molbank

MDPI

Short Note

(*E*)-1-(2′,4′-Dimethyl)-(5-acetylthiazole)-(2,4″-difluorophenyl)-prop-2-en-1-one

Afzal Shaik *, Mahamuda Sultana Shaik and Srinivasa Babu Puttagunta

Department of Pharmaceutical Chemistry, Vignan Pharmacy College, Vadlamudi-522 213, Guntur, Andhra Pradesh, India; skmdsultana@gmail.com (M.S.S.); psbabu1@yahoo.co.in (S.B.P.)

* Correspondence: bashafoye@gmail.com; Tel.: +91-996-601-43

Received: 27 August 2018; Accepted: 12 September 2018; Published: 13 September 2018

Abstract: Thiazole and chalcone motifs are of research interest to medicinal chemists due to their array of synthetic and biological utility. Hence, in the present study we intended to prepare (*E*)-1-(2′,4′-dimethyl)-(5-acetylthiazole)-(2,4″-difluorophenyl)-prop-2-en-1-one (**3c**) containing both these scaffolds. The compound **3c** was synthesized by the acid-catalyzed condensation of 2,4-dimethyl-5-acetylthiazole with 2,4-difluorobenzaldehyde. Purification and characterization of the compound were carried out by recrystallization and spectral techniques including UV, IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectrometry and X-ray powdered diffractometry. The molecule **3c** was successfully synthesized, purified, and characterized.

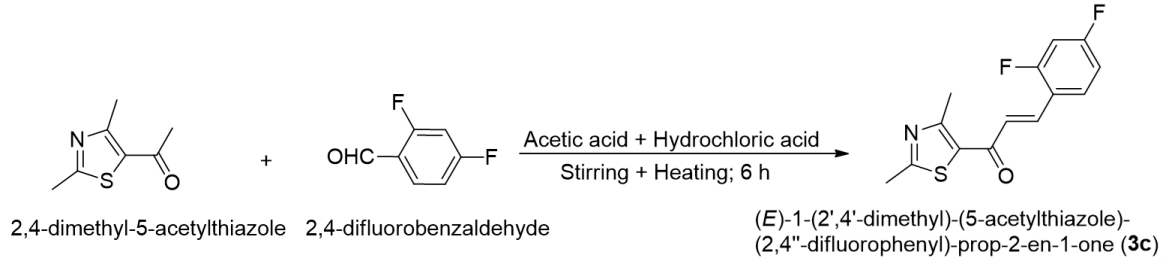
Keywords: thiazole; chalcone; acid-catalyzed condensation; (*E*)-1-(2′,4′-dimethyl)-(5-acetylthiazole)-(2,4″-difluorophenyl)-prop-2-en-1-one

1. Introduction

Diaryl-α,β-unsaturated ketones are the biogenic originator in flavonoid biosynthesis and are recognized as chalcones. Chemically, they are open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system [1]. Chalcones exhibit a wide range of biological activities such as antioxidant [2], antimicrobial [3], antitubercular [4], antihepatotoxic [5], neuroprotective [6], antibacterial [7], inhibitor of topoisomerase I [8], antimalarial [9], and anticancer activities [10]. Among pharmacologically important heterocyclic compounds, thiazole and its derivatives are well known in pharmaceutical chemistry because of their broad spectrum of biological activities such as antibacterial [11], antifungal [12], and anti-inflammatory activities [13] and their presence in naturally occurring compounds, e.g., antibiotics like penicillin, cephalosporin, and micrococcin, and vitamin B1 [14]. Thiazole motif is present in drug molecules such as Sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral drug), and Abafungin (antifungal drug). Synthetic thiazoles offer the opportunity to increase the structural diversity of natural thiazole substrates [4]. Chalcones attract many researchers to develop efficient synthetic methods and also to produce different structural variation of chalcones that are newer and unavailable in nature. In the present study we report the successful synthesis and characterization of (*E*)-1-(2′,4′-dimethyl)-(5-acetylthiazole)-(2″,4″-difluorophenyl)-prop-2-en-1-one (**3c**). The reason for selecting the substituents i.e., methyl groups and fluorine atoms present on thiazole and phenyl rings, respectively, is to study the influence of electron-releasing (methyl) and electron-withdrawing (fluorine) substituents on the synthesis of thiazole-containing chalcone. Usually the chalcones are synthesized by base-catalyzed Claisen-Schmidt condensation, but we were unable to derive the desired compound with this method. Hence, we utilized acid-mediated synthesis for preparing the compound **3c** and were successful. The chalcone can be easily prepared in high yields by acid-catalyzed condensation reaction; it is purified by recrystallization and characterized by physicochemical and spectral analysis data.

2. Results

The title compound was synthesized by acid-catalyzed condensation of aromatic aldehyde and aromatic ketone using acetic acid in hydrochloric acid as a catalyst, as shown in Scheme 1. Firstly, the purity of the product was analyzed by performing thin-layer chromatography and then by determining its melting point. The structural elucidation of the compound was done based on spectroscopic data and the results are displayed below. The product is assumed to exist in the *E* configuration based on its coupling constant, *J* at 16 Hz.



Scheme 1. Synthesis of (*E*)-1-(2′,4′-dimethyl)-(5-acetylthiazole)-(2,4″-difluorophenyl)-prop-2-en-1-one (**3c**).

(E)-1-(2′,4′-Dimethyl)-(5-acetylthiazole)-(2,4″-difluorophenyl)-prop-2-en-1-one (**3c**): Shining orange crystals (0.182 g, 95%, after recrystallization) (Figure 1), m.p. 80 °C, R_f = 0.44 (30% ethyl acetate in *n*-hexane), MS (*m*/*z*, %) 280.1 (M + 1, 99.56); UV (λ max): 320 nm (200 µg/mL in 0.1 M HCl); IR (KBr, cm^{-1}) 1656.38 (intense C=O conjugated band), 1596.55 (C=C of Ar), 1499.38 (str, CH=CH, conjugated), 1270.95, (C–F) and 1134.70 (C–F); ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) δ (ppm) 2.75 (s, 3H), 2.79 (s, 3H), 6.91 (d, 1H), 7.27 (d, 1H, *J* = 16 Hz), 7.23 (d, 1H), 7.61 (s, 1H), 7.81 (d, 1H, *J* = 16 Hz). ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) δ (ppm) 18.36 (methyl C at C-3′), 19.52 (methyl C at C-2′), 105.80 (C-5″), 112.29 (C-3″), 119.17 (C-1″), 126.80 (C-2), 126.89 (C-5′) 131.10 (C-6″), 135.97 (C-3), 160.86 (C-2″, C–F coupling constant value *J* = 12 Hz), 160.80 (C-4′), 162.84 (C-4″, C–F coupling constant value *J* = 12 Hz), 168.53 (C-2′), 182.36 (C-1). The X-ray powder diffraction pattern data of 3c are provided in Table 1.

Table 1. X-ray powder pattern of compound **3c**.

No.	2θ (deg)	d (ang.)	Height (cps)
1	7.083(5)	12.471(10)	1106(68)
2	12.922(10)	6.846(5)	2281(97)
3	14.047(9)	6.300(4)	5233(148)
4	14.202(4)	6.2312(18)	9485(199)
5	15.553(8)	5.693(3)	1276(73)
6	16.820(14)	5.267(4)	164(26)
7	21.387(8)	4.1512(16)	1638(83)
8	24.55(2)	3.623(3)	508(46)
9	25.534(4)	3.4857(5)	1059(66)
10	26.06(3)	3.416(3)	240(32)
11	26.74(2)	3.331(3)	262(33)
12	27.301(19)	3.264(2)	323(37)
13	28.764(8)	3.1011(9)	391(40)
14	31.31(2)	2.8546(18)	286(35)
15	33.898(9)	2.6423(7)	422(42)
16	36.06(3)	2.488(2)	70(17)
17	38.056(7)	2.3626(4)	314(36)
18	38.45(4)	2.339(2)	109(21)
19	42.41(6)	2.129(3)	101(21)
20	43.480(13)	2.0796(6)	130(23)

Figure 1. Titled compound **3c** after recrystallization with methanol.

3. Materials and Methods

3.1. General

The organic solvents such as methanol, hexane, and ethyl acetate were of spectral grade and used as such without further purification. Anhydrous methanol was obtained by fractional distillation and storing over type 4A molecular sieves. Some of the solvents were purchased from local manufacturers and some from S.D. Fine Chem. Ltd, Mumbai, India. All the chemicals used in the synthesis were obtained from standard commercial sources. TLC analysis was carried out on Merck grade precoated TLC silica gel 60 F_{254} plates (Merck KGaA, Darmstadt, Germany) and the spots were visualized under a UV lamp. 2,4-dimethyl-5-acetylthiazole was purchased from Tokyo Chemical Industry (Tokyo Chemical Industries Co., Ltd. Toshima, Kita-Ku, Tokyo, Japan). 2,4-difluorobenzaldehyde was purchased from Sigma Aldrich Chemical Co. (Milwaukee, WI, USA). Melting point was determined in open capillaries, using a Boetius melting point apparatus (expressed in °C) (Rapido, Dresden, Germany), and are uncorrected. UV spectra were recorded on an Elico SL-210 UV-Visible spectrophotometer (ELICO Ltd. B-90, A.P.I.E., Sanathnagar, Hyderabad 500 018, A.P., India). FT-IR spectra were recorded using Bruker alpha-T (BRUKER biospin International AG., Zug, Switzerland) and the ^{1}H- and ^{13}C-NMR spectra of the compound were recorded on a Bruker 400 Avance NMR spectrophotometer using TMS as an internal standard (values are expressed in δ ppm). MS spectra were recorded on an Agilent LC-MS spectrometer (Agilent technologies, 5301 Stevens Creek Blvd, Santa Clara, CA, USA.).

3.2. Preparation of the Title Compound

First, 135 μL (1 mmol) of 2,4-dimethyl-5-acetylthiazole were dissolved in a mixture of 4 mL of glacial acetic acid and 2 mL of hydrochloric acid. To the above solution, 109 μL (1 mmol) of 2,4-difluorobenzaldehyde were added and stirred on a magnetic stirrer at a temperature of 70 °C for 6 h. After completion of the reaction (observed through spots on the TLC plate using 30% ethyl acetate in *n*-hexane), the mixture was transferred onto crushed ice. This led to the precipitation of the compound, which was then filtered, washed thoroughly with cold water, and dried. The precipitate was further recrystallized with methanol to get the orange crystals of the title compound **3c** (Scheme 1).

4. Conclusions

We have demonstrated the synthesis of a (*E*)-1-(2′,4′-dimethyl)-(5-acetylthiazole)-(2,4″-difluorophenyl)-prop-2-en-1-o through an acid-catalyzed condensation reaction and characterization by physicochemical and spectral methods.

Supplementary Materials: UV, FTIR, ^{1}H-NMR, ^{13}C-NMR, MS, and X-ray spectra of the synthesized compounds are available online.

Author Contributions: Conceptualization, A.S.; Data curation, S.S.; Formal analysis, S.S.; Funding acquisition, S.B.P.; Investigation, A.S. and S.S.; Methodology, A.S.; Project administration, A.S.; Resources, S.B.P.; Supervision, A.S.; Validation, A.S. and S.B.P.; Visualization, A.S. and S.S.; Writing—original draft, S.S.; Writing—review & editing, A.S.

Funding: This research received no external funding.

Acknowledgments: The authors are thankful to the management of Vignan Pharmacy College, Vadlamudi, Guntur District, Andhra Pradesh, India for providing the chemicals and laboratory facilities to perform the research work. The authors are also grateful to Andhra University College of Pharmaceutical Sciences, Visakhapatnam, Andhra Pradesh, India for providing the IR, NMR and mass spectral data.

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

References

1. Suwito, H.; Haq, K.U.; Rahmah, N.N.D.; Kristanti, A.N.; Puspaningsih, N.N.T. 4-({4-[(2*E*)-3-(2,5-Dimethoxyphenyl)prop-2-enoyl]phenyl}amino)-4-oxobutanoic Acid. *Molbank* **2017**, *2017*, M938. [CrossRef]
2. Ayati, A.; Bakhshaiesh, T.O.; Moghimi, S.; Esmaeili, R.; Majidzadeh-A, K.; Safavi, M.; Firoozpour, L.; Emami, S.; Foroumadi, A. Synthesis and biological evaluation of new coumarins bearing 2,4-diaminothiazole-5-carbonyl moiety. *Eur. J. Med. Chem.* **2018**, *155*, 483–491. [CrossRef] [PubMed]
3. Liaras, K.; Geronikaki, A.; Glamoclija, J.; Ciric, A.; Sokovic, M. Thiazole-based chalcones as potent antimicrobial agents. *Synth. Biol. Eval.* **2011**, *19*, 3135–3140. [CrossRef]
4. Karuvalam Ranjith, P.; Haridas Karickal, R.; Nayak Susanta, K.; Guru Row Tayur, N.; Rajeesh, P.; Rishikesan, R.; Suchetha Kumari, N. Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents. *Eur. J. Med. Chem.* **2012**, *49*, 172–118. [CrossRef] [PubMed]
5. Khan, S.A.; Ahmed, B.; Alam, T. Synthesis and hepatotoxic activity of some new chalcones containing 1,4-dioxane ring system. *Pak. J. Pharm. Sci.* **2006**, *19*, 290–294. [PubMed]
6. Jung, J.-C.; Jang, S.; Lee, Y.; Min, D.; Lim, E.; Jung, H.; Oh, M.; Oh, S.; Jumg, M. Efficient synthesis and neuroprotective effect of substituted 1,3-diphenyl-2-propen-1-ones. *J. Med. Chem.* **2008**, *51*, 4054–4058. [CrossRef] [PubMed]
7. Sharma, M.; Chaturvedi, V.; Manju, Y.K.; Bhatnagar, S.; Srivastava, K.; Puri, S.K.; Chauhan, P.M.S. Substituted quinolinyl chalcones and quinolinyl pyrimidines as a new class of anti-infective agents. *Eur. J. Med. Chem.* **2009**, *44*, 2081–2091. [CrossRef] [PubMed]
8. Yoon, G.; Kang, B.Y.; Cheon, S.H. Topoisomerase I inhibition and cytotoxicity of lichochalcones A and E from Glycyrrhiza inflate. *Arch. Pharm. Res.* **2007**, *30*, 313–316. [CrossRef] [PubMed]
9. Suwito, H.; Pudjiastuti, P.; Fanani, M.Z.; Kimata-Ariga, Y.; Katahira, R.; Kawakami, T.; Fujiwara, T.; Hase, T.; Sirat, H.M.; Puspaningsih, N.N.T. Design and synthesis of chalcone derivatives as inhibitors of the ferredoxin—Ferredoxin-NADP+ reductase interaction of plasmodium falciparum: Pursuing new antimalarial agents. *Molecules* **2014**, *19*, 21473–21488. [CrossRef] [PubMed]
10. Altıntop, M.D.; Sever, B.; Çiftçi, G.A.; Özdemir, A. Design, Synthesis, and Evaluation of a New Series of Thiazole-Based Anticancer Agents as Potent Akt Inhibitors. *Molecules* **2018**, *23*, 1318. [CrossRef] [PubMed]
11. Sadek, B.; Al-Tabakha, M.M.; Fahelelbom, K.M.S. Antimicrobial Prospect of Newly Synthesized 1,3-Thiazole Derivatives. *Molecules* **2011**, *16*, 9386–9396. [CrossRef] [PubMed]
12. Kaplancıklı, Z.A.; Levent, S.; Osmaniye, D.; Sağlık, B.N.; Çevik, U.A.; Çavuşoğlu, B.K.; Özkay, Y.; Ilgın, S. Synthesis and Anticandidal Activity Evaluation of New Benzimidazole-Thiazole Derivatives. *Molecules* **2017**, *22*, 2051. [CrossRef] [PubMed]

13. Januario, J.P.; de Souza, T.B.; Lavorato, S.N.; Maiolini, T.C.S.; Domingos, O.S.; Baldim, J.L.; Folquitto, L.R.S.; Soares, M.G.; Chagas-Paula, D.A.; Dias, D.F.; et al. Design and Synthesis of New Benzophenone Derivatives with In Vivo Anti-Inflammatory Activity through Dual Inhibition of Edema and Neutrophil Recruitment. *Molecules* **2018**, *23*, 1859. [CrossRef] [PubMed]
14. Shivananda, W.; Vasudeva Adhikari, A.; Suchetha Kumari, N. Synthesis of Some Novel 2,4-Disubstituted Thiazoles as Possible Antimicrobial Agents. *Phosporus Sulfur Silicon Relat. Elem.* **2008**, *183*, 1285–1300.