PubMed]
5. Ivanova, Y.; Petrov, O.; Gerova, M.; Momekov, G. Synthetic chalcones of 2(3*H*)-benzothiazolones with potential cytotoxic activity. *C. R. Acad. Bulg. Sci.* **2007**, *60*, 642–650.
6. Ivanova, Y.; Momekov, G.; Petrov, O. Synthesis of novel substituted 1,3-diarylpropenone derivatives and their *in vitro* cytotoxic activity. *Lett. Drug Des. Discov.* **2009**, *6*, 353–357. [CrossRef]
7. Petrov, O.; Ivanova, Y.; Momekov, G.; Kalcheva, V. New synthetic chalcones: Cytotoxic Mannich bases of 6-(4-chlorocinnamoyl)-2(3*H*)-benzoxazolone. *Lett. Drug Des. Discov.* **2008**, *5*, 358–362. [CrossRef]
8. Ivanova, Y.; Momekov, G.; Petrov, O.; Karaivanova, M.; Kalcheva, V. Cytotoxic Mannich bases of 6-(3-aryl-2-propenoyl)-2(3*H*)-benzoxazolones. *Eur. J. Med. Chem.* **2007**, *42*, 1382–1387. [CrossRef] [PubMed]
9. Petrov, O.; Kalcheva, V.; Antonova, A. C-Formylation of Some 2(3*H*)-Benzazolones and 2*H*-1,4-Benzoxazin-3(4*H*)-one. *Collect. Czech. Chem. Commun.* **1997**, *62*, 494–497. [CrossRef]