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Novel chalcone analogs derived from 4-(benzyloxy)benzaldehyde

Mihaela BALAN-PORCĂRAŞU[1] and Gheorghe ROMAN[*,2]

[1]*Petru Poni Institute of Macromolecular Chemistry, Department of Polycondensation and Thermostable Polymers, 41A Aleea Gr. Ghica Vodă, 700847, Iaşi, Romania*
[2]*Petru Poni Institute of Macromolecular Chemistry, Department of Inorganic Polymers, 41A Aleea Gr. Ghica Vodă, 700847, Iaşi, Romania*

Abstract. Eight chalcone analogs were prepared through an aldol condensation starting from 4-(benzyloxy)benzaldehyde and either less common acetophenones or a few selected heteroaryl methyl ketones. The reaction has been performed through the classical approach that employs an alkali as catalyst for five chalcone analogs, while a variant that uses piperidine as basic catalyst was employed for the other three chalcone analogs. The structure of the resulting enones has been established by NMR spectroscopy. Photoinduced dimerization of a selected benzyloxy-substituted chalcone analog under irradiation with UV light for periods of time ranging from 30 minutes to 24 h has also been monitored using NMR spectroscopy. Analysis of the results demonstrated the presence of the *E* isomer of the chalcone analog along with three regioisomeric cyclobutanes in the irradiated sample.

***Keywords*:** Claisen–Schmidt; enone; reactive intermediate; photodimerization; cyclobutane.

1. Introduction

Chalcone (1,3-diphenylprop-2-en-1-one) along with its analogs are organic compounds that are defined by the presence in their structure of an α,β-enone motif featuring terminal (hetero)aromatic moieties. Numerous chalcone analogs, especially those belonging to the group of polyhydroxylated chalcones, are naturally occurring compounds that are biosynthesized in plants as precursors to flavonoids [1, 2]. Besides these natural chalcone analogs, a plethora of synthetic counterparts have been prepared particularly through the Claisen–Schmidt base-catalyzed condensation between an (hetero)aryl methyl ketone and a (hetero)aromatic aldehyde [3, 4]. This widely used carbon-carbon bond-forming reaction allows facile access to structurally diverse prop-2-en-1-ones that can serve as reactive intermediates in Michael-type addition reactions [5] or for the synthesis of heterocycles [6]. In addition to the significant use of chalcone analogs in organic synthesis, many members of this class of compounds have found promising applications as biologically active compounds [7–10]. Specifically, chalcone analogs derived from 4-(benzyloxy)benzaldehyde have been reported as antioxidants with a radical scavenging activity [11], as anti-proliferative agents toward a human adenocarcinoma gastric cell line [12], as agonists of peroxisome proliferator-activated receptors with anti-hyperlipidemic activity [13], as antimicrobial agents [14], as inhibitors of monoamine oxidases and cholinesterases [15], interferon alpha [16], human inosine 5′-monophosphate dehydrogenase 2 [17], or α-amylase [18], among others. Furthermore, cycloaddition reaction of alkenes is one of the most studied reactions in organic photochemistry. As a particular type of alkenes, chalcone and its analogs have long acted as substrates in photoinduced reactions that afford mostly cyclobutane derivatives through [2 + 2] intermolecular photodimerization processes, with one molecule of chalcone analog acting as a non-excited olefin reaction partner.

The present study reports the synthesis and characterization of novel chalcone analogs from less common (hetero)aryl methyl ketones and 4-(benzyloxy)benzaldehyde that could be useful as starting materials for various acyclic and cyclic organic compounds or could exhibit interesting biological activities. In addition, photoinduced cyclodimerization of a selected chalcone analog bearing a benzyloxy substituent has been monitored by NMR with the view to assess the progress of the reaction and the formation of intermediates and final products.

2. Experimental

2.1. Materials and instrumentation

The organic reagents used in this study (4-(benzyloxy)benzaldehyde **1**, 2′-nitroacetophenone **2**, 4-acetylbenzonitrile **3**, 1-(furan-2-yl)ethanone **4**, 1-(5-bromothiophen-2-yl)ethanone **5**, 3-acetylcoumarin **9**, 4-bromoaniline, pentane-2,4-dione, 5-bromosalicylaldehyde, chloroacetone, phenylene-1,2-diamine, (±)-lactic acid, dimethyl sulfate) were purchased from Merck–Sigma–Aldrich, and were used without prior purification. The inorganic reagents (K_2CO_3, 36% HCl, Na_2SO_4, KOH, 96% H_2SO_4, NaOH) were also Merck–Sigma–Aldrich products. Ammonia solution 25% and $K_2Cr_2O_7$ were provided by Reactivul

* Corresponding author. *E-mail address*: gheorghe.roman@icmpp.ro (Gheorghe Roman).

București (Romania). 4-Bromophenyl azide was obtained in 95% yield through the one-pot sequence comprising the diazotization of 4-bromoaniline and reaction of 4-bromophenyl diazonium chloride with sodium azide in an adaptation of a procedure employed for the synthesis of similar aryl azides [19]. The solvents were obtained from Merck–Sigma–Aldrich or VWR International, and were used without prior purification. Melting points were taken on a Mel-Temp II apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra (δ = 7.26 ppm for $CDCl_3$ and δ = 2.51 ppm for DMSO-d_6). The chemical shifts for the carbon atoms are given relative to residual chloroform (δ = 77.16 ppm) or dimethyl sulfoxide (δ = 39.52 ppm) in the corresponding deuterated solvents. UV irradiation experiments were performed using an Hg–Xe lamp (Hamamatsu Lightningcure Type LC8, Model L9588).

2.2. Synthesis of heteroaryl ethanones required for the preparation of chalcone analogs derived from 4-(benzyloxy)benzaldehyde

2.2.1. Synthesis of 1-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone ***6***. A mixture of 4-bromophenyl azide (990 mg, 5 mmol), pentane-2,4-dione (500 mg, 5 mmol) and anhydrous K_2CO_3 (1.38 g, 10 mmol) in absolute ethanol (10 mL) was heated at reflux temperature for 2 h. The solvent was then removed under reduced pressure, water (40 mL) was added to the residue, and the mixture was gradually treated with 36% HCl until pH 2. The solid material was filtered, washed with water (2 × 10 mL), and dissolved in chloroform (20 mL). The solution was dried over anhydrous Na_2SO_4, and then the drying agent was filtered. Removal of chloroform from the filtrate under reduced pressure gave a material that was recrystallized from 2-propanol to afford tan crystals (1.09 g, 78%), mp 112–113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.59 (s, 3H), 2.75 (s, 3H), 7.34 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.1, 27.9, 124.3, 126.7, 133.0, 134.3, 137.3, 143.8, 194.3.

2.2.2. Synthesis of 1-(5-bromobenzofuran-2-yl)ethanone ***7***. 5-Bromosalicylaldehyde (2.01 g, 10 mmol) was added to a cold solution of KOH (660 mg, 10 mmol, 85% purity) in methanol (25 mL), and the mixture was stirred until complete dissolution of the solid occurred. Chloroacetone (1.11 g, 12 mmol) was then added dropwise to the solution, which was afterwards heated at reflux temperature for 2.5 h. The solvent was removed under reduced pressure, and the resulting solid material was recrystallized from 85% ethanol to give yellow crystals (1.58 g, 66%), mp 109–110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.61 (s, 3H), 7.43 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.57 (dd, J = 1.2 and 8.8 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.5, 111.9, 114.0, 117.0, 125.8, 128.9, 131.2, 153.5, 154.3, 188.5.

2.2.3. Synthesis of 1-(1-methyl-1H-benzo[d]imidazol-2-yl)ethanone ***8***. A mixture of phenylene-1,2-diamine (10.8 g, 100 mmol), (±)-lactic acid (10 g, 111 mmol), 36% HCl (40 mL) and water (60 mL) was heated at reflux temperature for 2 h, and then the cold solution was gradually treated with small volumes of 25% w/w ammonia solution under efficient stirring until pH reached 8. The solid material was filtered, washed thoroughly with water, and air-dried. Recrystallization from water with the use of active carbon afforded 8.75 g (54%) of 1-(1*H*-benzo[*d*]imidazol-2-yl)ethanol as colorless crystals, mp 180–181 °C; ^{1}H NMR (400 MHz): δ 1.51 (d, J = 6.4 Hz, 3H), 4. 89–4.99 (m, 1H), 5.75 (d, J = 4.8 Hz, 1H), 7.07–7.19 (m, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.54 (d, J = 6.8 Hz, 1H), 12.23 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.9, 63.6, 111.2, 118.3, 120.8, 121.5, 134.1, 143.0, 158.5.

1-(1*H*-Benzo[*d*]imidazol-2-yl)ethanol (4.05 g, 25 mmol) was dissolved in a solution that had been previously obtained by mixing 96% H_2SO_4 (1.05 g) with water (19 mL). Separately, $K_2Cr_2O_7$ (14.7 g, 50 mmol) was suspended in a solution that was prepared from 96% H_2SO_4 (10 mL) and water (30 mL) (Jones reagent). The solution containing the alcohol was then dropwise added to the Jones reagent under efficient stirring at room temperature over 8 to 10 min. The resulting mixture was further stirred at room temperature for 2 h, then the orange solid was filtered and rapidly washed with water (10 mL). The cake was then suspended in water (30 mL) and was treated with 10% ammonia solution under efficient stirring until pH of the mixture was in the range of 6 to 7. The solid material was filtered, washed with water (2 × 10 mL), and air-dried to give 2.56 g (64%) of practically pure 1-(1*H*-benzo[*d*]imidazol-2-yl)ethanone as colorless crystals, mp 188–190 °C; ^{1}H NMR (DMSO-d_6 + TFA, 400 MHz): δ 2.72 (s, 3H), 7.41 (dd, J = 2.8 and 6.0 Hz, 2H), 7.73 (dd, J = 2.8 and 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6 + TFA, 100 MHz): δ 26.3, 116.7, 124.9, 137.5, 147.4, 190.5.

1-(1*H*-Benzo[*d*]imidazol-2-yl)ethanone (800 mg, 5 mmol) was dissolved in a slightly warm (approximately 35 °C) solution of 10% NaOH (2.4 g containing 6 mmol NaOH), and then dimethyl sulfate (820 mg, 6.5 mmol) was added in one portion. The mixture was further stirred while being kept in an oil bath at 80 °C for 15 min. The product that separated as a heavy oil turned into a solid upon gradual cooling of the reaction mixture to room temperature under efficient stirring and slow dilution of the reaction mixture with water up to 30 mL. The material was filtered, washed with water (2 × 5 mL), and air-dried to afford 1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanone **9** (750 mg, 86%) as a practically pure colorless solid, mp 70–71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.84 (s, 3H), 4.13 (s, 3H), 7.32–7.41 (m, 1H), 7.41–7.48 (m, 2H), 7.89 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.1, 32.3, 110.5, 121.9, 123.7, 125.9, 136.9, 141.6, 146.1, 193.4.

2.2.4. Synthesis of chalcone analogs ***10***–***14*** *derived from 4-(benzyloxy)benzaldehyde using NaOH as catalyst.* A solution of 4-(benzyloxy)benzaldehyde **1** (212 mg, 1 mmol) and either 2′-nitroacetophenone **2**, or 4-acetylbenzonitrile **3**, or 1-(furan-2-yl)ethanone **4**, or 1-(5-bromothiophen-2-yl)ethanone **5**, or 1-(1-(4-bromophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone **6** (1 mmol) in 96% ethanol (10 mL) was treated with

10% aqueous NaOH (0.1–0.2 mL). The reaction mixture was stirred at room temperature for 1 h, and then the resulting suspension of the chalcone analog was set aside overnight. The solid was filtered, washed sequentially with a mixture of hexanes–2-propanol (2 × 6 mL, 1:2 *v*/*v*) and hexanes (2 × 10 mL), and air-dried. The material was dissolved in ethyl acetate (25 mL), the resulting light suspension was filtered gravitationally, and then ethyl acetate from the filtrate was removed under reduced pressure to give the crude chalcone, which was recrystallized from the appropriate solvent.

(E)-3-[4-(Benzyloxy)phenyl]-1-(2-nitrophenyl)prop-2-en-1-one ***10***. Yellow plates (230 mg, 64%), mp 115–116 °C (96% ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.10 (s, 2H), 6.89 (d, J = 16.0 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 16.4 Hz, 1H), 7.30–7.54 (m, 7H), 7.50 (dd, J = 1.2 and 7.6 Hz, 1H), 7.60–7.68 (m, 1H), 7.71–7.89 (m, 1H), 8.17 (dd, J = 0.8 and 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.1, 115.4, 124.1 (C2), 124.5, 126.9, 127.5, 128.2, 128.7, 128.9, 130.4, 130.5, 133.9, 136.2, 136.6, 146.3 (C3), 146.8, 161.2, 192.9.

(E)-4-{3-[4-(Benzyloxy)phenyl]-1-oxoprop-2-enyl}-benzonitrile ***11***. Yellow crystals (210 mg, 62%), mp 154–155 °C (ethyl acetate–96% ethanol 1:1 *v*/*v*); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.13 (s, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.30–7.48 (m, 6H), 7.61 (d, J = 8.8 Hz, 2H), 7.76–7.84 (m, 3H), 8.07 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.2, 115.4, 115.7, 118.1, 118.9 (C2), 127.3, 127.5, 128.2, 128.7, 128.8, 130.6, 132.4, 136.2, 141.8, 146.4 (C3), 161.3, 189.1.

(E)-3-[4-(Benzyloxy)phenyl]-1-(furan-2-yl)prop-2-en-1-one ***12***. Light yellow leaflets (140 mg, 44%), mp 107–108 °C (96% ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.12 (s, 2H), 6.59 (dd, J = 1.6 and 4.8 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 7.28–7.48 (m, 7H), 7.61 (d, J = 8.8 Hz, 2H), 7.64 (s, 1H), 7.85 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.1, 112.4, 115.3, 117.1, 119.0 (C2), 127.5, 127.7, 128.2, 128.7, 130.3, 136.4, 143.7 (C3), 146.3, 153.9, 160.9, 178.1.

(E)-3-[4-(Benzyloxy)phenyl]-1-(5-bromothiophen-2-yl)prop-2-en-1-one ***13***. Yellowish crystals (205 mg, 51%), mp 133–134 °C (96% ethanol); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.12 (s, 2H), 7.01 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 4.0 Hz, 1H), 7.20 (d, J = 15.6 Hz, 1H), 7.31–7.47 (m, 5H), 7.55–7.62 (m, 3H), 7.81 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.1, 115.3, 118.2 (C2), 122.4, 127.5 (2 carbon atoms), 128.2, 128.7, 130.4, 131.3, 131.4, 136.3, 144.4 (C3), 147.3, 161.0, 180.9.

(E)-3-[4-(Benzyloxy)phenyl]-1-[1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]prop-2-en-1-one ***14***. Light yellow needles (285 mg, 60%), mp 155–156 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.68 (s, 3H), 5.13 (s, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.31–7.48 (m, 7H), 7.69 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 16.0 Hz, 1H), 7.98 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.3, 70.1, 115.3, 120.7 (C2), 124.2, 126.7, 127.5, 127.9, 128.2, 128.7, 130.6, 132.9, 134.4, 136.4, 138.2, 143.7 (C3), 144.2, 160.9, 184.3.

2.2.5. Synthesis of chalcone analogs ***15***–***17*** *derived from 4-(benzyloxy)benzaldehyde using piperidine as catalyst*

A mixture containing 4-(benzyloxy)benzaldehyde **1** (212 mg, 1 mmol), piperidine (3 drops), and either 1-(5-bromobenzofuran-2-yl)ethanone **7**, or 1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanone **8**, or 3-acetylcoumarin **9** (1 mmol) in methanol (5 mL) was heated at reflux temperature for 6 h. After the reaction mixture had been allowed to reach to room temperature, it was refrigerated overnight, then the solid material was filtered, washed with a mixture of hexanes–2-propanol (2 × 10 mL, 9:1, *v*/*v*), air-dried, and recrystallized from a suitable solvent.

(E)-3-[4-(Benzyloxy)phenyl]-1-(5-bromobenzofuran-2-yl)prop-2-en-1-one ***15***. Yellow needles (310 mg, 71%), mp 191–192 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.13 (s, 2H), 7.03 (d, J = 8.8 Hz, 2H), 7.31–7.52 (m, 7H), 7.54 (d, J = 0.4 Hz, 1H), 7.57 (dd, J = 2.0 and 4.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.2, 111.6, 113.9, 115.4, 116.9, 118.6 (C2), 125.6, 127.5 (2 carbon atoms), 128.2, 128.7, 129.2, 130.7, 131.0, 136.3, 145.0 (C3), 154.3, 154.9, 161.3, 179.5.

(E)-3-[4-(Benzyloxy)phenyl]-1-(1-methyl-1H-benzo[d]imidazol-2-yl)prop-2-en-1-one ***16***. Light yellow needles (210 mg, 57%), mp 160–161 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.23 (s, 3H), 5.12 (s, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.31–7.50 (m, 8H), 7.72 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 16.0 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 8.13 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.4, 70.1, 110.5, 115.2, 120.9 (C2), 121.7, 123.7, 125.8, 127.5, 127.8, 128.2, 128.7, 130.9, 136.4, 137.1, 141.7, 144.5 (C3), 147.4, 161.1, 182.9.

(E)-3-{3-[4-(Benzyloxy)phenyl]-1-oxo-prop-2-enyl}-2H-chromen-2-one ***17***. Bright yellow needles (145 mg, 38%), mp 171–172 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.12 (s, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.31–7.48 (m 7H), 7.60–7.71 (m, 4H), 7.82 (d, J = 16.0 Hz, 1H), 7.87 (d, J = 16.0 Hz, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.1, 115.3, 116.7, 118.6, 121.7 (C2), 124.9, 125.5, 127.5, 127.8, 128.2, 128.7, 130.0, 130.8, 134.1, 136.4, 145.0 (C3), 147.8, 155.2, 159.4, 161.1, 186.3.

2.2.6. UV irradiation of chalcone analog ***13*** *in DMSO-d_6.* A solution of compound **13** (9.7 mg) in DMSO-d_6 (0.55 mL) in a 5 mm Wilmad quartz NMR tube was irradiated with UV light (λ = 365 nm) with an intensity of 2 mW/cm^{-2}. Only the ^{1}H NMR spectrum was recorded for the sample after 30 minutes and 60 minutes of UV irradiation, while a complete array of NMR spectra (^{1}H, ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HMBC and ^{1}H,^{13}C-HSQC) was recorded for the same sample after 6 h and after 24 h of irradiation.

3. Results and discussion

With the exception of 2′-nitroacetophenone **2**, 4-acetylbenzonitrile **3**, 2-acetylfuran **4**, 2-acetyl-5-bromothiophene **5**, and 3-acetylcoumarin **9**, which were commercially available, all other acetylated heterocycles have been prepared by design prior to their Claisen–Schmidt condensation with 4-

(benzyloxy)benzaldehyde **1**. 1-(1-(4-Bromophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone **6** was prepared through the Dimroth cyclocondensation between 4-bromophenyl azide and pentane-2,4-dione in the presence of anhydrous K_2CO_3 as base [20]. 1-(5-Bromobenzofuran-2-yl)ethanone **7** was synthesized through the Rap–Stoermer condensation between 5-bromosalicylaldehyde and chloroacetone in the presence of KOH, using a slightly modified variant of a reported procedure [21]. 1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanone **8** was obtained *via* a three-step reaction sequence that comprised the acid-catalyzed Phillips reaction of phenylene-1,2-diamine with (±)-lactic acid in the first stage, oxidation of the intermediate alcohol using the dichromate/H^+ system to 1*H*-benzo[*d*]imidazol-2-yl)ethanone in the second stage, and the methylation of the aforementioned ketone at N^1 of the benzimidazole ring in the final stage. The condensation of ketones **2**–**9** with 4-(benzyloxy)benzaldehyde **1** and the structures of the resulting compounds **10**–**17** are presented in Figure 1.

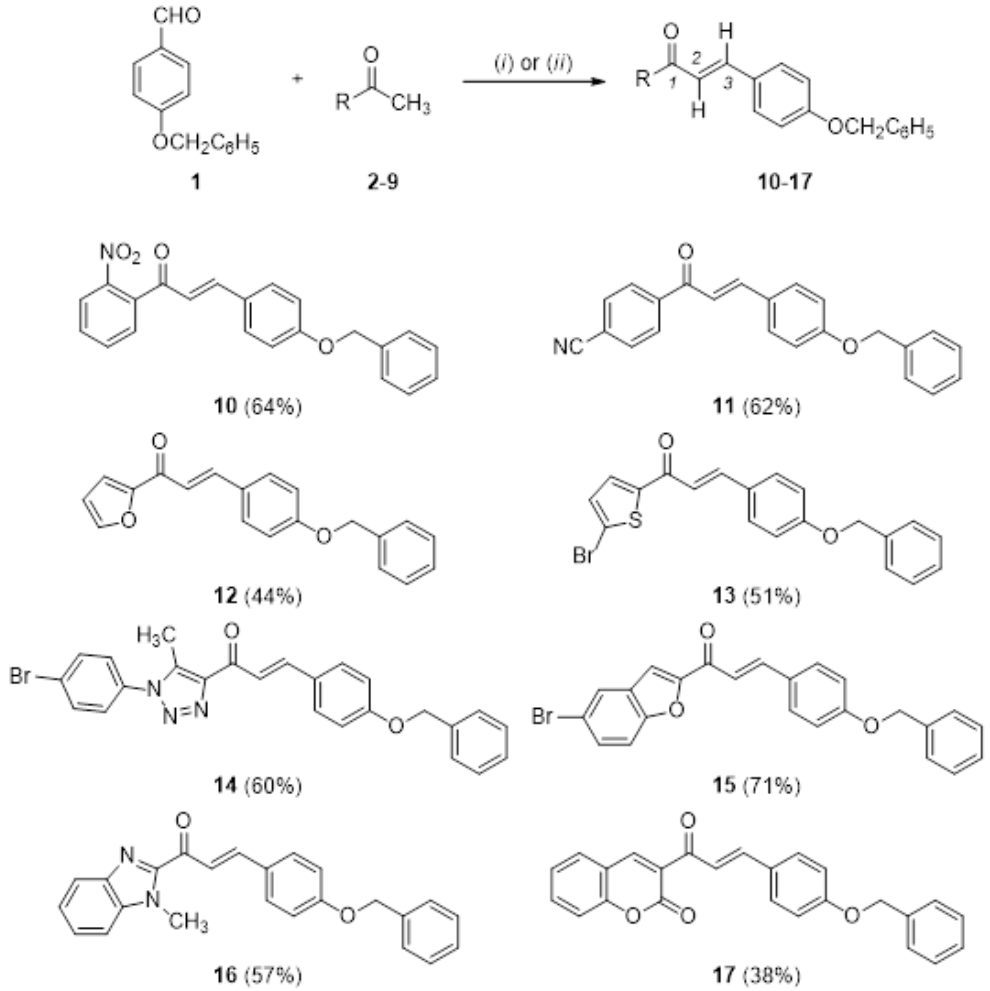

Figure 1. Synthesis and structures of the target benzyloxy-substituted chalcone analogs **10** – **17**. Experimental conditions: (*i*) ethanol, aqueous 10% NaOH, r.t., overnight; (*ii*) methanol, piperidine, reflux, 6 h

A classical approach of the Claisen–Schmidt condensation that involves of the reaction of the ketones with the aldehyde reagent in 96% ethanol in the presence of NaOH at room temperature was used for the preparation of five chalcone analogs having a 4-(benzyloxy)phenyl moiety at C-3 of the propenone motif. Under these experimental conditions, the chalcone analogs **10**–**14** usually separated out from the reaction mixture as solid materials in less than 30 minutes. Purification of these solid materials normally entails recrystallization from an appropriate solvent or solvent mixture, but it was found out that the separated crude chalcone analogs always contained a small amount of impurities that would not go into solution, and had therefore to be removed by filtration of the hot concentrated mixture, which resulted, even when conducted properly, in the crystallization of a part of the desired compound on the filter paper. In order to avoid this loss of useful material by direct recrystallization, the crude chalcone analogs were rather dissolved freely in ethyl acetate (or chloroform) at room temperature, the insoluble impurities were filtered off, and the crude chalcone analog was finally recovered from the filtrate by removal of ethyl acetate under reduced pressure prior to recrystallization from the appropriate solvent. The yields of the crude materials ranged of 68% (in the case of compound **12**) to 93% (for compound **10**), but the aforementioned processing combined with recrystallization brought them to the range of 44% (in the case of compound **12**) to 64% (for compound **10**). An inspection of the literature showed that compound **14** has been recently mentioned as an intermediate in a

study reporting the antibacterial activity of a series of pyrazolines, but no structural characterization has been provided in the article [22]. Surprisingly, chalcone analog **12** based on the common ketone 2-acetylfuran **4** as starting material was not recovered from the database search, and is thus reported herewith as a novel compound for the first time.

A variant of the Claisen–Schmidt condensation that involved the use of piperidine as the basic catalyst and was conducted at reflux temperature of the solvent of choice methanol was also explored as an alternative for the preparation of chalcone analogs having a 4-(benzyloxy)phenyl moiety at C-3 of the propenone motif. Compounds **15**–**17** were obtained under these conditions as solid materials at the end of the reaction time, with the exception of chalcone analog **16** which started to precipitate from the after approximately one hour. In contrast to the purification of their counterparts **10**–**14** that were synthesized using NaOH as catalyst, no insoluble impurities were observed upon recrystallization of chalcone analog **15**–**17** from the appropriate solvents. For compounds **15** and **16**, good yields of crude materials (82% and 72%, respectively) were recorded after isolation from the reaction mixture, but the condensation of 3-acetylcoumarin **9** with aldehyde **1** under the same reaction conditions afforded only a moderate yield (49%) of crude chalcone analog **17**. While compound **17** has been mentioned in literature twice (although no structural characterization has been provided in either of these cases), no yield has been provided for compound **17** when an approach similar to that disclosed in this paper was employed [23]. On the other hand, for the process in which 3-acetylcoumarin **9** and aldehyde **1** have been heated at reflux in ethanol in the presence of KOH for 36 h, and the crude reaction product was subsequently recrystallized from chloroform (which is actually a remarkably good solvent for compound **17** at room temperature), a claim of a quantitative yield for pure chalcone analog **17** that resulted seems doubtful [24]. Because of the reduced solubility of these chalcone analogs in 96% ethanol, ethyl acetate was the preferred solvent for recrystallization, a process which further lowered the yields for these chalcone analogs by 10–15%.

The structure of chalcone analogs **10**–**17** has been ascertained using NMR analysis. The main characteristic of the ^{1}H NMR spectra of compounds **10**–**17** is the presence of two doublets with coupling constants of approximately 15–16 Hz, assigned to the *trans* protons at the double bond joining C-2 and C-3 (Figure 1). The signals for these protons could be clearly discerned in the case of target compounds **10**, **13**, **14**, **16** and **17**, whereas only one of these vinylic protons could be easily spotted from the proton spectra of compounds **12** and **15**. The rest of the vinylic protons, whose signals mingled with the aromatic protons in ^{1}H NMR spectra of compounds **11**, **12** and **15**, have been identified using 2D NMR experiments. Despite the fact that the aromatic region of the NMR spectra of these chalcones analogs is quite crowded, the correct number of protons and carbon atoms for the proposed structure has been found in each and every case. In their ^{13}C NMR spectra, the peaks for C-2 in these chalcone analogs resonate between 118 ppm and 124 ppm, while the signals for C-3 in compounds **10**–**17** are in the narrow range of 143 to 146 ppm (see Experimental). Again, these assignments have been accurately made using 2D NMR experiments. Additionally, it can be gleaned from a comparison of the chemical shifts for the carbonyl carbon C-1 in enones **10**–**17** (Table 1) that the value generally increases with the increase of aromaticity of the heterocyclic substituent directly attached to C-1, while the presence of electron withdrawing substituents in the phenyl ring also results in high values for the chemical shift of C-1.

Table 1. Chemical shift values for C-1 in compounds **10**–**17**

Compound	**12**	**15**	**13**	**16**	**14**	**17**	**11**	**10**
$\delta_{C\text{-}1}$ (ppm)	178.1	179.5	180.9	182.9	184.3	186.3	189.1	192.9

Given the presence of structurally different substituents at the double carbon bond involved in the photodimerization, (*E*)-chalcone analogs can theoretically give rise to mixtures of four different regioisomeric cyclobutanes. The [2 + 2] photodimerization may occur in a head-to-head fashion to afford regioisomers with identical substituents positioned in a 1,2-relationship, but it can also take place in a head-to-tail fashion, and produce regioisomers with identical substituents positioned in a 1,3-relationship (Figure 2). In addition, the relative configuration of the substituents at those two single cyclobutane bond that were generated through cyclodimerization is referred to as *syn* versus *anti* [25]. In general, if there are no constraints, the *anti* head-to-head is the major component in the mixture of regioisomers, but yields of the cyclodimerization products and the composition of the mixtures that result from photoinduced dimerization reactions of chalcone analogs depend greatly on the experimental conditions. [26–28]. When the possibility for the chalcone analogs to participate also as *Z* isomers in the photodimerization process is considered, a number of eleven theoretical positional and configurational cyclobutane regioisomers [29].

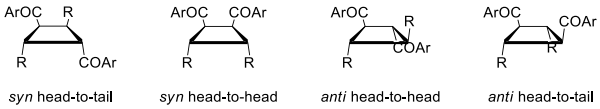

Figure 2. Depiction of regioisomeric cyclobutanes that may be theoretically produced by photoinduced dimerization of *E*-ArCOCH=CHR

In order to investigate the photodimerization of (*E*)-chalcone analog **13**, the sample for the NMR experiments was dissolved in DMSO-d_6, and its ^{1}H NMR spectra were recorded after different irradiation times (30 min, 60 min, 6 h and 24 h) in order to monitor the dimerization process. After 30 minutes of UV irradiation, new peaks in the proton NMR spectrum of the sample (Figure 3) that have been assigned to the *Z* isomer of compound **13** are noticeable at 6.79 ppm (d, J = 13.0 Hz) and 7.02 ppm (d, J = 13.0 Hz) for vinylic protons, as well as a new singlet at 5.15 ppm associated with the protons in the methylene group of the benzyl

moiety. The peaks for the vinylic protons in the *Z* isomer were assigned based on the HMBC spectrum of sample that has been irradiated for 6 h (Figure 4) through their coupling with C-1 (δ = 183 ppm) and were confirmed by their correlation peaks from the COSY experiment. The concentration of the *Z* isomer of chalcone analog **13** in the sample varies with irradiation time, and it was high enough after 6 h of UV irradiation to allow an accurate assignment for the vinylic protons. As the concentration of (*Z*)-**13** does not appear to increase with increasing irradiation time, it seems logical to assume that this intermediate does not accumulate in the system, but it is produced continuously from the *E* isomer, and is presumably retro-converted into the *E* isomer (equilibration process), or even consumed (along with the *E* isomer) in the generation of the final cyclodimerization products.

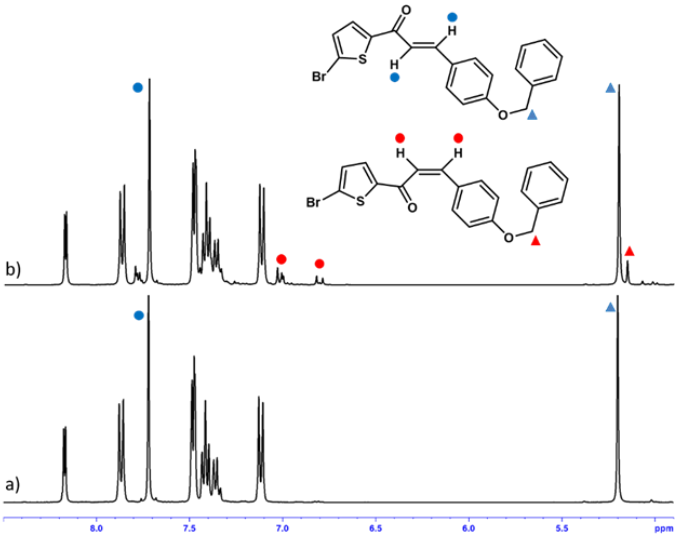

Figure 3. ^{1}H NMR spectrum of chalcone analog **13** initially (a) and after 30 minutes of irradiation (b) with UV light, showing partial assignment of the peaks for the *Z* (blue marks) and *E* (red marks) isomers of **13**

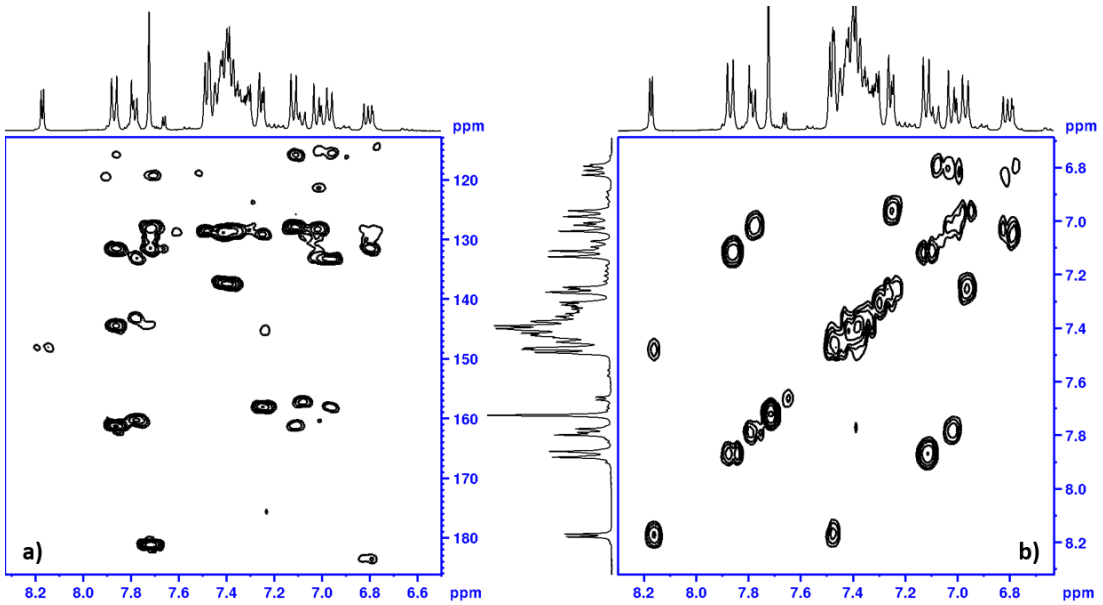

Figure 4. Partial 2D NMR spectra [^{1}H,^{13}C-HMBC (a) and ^{1}H,^{1}H-COSY (b)] for the sample of chalcone analog **13** after 6 hours of UV irradiation

In addition, two new sets of doublets of doublets with an AA′BB′ spin pattern can be observed in the proton spectrum of the irradiated sample of compound **13**, and these signals have been associated with the newly formed cyclobutanes. The set for the major regioisomeric cyclobutane is comprised of the signals at 3.72 ppm (*J* = 9.5 Hz) and 4.36 ppm (*J* = 9.1 Hz), which could be tentatively attributed to the *anti* head-to-head cyclobutane **A** based on the similarities between the experimental values for the coupling constant recorded in this experiment of those reported in literature [30] for similar regioisomers, on the shape and multiplicity of the signals (spin system AA′BB′), and also based on the observation that this regisomer is usually the most abundant in the mixture of cyclobutanes produced through irradiation of chalcone analogs. Other assignments for a few selected hydrogen and carbon atoms in the structure of regioisomer **A** have been gleaned through a careful inspection of the 2D NMR spectra of the sample after 6 h of UV irradiation, and are given in Table 2. Unfortunately, the excessive crowding in the aromatic region prevented any further

substantiation for the proposed structure of regioisomer **A** using 2D NMR analysis.

Table 2. Chemical shifts (ppm) for selected protons and carbon atoms in the structure of cyclobutane regioisomers **A**, **B** and **C**

Isomer	Chemical shifts (ppm)					
	δ_H (C-2)	δ_H (C-3)	δ_H (CH_2)	δ_{C-2}	δ_{C-3}	δ_{C-1}
A	4.36	3.72	5.07	47.3	46.9	189.0
B	4.91	4.22	5.00	47.2	43.7	190.5
C	4.84	4.50	5.04	n.a.	n.a	n.a

The second set is represented by the doublets at 4.22 ppm (J = 5.8 Hz) and 4.91 ppm (J = 9.5 Hz), and the shape and multiplicity of these doublets are similar to those of an AA′BB′ spin system. Of the four regioisomeric cyclobutane dimers that may form from the *E* isomers of chalcone analogs, only the *anti* head-to-tail isomer should give an A_2B_2 type spin system in the aliphatic region of its proton spectra, while the other three cyclobutane regioisomers (*anti* head-to-head, *syn* head-to-head and *syn* head-to-tail) should all present AA′BB′ spin systems in their proton spectra. As the *anti* head-to-head cyclobutane is very likely cyclobutane **A**, this leaves only the two *syn* regioisomers (Figure 2) as plausible options for the second cyclobutane regioisomer identified in the proton NMR spectrum of the irradiated sample. However, by entertaining the possibility that the cyclobutanes formed in our experiment could be also derived from *Z* isomers of chalcone analogs, the set of potential structures for cyclobutanes featuring an AA′BB′ spin system in their NMR spectra should be broaden to include two extra regioisomers **I** and **II** (Figure 5) [29]. However, the formation of regioisomers **I** and **II** requires both two molecules of chalcone analogs involved in dimerization to be in *Z* configuration, and these particular type of regioisomers have not been reported in the literature so far, to the best of our knowledge. Moreover, the excessive sterical hindrance in the structure of regioisomer **I** renders its formation highly improbable. Therefore, *syn* head-to-head and *syn* head-to-tail regioisomers appear to be the most likely candidates for the structure of this second cyclobutane **B**. Again, while accurate assignments for a small number of hydrogen and carbon atoms in the structure of regioisomer **B** can be obtained from the analysis of the 2D NMR spectra of the sample after 6 h of UV irradiation (Table 2), the extensive overlapping in the aromatic region precluded the definite determination of the structure of regioisomer **B**. The molar ratio between regioisomers **A** and **B** is approximately 2:1 after an irradiation time of 30 minutes, as calculated from the integral ratio.

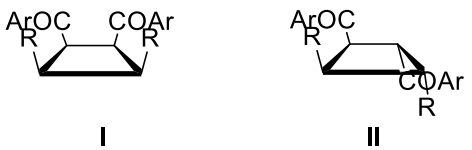

Figure 5. Cyclobutanes that would feature an AA′BB′ spin system in the aliphatic region of their NMR spectra theoretically obtained through dimerization involving (*Z*)-chalcone analogs

After the sample had been irradiated with UV light for 60 minutes, a third set of doublets is observed in the ^{1}H NMR spectrum at 4.50 ppm (J = 5.6 Hz) and 4.84 ppm (J = 6.0 Hz), which were attributed to a cyclobutane **C**. The spin system for the protons in the cyclobutane ring in regioisomer **C** also resembles an AA′BB′ spin system. Therefore, the rationale previously developed for the case of regioisomer **B** also applies for cyclobutane **C**, which could be either the *syn* head-to-head regioisomer or the *syn* head-to-tail regioisomer, both resulted from the cyclodimerization of the *E* isomer of chalcone analog **13**. The molar ratio between **A**, **B** and **C** is approximately 2:1:0.4. After 6 hours of irradiation, the molar ratio **A**:**B**:**C** is still approximately 2:1:0.4, and the same molar ratio is 2:1:0.2 after 24 hours of irradiation (Figure 6). This suggests that the rate of formation of regioisomer **C** is slower than those for **A** or **B**. It is worth mentioning that while only traces of *E* isomer of starting material **13** could be evidenced in the sample after 24 h of irradiation, while its *Z* isomer is still present, but in even smaller amounts.

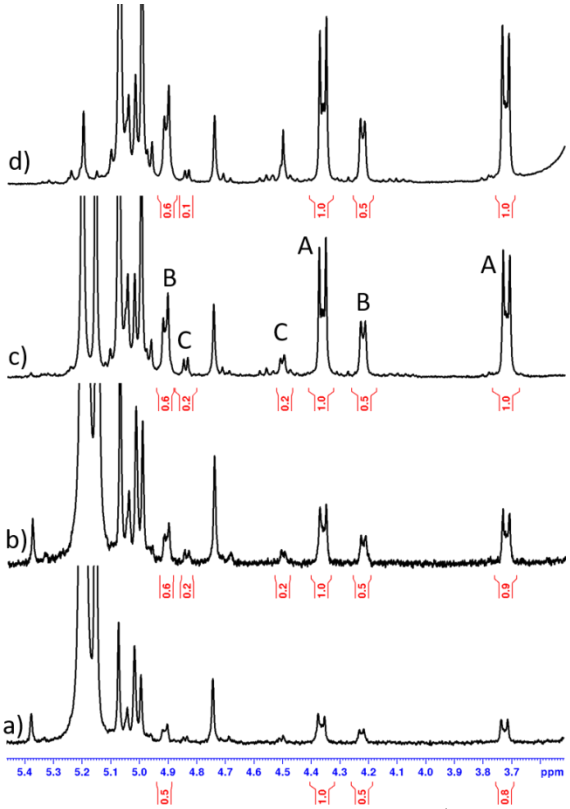

Figure 6. Detail of the aliphatic region of the ^{1}H NMR spectra for compound **13** recorded at different irradiation times: a) after 30 minutes of irradiation; b) after 60 minutes of irradiation; c) after 6 hours of irradiation; d) after 24 hours of irradiation. The peaks assigned to regioisomeric cyclobutanes **A**, **B** and **C** are marked on the spectrum recorded after 6 h of irradiation.

4. Conclusions

A series of eight chalcone analogs derived from 4-(benzyloxy)benzaldehyde as the aldehyde component in the Claisen–Schmidt condensation have been successfully synthesized. Five of these chalcone analogs were obtained using NaOH as catalyst, while the others were prepared using piperidine as catalyst. Moderate to

good yields have been obtained for most of the reaction products using either of these two variants. Poorer yields have been also recorded in a few cases for products that were synthesized through either of these two approaches (*e.g.*, chalcone analog **12** that was obtained using NaOH as catalyst, and chalcone analog **17** that resulted from the condensation using piperidine as catalyst), which suggest that the quantitative outcome of the condensation depends appreciably on the nature of ketone component in the Claisen–Schmidt condensation rather than on the nature of the basic catalyst. NMR analysis may be used for the monitoring in time and detection of cyclobutanes produced during irradiation of a chalcone analog with UV light, but its use in the accurate assignment of a specific configuration to the regioisomers of the dimerization product that were identified is heavily limited by the difficulties arisen from the presence of a large number of magnetically non-equivalent signals in the aromatic region of the spectra, which impede the establishment of any practically useful correlations in 2D NMR spectra of the irradiated sample.

Conflict of interest

The authors do not declare any conflict of interest.

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