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Short Note

(*E*)-2-(2-Oxo-4-phenylbut-3-en-1-yl)benzo[*d*]thiazole-3(2*H*)-carboxylates

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Abstract: An convenient one-pot approach for the synthesis of new (*E*)-2-(2-oxo-4-phenylbut-3-en-1-yl)benzo[*d*]thiazole-3(2*H*)-carboxylates is demonstrated. The method is based on a three-component reaction of benzylideneacetone with electrophilic *N*-alkoxycarbonylbenzothiazolium species formed *in situ*. The newly synthesized compounds were fully characterized by 1D ^{1}H, ^{13}C- NMR, IR and MS.

Keywords: benzothiazole; benzylideneacetone; α-amidoalkylation; multicomponent reaction

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1. Introduction

Cancer is one of the most prevalent lethal diseases worldwide, and is a serious concern of modern medicine. It is of great attention to the scientific community for drug development and precision therapy [1,2]. Benzothiazole (BT) (1) is a privileged heterocycle structure with significant pharmacological applications [3]. In this regard, during the last ten years, the functionalization of BT scaffold has modulated a broad range of anticancer activities [4–7]. The interest drawn by a BT moiety has led to the preparation of many 2-substituted derivatives, with proven antiproliferative effects [8,9]. In this context, various (*E*)-2-benzothiazole hydrazones have been described as actual active structures [10,11]. The α,β-unsaturated ketones are subject to scientific interest [12] and are present in many bioactive heterocycle hybrids [13–15]. In a previously published paper, we demonstrated the effective application of α-amidoalkylation for the synthesis of 1,2,3-substituted benzimidazoles containing benzylidenacetonyl fragments [16]. One of the obtained compounds (Figure 1) showed selective antiproliferative activity in vitro against the human metastatic melanoma cells—inhibition by 93% after 96 h treatment at 10^{-4} M [17]. Considering the existing interest in the structure–activity relationship of various benzothiazoles, we saw an opportunity to apply this convenient approach for the synthesis of some novel, structurally similar derivatives. In recent scientific research, we successfully functionalized indole and some hydroxyarenes to 2-substituted benzothiazoles with bioactive profiles [18,19].

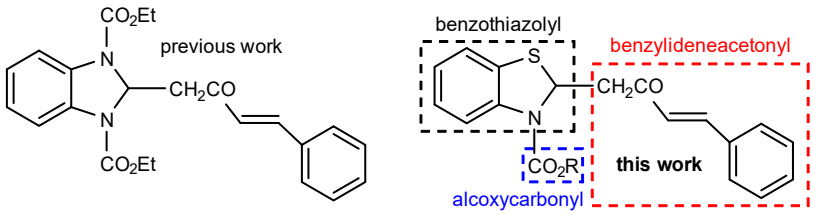
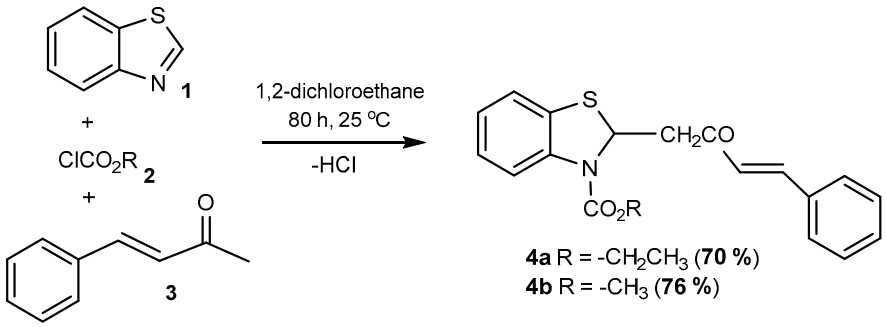


Figure 1. Benzylidenacetonyl substituted heterocyclic compounds.

2. Results

Here, we report the investigations on the application of adducts obtained from benzothiazole (**1**) with alkyl chloroformates (**2**) in a one-pot α-amidoalkylation reaction with

benzylideneacetone (**3**). The above-mentioned adducts react successfully with the α,β-unsaturated ketone to form products (**4a**,**b**, Scheme 1).



Scheme 1. Synthesis of (*E*)-2-(2-oxo-4-phenylbut-3-en-1-yl)benzo[*d*]thiazole-3(2*H*)-carboxylates (**4a**,**b**).

The reaction conditions were optimized by varying the solvent, temperature, and time (Table 1).

Table 1. The optimized reaction conditions and yields of products 4, prepared according to Scheme 1.

Product 4	R	Time, h	T, °C	Yield, %	
a	−Et	80	25	50	70 *
b	−Me	80	25	55	76 *

* Obtained with benzothiazole (2 mmol), alkyl chloroformates (2 mmol) and benzylidenacetone (1 mmol).

The three-component reactions were successfully completed under mild reaction conditions for 5–80 h at room temperature. The reactions were initially carried out in acetonitrile for 5 h at room temperature to result in products 4a and b with low yields (24%, **4a**) and (28%, **4b**). It was found that 1,2-dichloroethane performed better than acetonitrile and led to a higher yield of products (**4a,b**, Table 1).

The best yields of products were obtained with twofold excess of benzothiazole and alkyl chloroformates in 1,2-dichloroethane at 25 °C for 80 h (70%, **4a**; 76%, **4b**). Analytically pure samples were isolated by column chromatography on silica, using a mixture of petroleum/diethyl ether as eluents and the yields indicated in Table 1.

The ^{1}H-NMR spectra of compounds (**4a,b**), indicated (*E*)-*trans* configuration, exhibiting two characteristic doublets in the range of δ = 6.83–6.85, 7.64–7.70 ppm with coupling constant (*J* = 16.4 Hz) for vinyl protons.

The resulting products were structurally characterized by ^{1}H, ^{13}C-NMR, IR, and MS spectra (copies can be found via "Supplementary Materials" section).

3. Materials and Methods

All reagents and solvents were purchased from commercial suppliers (Sigma-Aldrich or Merck) and were used without further purification. NMR spectra were run on a Bruker Avance AV600 (600/150 MHz ^{1}H/^{13}C) spectrometer at BAS-IOCCP—Sofia, and chemical shifts (δ, ppm) were downfield from TMS. To average out the rotamers observed, the spectrum of compound (**4a**) was measured at 80 °C, as indicated in the text below. High-resolution mass spectral measurements were performed on a Thermo Scientific Q Exactive hybrid quadrupole-orbitrap mass spectrometer. IR spectra were measured on a VERTEX 70 FT-IR spectrometer (Bruker Optics, Germany). TLC was performed on aluminium-backed silica gel 60 sheets (Merck) with cerium sulfate staining. Melting points were measured on Boetius hot stage apparatus and were not corrected.

Synthetic Procedures

Synthesis of (*E*)-2-(2-oxo-4-phenylbut-3-en-1-yl)benzo[*d*]thiazole-3(2*H*)-carboxylates (**4a**,**b**), general procedure: ethyl chlorofomate (0.217 g, 2 mmol, 0.19 mL) or methyl chloro-

formate (0.189 g, 2 mmol, 0.16 mL) was added dropwise to a magnetically stirred solution of benzothiazole (0.270 g, 2 mmol, 0.22 mL) in 1,2-dichloroethane (5 mL/mmol), followed immediately by the benzylideneacetone (0.292 g, 2 mmol). The stirring was then continued under the conditions indicated in Table 1. After completion of the reaction (monitored by TLC), the mixture was transferred to a separatory funnel with dichloromethane (10 mL/mmol) and consecutively washed with 50 mL water. For the reactions with acetonitrile, we first proceeded with solvent evaporation under reduced pressure, before the following work-up. The organic layer was dried (Na_2SO_4), and the crude mixture was dry-loaded onto silica gel. The products were isolated by column chromatography on silica gel with mixtures of petroleum/diethyl ether as the eluents and successfully crystallized.

Ethyl (*E*)-2-(2-oxo-4-phenylbut-3-en-1-yl)benzo[*d*]thiazole-3(2*H*)-carboxylate (**4a**): white solid; isolated with petroleum/diethyl ether (8:1 increasing polarity to 4:1); Rf = 0.61 (petroleum:diethyl ether 2:1); yield:50%, 70%; mp: 85–87 °C.

Results of ^{1}H-NMR (600 MHz, 80 °C, DMSO-d_6, δ ppm): 1.29 (t, J = 7.0 Hz, 3H, -COOCH$_2$CH$_3$), 3.37 (dd, ^2J = 16.4 Hz, ^3J = 4.7 Hz, 1H, -CH$_2$-), 3.42 (dd, ^2J = 16.4 Hz, ^3J = 9.4 Hz, 1H, -CH$_2$-), 4.22–4.30 (m, 2H, -COOCH$_2$CH$_3$), 6.14 (dd, ^2J = 8.8 Hz, ^3J = 4.7 Hz, 1H, -CH*), 6.83 (d, J = 16.4 Hz, 1H, -CH=CH-), 7.02 (t, J = 7.6 Hz, 1H, Ar), 7.13 (t, J = 7 Hz, 1H, Ar), 7.25 (d, J = 7.6 Hz, 1H, Ar), 7.42–7.43 (m, 3H, Ar), 7.64 (d, J = 16.4 Hz, 1H, -CH=CH-), 7.66–7.68 (m, 3H, Ar).

Results of ^{13}C-NMR (150 MHz, 80 °C, DMSO-d_6, δ ppm): 14.6 (-COOCH$_2$CH$_3$), 48.1 (-CH$_2$), 62.1 (-CH*), 62.7 (-COOCH$_2$CH$_3$), 117.8 (-CH), 123.0 (-CH), 124.7 (-CH), 125.7 (-CH), 127.0 (-CH), 128.9 (-CH), 129.0 (-CH), 129.4 (-CH), 131.0 (-CH), 134.9 (-CH), 137.7 (-CH), 143.9 (-CH), 152.3 (-COO), 197.2 (-CO).

IR (KBr, cm^{-1}): 3057 ν(C-sp^2-H), 2980 ν_{as}(C-sp^3-H, > sp^2), 2911 ν_s(C-sp^3-H, > sp^2), 1700 ν(C=O, α,β-unsaturated ketone), 1653 ν(C=O, ester), 1580, 1471 ν(C=C, Ph), 1377 δ_s(CH^3), 1256, 1183 ν(C-N), 752 γ(C-sp^2-H), 692, 580, 459 δ(C-N-C);

HRMS m/z (ESI): calcd for $C_{20}H_{19}NNaO_3S^+$ [M + Na]$^+$ 376.0978, found 376.0988; calcd for $C_{40}H_{38}N_2NaO_6S_2^+$ [2M + Na]$^+$ 729.2063, found 729.2057.

Methyl (*E*)-2-(2-oxo-4-phenylbut-3-en-1-yl)benzo[*d*]thiazole-3(2*H*)-carboxylate (**4b**): pale yellow solid; isolated with petroleum/diethyl ether (8:1 increasing polarity to 4:1); Rf = 0.48 (petroleum:diethyl ether 2:1); yield: 55%, 76%; mp: 136–137 °C.

Results of ^{1}H-NMR (600 MHz, 20 °C, DMSO-d_6, δ ppm): 3.40 (dd, ^2J = 17.6 Hz, ^3J = 3.5 Hz, 1H, -CH$_2$-), 3.49 (dd, ^2J = 17.6 Hz, ^3J = 10.0 Hz, 1H, -CH$_2$-), 3.78 (s, 3H, -COOCH$_3$), 6.08 (dd, ^2J = 10 Hz, ^3J = 3.5 Hz, 1H, -CH*), 6.85 (d, J = 16.4 Hz, 1H, -CH=CH-), 7.03 (t, J = 7.6 Hz, 1H, Ar), 7.13 (t, J = 7.6 Hz, 1H, Ar), 7.27 (d, J = 7.6 Hz, 1H, Ar), 7.42–7.44 (m, 3H, Ar), 7.70 (d, J = 16.4 Hz, 1H, -CH=CH-), 7.69–7.71 (m, 3H, Ar).

Results of ^{13}C-NMR (150 MHz, 20 °C, DMSO-d_6, δ ppm): 47.5 (-CH$_2$), 53.8 (-COOCH$_3$), 61.9 (-CH*), 117.6 (-CH), 121.7 (-CH), 123.1 (-CH), 124.8 (-CH), 125.8 (-CH), 126.7 (-CH), 129.0 (-CH), 129.5 (-CH), 131.2 (-CH), 134.5 (-CH), 134.7 (-CH), 144.5 (-CH), 152.7 (-COO), 197.9 (-CO).

IR (KBr, cm^{-1}): 3019 ν(C-sp^2-H), 2958 ν_{as}(C-sp^3-H, > sp^2), 2900 ν_s(C-sp^3-H, > sp^2), 1717 ν(C=O, α,β-unsaturated ketone), 1649 ν(C=O, ester), 1576, 1474 ν(C=C, Ph), 1361 δ_s(CH^3), 1259, 1181 ν(C-N), 759 γ(C-sp^2-H), 684, 576, 433 δ(C-N-C).

HRMS m/z (ESI): calcd for $C_{19}H_{17}NNaO_3S^+$ [M + Na]$^+$ 362.0821, found 362.0819; calcd for $C_{38}H_{34}N_2NaO_6S_2^+$ [2M + Na]$^+$ 701.1750, found 701.1756.

4. Conclusions

We have successfully prepared two new 2-(benzylideneacetonyl)benzothiazoles via an efficient one-pot approach. The applied three-component reactions offer several advantages, such as a simple procedure, clean reaction conditions, and good yields. The obtained compounds are of interest due to their potential cytotoxic activities.

Supplementary Materials: The following are available online, S1. PDF—processed ^{1}H, ^{13}C-NMR, MS, IR spectra and TLC separation of (**4a**,**b**), S2.zip—Raw NMR data, S3.zip—mol files.

Author Contributions: Visualization, Y.S.; conceptualization and supervision, S.S.-A.; chemical synthesis and spectral characteristics: Y.S. and S.S.-A.; writing—original draft preparation, Y.S.; review and editing, Y.S and S.S.-A. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in this article and supplementary information.

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

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