Synthesis of 3-Cyclohexanecarbonyl-2(3*H*)-Benzoxazolone and 3-Cyclohexanecarbonyl-2(3*H*)-Benzothiazolone Derivatives

Guenadil Faouzi

Laboratory of Chemistry, Department of Chemistry, faculty of Science and Technology University of Chadli Bendjedid El Tarf-36000 (Algeria), E-mail: guenadil-faouzi@univ-eltarf.dz

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Abstrat.

In this study, 3- cyclohexanecarbonyl-2(3*H*)-benzoxazolone and 3- cyclohexanecarbonyl-2(3*H*)-benzothiazolone derivatives have been synthesized in excellent yields by condensation of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone derivatives with cyclohexanecarbonyl acid chloride using sodium ethylate in a mixture of acetone-water (9/1) as solvent. The structures of synthesized derivatives were identified by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Keywords: 2(3*H*)-benzoxazolone, 2(3*H*)-benzothiazolone, FC-acylation, Cyclohexanecarbonyl acid chloride, *N*-acylation.

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Introduction

2(3H)-benzoxazolone and its corresponding sulfur bioisoster 2(3H)-benzothiazolone constitute an essential class of heterocyclic compounds, due to their various Biological properties [1-13]. Many derivatives bearing various substituents have been reported to have different biological activities [14-22].

In particular, 6-Benzoyl-2(3H)-benzoxazolone (10194 CERM) and 6-benzoyl-2(3H)-benzothiazolone (S-14080) with analgesic and anti-inflammatory activities, were tested clinically as potential surrogates of the classical non-steroidal anti-inflammatory agent. They were shown to exhibit a peculiar pharmacological profile that acts not only as an inhibitor of COX-1 and COX-2 but also promotes the release of an opioid peptide (endomorphin) in the periphery [5,6].

In this connection and in an effort to generate dual mode of action analgesics endowed with COX inhibition, we designed a new series of 3-cyclohexanecarbonyl-2(3H)-benzoxazolones and 3-cyclohexanecarbonyl-2(3H)-benzothiazolones of general structure Figure 1.

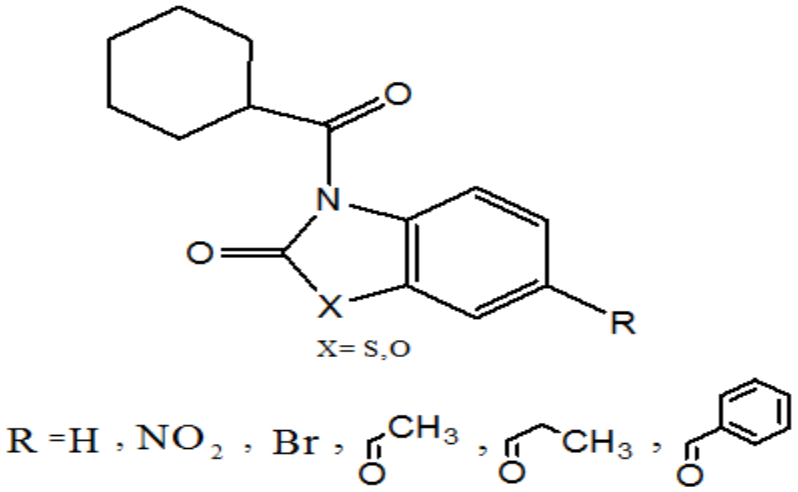


Figure 1 : General structure of the new series

Experimental

General

All reactions were monitored by thin layer chromatography using Merk TLC silica gel 60 F 254 and visualized with UV light, using Ethyl acetate: cyclohexane (7:3 v/v), a solvent system as eluent. Melting points were measured in open capillary tubes on an Electro thermal apparatus. The IR spectra were obtained on a Perkin-Elmer 457 spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 400 spectrometer using DMSO-D_6 or $CDCl_3$ as solvents and (TMS) as an internal standard.

Methods and procedures

Synthesis of 6-nitro-2(3*H*)-benzoxazolone and 6-nitro-2(3*H*)-benzothiazolone (1b-2b)

To nitric acid (68%, 10 cm^3, 150 mmol) cooled to -0-5°C was added dropwise, (10 mmol) of 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone. The reaction mixture was heated at 50°C for 30 min and kept at room temperature for 2h. After that, 100 cm3 of ice water was added to the reaction mixture and stirred for 15 min. The precipitate was filtered, washed with water, dried and recrystallized from ethanol to afford the corresponding 6-nitro-2(3*H*)-benzoxazolone and 6-nitro-2(3*H*)-benzothiazolone.

Synthesis of 6-bromo-2(3*H*)-benzoxazolone and 6-bromo-2(3*H*)-benzothiazolone 1b-2b

(0.004 mol) of 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone was dissolved under stirring in 50 ml of dichloromethane/tetrahydrofuran (8/2). After that, (6.87g, 0.043 mol) of Br_2 dissolved in a small amount of dichloromethane was slowly added. The reaction mixture was heated at 60°C for 2 hours and kept at room temperature for 48 hours. After evaporation of the solvent, the residue triturated with water, filtered, dried, and crystallized from ethanol to afford the corresponding 6-bromo-2(3*H*)-benzoxazolone and 6-bromo-2(3*H*)- benzothiazolone. The physical properties (m.p, IR, 1H NMR) are in accordance with published data [6, 25].

Synthesis of 6-acyl-2(3*H*)-benzoxazolones and 6-acyl-2(3*H*)- benzothiazolone derivatives, using $FeCl_3$-DMF complex (1c-6c).

(4,7 ml, 0.066 mol) of Dimethylformamide was added to ferric chloride (38.92 g, 0.24 mol). The mixture was then placed in an oil bath and heated at 90°C for 15 min. 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone (60 mmol) was added in portions. When the mixture was uniformly mixed, acid (6,4 ml, 0.06 mol) was added. Then the reaction mixture was heated at 170°C under stirring for 3 h. The products were poured into ice water with HCl (5ml, 37%). The precipitated was collected by filtration, dried and crystallized.

General procedure for the synthesis of 3-(cyclohexanecarbonyl)-2(3*H*)-benzoxazolone and 3-(cyclohexanecarbonyl)-2(3*H*)-benzothiazolone derivatives (1d-12d).

(0.004 mol) of 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone or their derivatives was dissolved under stirring in 50 ml of absolute ethanol. After that, (2.72g, 0.040 mol) of sodium ethylate was added under stirring to insure the formation of sodium derivatives. After evaporation of ethanol, 50 ml of acetone and 5 ml of water were added and then (5.44 ml, 0.041 mol) of cyclohexanecarbonyl acid chloride was slowly added. The mixture was stirred at room temperature for 15 min. After evaporation of the acetone, the residue triturated with a solution of 10% of ($NaHCO_3$), filtered, washed with water and dried, and crystallized from ethanol to afford good purity of the compounds with a yield (92-99%).

3-(Cyclohexanecarbonyl)-2(3*H*)-benzoxazolone (1d). Yields: 99%. M.p: 84-85°C. IR (KBr, cm-1): 2930 (νCH_2), 1805 (νC=O), 1723 (νC=O), 1592.09 (νC=Caromatic). ^{1}H-NMR (400 MHz, $CDCl_3$: *δ*=1.24-1.59 (m, 6H), 1.68-1.94 (m, 4H), 3.69 (m, 1H), 7.11-7.38 (m, 3H, Ar-H), 8.07 (d, *J* = 8.0 Hz, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): *δ*= 175.82 (C=O), 151.33 (C=O), 142.33, 128.11, 125.15, 124.75, 116.43, 109.78 (aromatic carbons), 43.46 (CH), 28.92 (CH_2), 25.77 (CH_2), 25.45 (CH_2).

6-Bromo-3-(cyclohexanecarbonyl)-2(3*H*)-benzoxazolone (2d). Yields: 98%. M.p: 125-126°C. IR (KBr, cm-1): 2932 (νCH_2), 1789 (νC=O), 1718 (νC=O), 1600 (νC=Caromatic). ^{1}H-NMR (400 MHz, $CDCl_3$: *δ*=1.19-1.55 (m, 6H), 1.54-1.96 (m, 4H), 3.58 (m, 1H), 7.16-7.31 (m, 2H, Ar-H), 7.89 (d, *J* = 7.9 Hz, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): *δ*= 175.58 (C=O), 150.41 (C=O), 142.71, 130.84, 129.35, 127.80, 117.33, 113.48 (aromatic carbons), 43.47 (CH), 28.86 (CH_2), 25.64 (CH_2), 25.26 (CH_2).

6-Nitro-3-(cyclohexanecarbonyl)-2(3*H*)-benzoxazolone (3d). Yields: 94%. M.p: 123-124°C. IR (KBr, cm-1): 2928 (νCH_2), 1790 (νC=O), 1718 (νC=O), 1600 (νC=Caromatic), 1338.49 (νNO2). ^{1}H-NMR (400 MHz, DMSO-d6: *δ*=1.25-1.58 (m, 6H), 1.67-1.95 (m, 4H), 3.71 (m, 1H), 8.08 (d, *J* = 7.91 Hz, 1H, Ar-H), 8.20-8.27 (m, 2H, Ar-H),. ^{13}C-NMR (400 MHz, DMSO-d6): *δ*= 175.93 (C=O), 152.90 (C=O), 142.29, 128.56, 126.15, 125.15, 117.32, 110.28 (aromatic carbons), 43.56 (CH), 28.96 (CH_2), 25.87 (CH_2), 25.55 (CH_2).

6-Acetyl-3-(cyclohexanecarbonyl)-2(3*H*)-benzoxazolone (4d). Yields: 95%. M.p: 107-108°C. IR (KBr, cm-1): 2928 (νCH_3), 1760 (νC=O), 1719 (νC=O), 1676 (νC=O), 1600

(νC=Caromatic). ^{1}H-NMR (400 MHz, DMSO-d6: *δ*=1.24-1.56 (m, 6H), 1.64-1.93 (m, 4H), 2.68 (s, 3H), 3.86 (m, 1H), 7.75-7.86 (m, 2H, Ar-H), 8.17 (d, *J* = 7.76 Hz, 1H, Ar-H). ^{13}C-NMR (400 MHz, DMSO-d6): *δ*= 198.62 (C=O), 174.72 (C=O), 152.79 (C=O), 142.43, 132.34, 129.75, 123.63, 109.63, 108.85 (aromatic carbons), 43.36 (CH), 28.94 (CH_3), 25.74 (CH_2), 25.52 (CH_2), 24.46 (CH_2).

6-Propionyl-3-(cyclohexanecarbonyl)-2(3*H*)-benzoxazolone (5d). Yields: 93%. M.p: 149-150°C. IR (KBr, cm-1): 2931 (νCH$_3$), 1780 (νC=O), 1724 (νC=O), 1683 (νC=O), 1609 (νC=Caromatic). ^{1}H-NMR (400 MHz, $CDCl_3$: *δ*=1.22-1.55 (m, 9H), 1.65-1.97 (m, 4H), 2.92 (q, 2H), 3.84 (m, 1H), 7.76-7.85 (m, 2H, Ar-H), 8.17 (d, *J* = 7.79 Hz, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): *δ*= 198.64 (C=O), 175.82 (C=O), 151.78 (C=O), 142.23, 133.30, 130.75, 124.63, 115.86, 109.25 (aromatic carbons), 43.35 (CH), 31.82 (CH_2), 28.85 (CH_2), 25.76 (CH_2), 25.54 (CH_2), 8.59 (CH_3).

6-Benzoyl-3-(cyclohexanecarbonyl)-2(3*H*)-benzoxazolone (6d). Yields: 92%. M.p: 135-136°C. IR (KBr, cm-1): 2933 (νCH$_2$), 1790 (νC=O), 1725 (νC=O), 1652 (νC=O), 1600.09 (νC=Caromatic). ^{1}H-NMR (400 MHz, DMSO-d6: *δ*=1.26-1.57 (m, 6H), 1.65-1.97 (m, 4H), 3.84 (m, 1H), 7.40-7.73 (m, 7H), 8.14 (d, *J* = 7.71 Hz, 1H).. ^{13}C-NMR (400 MHz, DMSO-d6): *δ*= 193.58 (C=O), 176.78 (C=O), 151.18 (C=O), 141.73, 137.06, 134.50, 133.47, 130.97, 129.79, 128.36, 127.64, 115.42, 111.16 (aromatic carbons), 44.06 (CH), 27.92 (CH_2), 25.75 (CH_2), 25.35 (CH_2).

3-(Cyclohexanecarbonyl)-2(3*H*)-benzothiazolone (7d). Yields: 99%. M.p: 48-49°C. IR (KBr, cm-1): 2938 (νCH$_2$), 1710 (νC=O), 1665 (νC=O), 1598 (νC=Caromatic). ^{1}H-NMR (400 MHz, $CDCl_3$: *δ*=1.17-1.53 (m, 6H), 1.65-1.96 (m, 4H), 3.56 (m, 1H), 7.16-7.39 (m, 3H, Ar-H), 8.04 (d, *J* = 7.96 Hz, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): *δ*= 177.36 (C=O), 170.22 (C=O); 134.85; 126.24; 124.87; 122.96; 121.81; 111.31 (aromatic carbons). 44.13 (CH); 28.62 (CH_2); 25.54 (CH_2); 25.31 (CH_2).

6-Bromo-3-(cyclohexanecarbonyl)-2(3*H*)-benzothiazolone (8d). Yields: 98%. M.p: 81-82°C. IR (KBr, cm-1): 2935 (νCH$_2$), 1725 (νC=O), 1677 (νC=O), 1595 (νC=Caromatic). ^{1}H-NMR (400 MHz, $CDCl_3$: *δ*=1.18-1.56 (m, 6H), 1.53-1.98 (m, 4H), 3.57 (m, 1H), 7.16-7.28 (m, 2H, Ar-H), 7. 91 (d, *J* = 7.89 Hz, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): *δ*= 175.24 (C=O), 169.18 (C=O), 134.75, 131.37, 127.49, 125.54, 117.57, 110.89 (aromatic carbons), 44.86 (CH), 29.10 (CH_2), 25.52 (CH_2), 25.14 (CH_2).

6-Nitro-3-(cyclohexanecarbonyl)-2(3*H*)-benzothiazolone (9d). Yields: 92%. M.p: 137-138°C. IR (KBr, cm-1): 2934 (νCH$_2$), 1715 (νC=O), 1672 (νC=O), 1600 (νC=Caromatic), 1338.49 (νNO2). ^{1}H-NMR (400 MHz, $CDCl_3$: *δ*=1.16-1.56 (m, 6H), 1.65-1.98 (m, 4H), 3.58 (m, 1H), 8.15 (d, *J* = 7.79 Hz, 1H, Ar-H), 8.19-8.25 (m, 2H, Ar-H),. ^{13}C-NMR (400 MHz, $CDCl_3$): *δ*= 174.34 (C=O), 169.62 (C=O), 137.36, 131.56, 124.34, 122.86, 121.71, 110.81 (aromatic carbons), 43.70 (CH), 27.08 (CH_2), 25.84 (CH_2), 24.88 (CH_2).

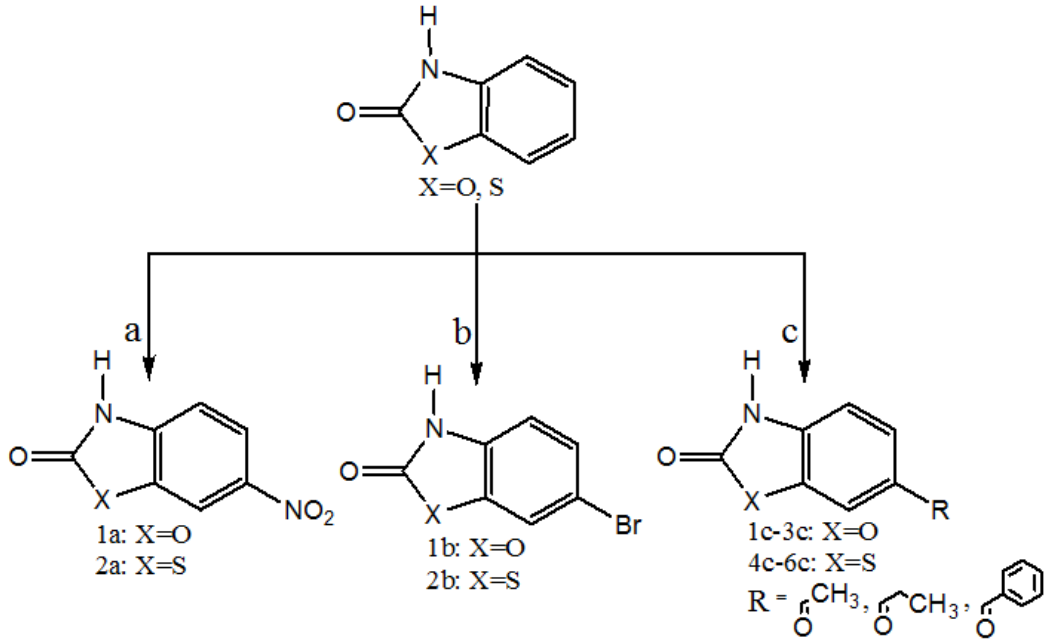
6-Acetyl-3-(cyclohexanecarbonyl)-2(3*H*)-benzothiazolone (10d). Yields: 95%. M.p: 99-100°C. IR (KBr, cm-1): 2937 (νCH$_3$), 1710 (νC=O), 1683 (νC=O), 1675 (νC=O), 1598 (νC=Caromatic). ^{1}H-NMR (400 MHz, DMSO-d6: *δ*=1.24-1.59 (m, 6H), 1.63-1.96 (m, 4H), 2.64 (s, 3H), 3.85 (m, 1H), 7.93-8.10 (m, 2H, Ar-H), 8.14 (d, *J* = 7.86 Hz, 1H, Ar-H). ^{13}C-NMR (400 MHz, DMSO-d6): *δ*= 197.62 (C=O), 176.72 (C=O), 169.79 (C=O), 140.43, 135.34, 128.75, 123.73, 122.93, 117.85 (aromatic carbons), 43.46 (CH), 28.97 (CH$_3$), 25.69 (CH$_2$) , 25.49 (CH$_2$), 24.47 (CH$_2$).

6-Propionyl-3-(cyclohexanecarbonyl)-2(3*H*)-benzothiazolone (11d). Yields: 96%. M.p: 103-104°C. IR (KBr, cm-1): 2935 (νCH$_3$), 1728 (νC=O), 1680 (νC=O), 1677 (νC=O), 1610 (νC=Caromatic). ^{1}H-NMR (400 MHz, DMSO-d6: *δ*= 1.22-1.56 (m, 9H), 1.63-1.98 (m, 4H), 2.90 (q, 2H), 3.89 (m, 1H), 7.86-7.98 (m, 2H, Ar-H), 8.15 (d, *J* = 7.89 Hz, 1H, Ar-H). ^{13}C-NMR (400 MHz, DMSO-d6): *δ*= 194.64 (C=O), 177.82 (C=O), 169.98 (C=O), 139.23, 133.25, 127.15, 123.63, 121.86, 116.25 (aromatic carbons), 43.33 (CH), 32.26 (CH$_2$), 28.82 (CH$_2$), 25.69 (CH$_2$), 25.54 (CH$_2$), 8.29 (CH$_3$).

6-Benzoyl-3-(cyclohexanecarbonyl)-2(3*H*)-benzothiazolone (12d). Yields: 93%. M.p: 127-128°C. IR (KBr, cm-1): 2934 (νCH$_2$), 1695 (νC=O), 1670 (νC=O), 1648 (νC=O), 1595.10 (νC=Caromatic). ^{1}H-NMR (400 MHz, DMSO-d6: *δ*=1.25-1.58 (m, 6H), 1.64-1.96 (m, 4H), 3.87 (m, 1H), 7.43-7.82 (m, 7H), 8.13 (d, *J* = 8.01 Hz, 1H).. ^{13}C-NMR (400 MHz, DMSO-d6): *δ*= 196.58 (C=O), 174.78 (C=O), 165.88 (C=O), 140.73, 137.25, 134.30, 132.79, 129.97, 129.39, 128.46, 127.60, 123.42, 116.66 (aromatic carbons), 44.16 (CH), 28.12 (CH$_2$), 25.82 (CH$_2$), 25.36 (CH$_2$).

Results and discussions

The 2(*3H*)-benzoxazolone and 2(*3H*)-benzothiazolone derivatives used as intermediates were synthesized via the route outlined in Scheme 1. The classical nitration of the aromatic ring of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone with nitric acid produced the 6-nitro-2(3*H*)-benzoxazolone and 6-nitro-2(3*H*)-benzothiazolone **1a-2a**, in 68 to 70% yields [29, 30]. The bromination procedure using Br_2 in CH_2Cl_2/THF (8/2) yielded the corresponding 6-bromo-2(3*H*)-benzoxazolone and 6-bromo-2(3*H*)-benzothiazolone **1b-2b** in 86 and 89% yields after 48h [31].

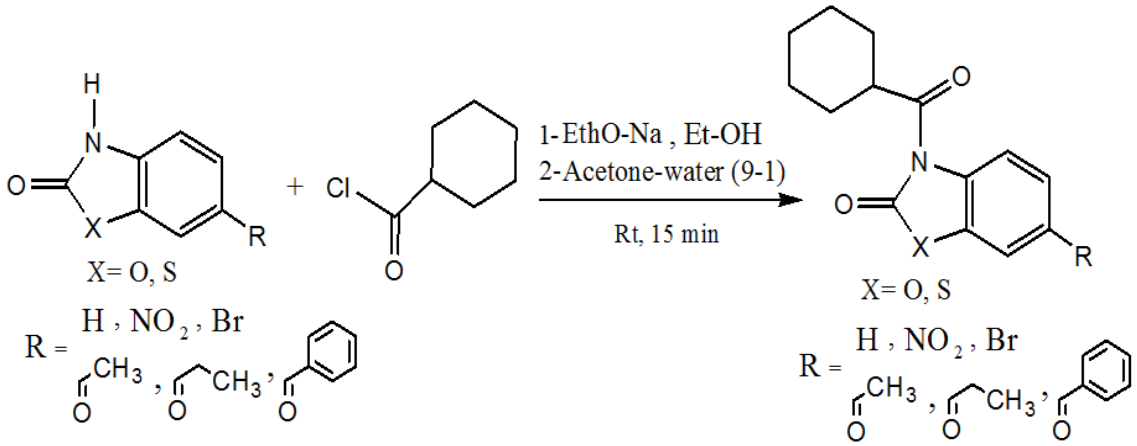


Scheme 1: Reagents and conditions: (a) HNO_3 (68%), -5-0°C; (b) Br_2, CH_2Cl_2/THF, 60°C 1h, 48h

rt; (c) $FeCl_3$-DMF, RCOCl, 170°C.

The 6-acyl-2(3*H*)-benzoxazolone and 6-acyl-2(3*H*)-benzothiazolone derivatives (1c-6c) were obtained in satisfactory yields (67-75%) using acid chlorides as acylting agents in the presence of $FeCl_3$-DMF complex used as Friedel-Crafts catalyst [12].

The 3-cyclohexanecarbonyl-2(*3H*)-benzoxazolone and 3-cyclohexanecarbonyl-2(*3H*)-benzothiazolone derivatives (**1d-12d)** were obtained after 15 min at room temperature by a series of reactions from 2(*3H*)-benzoxazolone and 2(*3H*)-benzothiazolone derivatives with cyclohexancarbonyl acid chloride, using sodium ethylate instead of sodium hydroxide (Scheme 2) [6].



Scheme 2: Synthesis of 3-cyclohexanecarbonyl-2(*3H*)-benzoxazolone and 3-cyclohexanecarbonyl-

2(*3H*)-benzothiazolone derivatives (1d-12d)

The synthesized products were obtained with a very high purity, which was characterized by thin-layer chromatography. The yields of the synthesized compounds are presented in Table 1.

Table 1. Physicochemical data of the synthesized 3-(cyclohexanecarbonyl)-2(3*H*)-Benzoxazolone

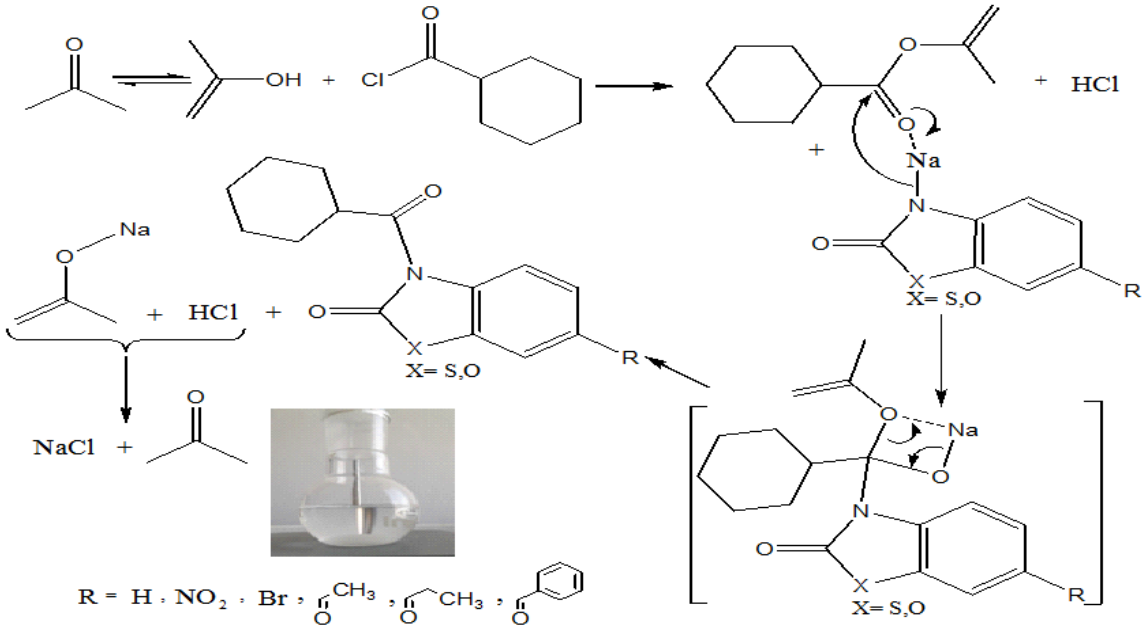
and 3-(cyclohexanecarbonyl)-2(3*H*)-benzothiazolones compounds 1d-12d.

Product	X	R	[a]Mp (C)	Time (min)	[b] Yield (%)	[c]Mol. F
1d	O	H	84-85	15	99	$C_{14}H_{15}NO_3$
2d	O	Br	125-126	15	98	$C_{14}H_{14}NO_3Br$
3d	O	NO_2	123-124	15	94	$C_{14}H_{14}N_2O_5$
4d	O	C_6H_5	135-136	15	92	$C_{21}H_{19}NO_4$
5d	O	CH_3	107-108	15	95	$C_{16}H_{17}NO_4$
6d	O	CH_2CH_3	149-150	15	93	$C_{17}H_{19}NO_4$
7d	S	H	48-49	15	99	$C_{14}H_{15}NO_2S$
8d	S	Br	81-82	15	98	$C_{14}H_{14}NO_2SBr$
9d	S	NO_2	137-138	15	92	$C_{14}H_{14}N_2O_4S$
10d	S	C_6H_5	127-128	15	93	$C_{21}H_{19}NO_3S$
11d	S	CH_3	99-100	15	95	$C_{16}H_{17}NO_3S$
12d	S	CH_2CH_3	103-104	15	96	$C_{17}H_{19}NO_3S$

[a]Melting point; [b]Isolated yield after crystallization; [c]Molecular formula

Under the experimental conditions, we observed a transformation of the heterogeneous reaction medium to a homogeneous phase, after the addition of cyclohexanecarbonyl chloride, and after

that the precipitation of sodium chloride (NaCl) as a white powder at the end of the reaction. This transformation can be expounded by the formation of an intermediate according to the proposed reaction mechanism reported in Scheme 3.



Scheme 3: the proposed mechanism of the formation of 3-cyclohexanecarbonyl derivatives

The addition of cyclohexanecarbonyl acid chloride leads to the formation of the isopropenyl cyclohexane carboxylate by reaction with the enol form of acetone, whose reacted with the sodium derivatives of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone, leading to the formation of the intermediate, and after rearrangement, conducted to the formation of *N*-acyl compounds and the sodium chloride NaCl at the end of the reaction.

Conclusions

Through this work, we confirmed the efficacity of the experimental protocol using the sodium ethylate in the mixture of acetone water for the synthesis of *N*-acyl derivatives. These mild conditions leads to the formation of the isopropenyl cyclohexane carboxylate intermediate, and after rearrangement permitted rapid access to 3-(cyclohexancarbonyl)-2(3*H*)-benzoxazolones and 3-(cyclohexancarbonyl)-2(3*H*)-benzothiazolones derivatives with good yields.

Reference

[1]. *D.D. Erol, M.D. Aytemir, N. Yulug*, "Synthesis and antimicrobial activity of thiazolinomethyl- 2(3H)-benzoxazolone derivatives", European journal of medicinal chemistry, **vol. 30**, 1995, pp 521-524

[2]. *H. Ucar, S. Cacciaguerra, S. Spampinato, M. Isa, M. Kanyonyo, J.H. Poupaert*, "2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone derivatives: Novel, potent and selective σ1 receptor ligands", European Journal of Pharmacology, **vol. 335**, no. 2-3, 1997, pp 267-273

[3]. D. Lesieur, P. Carato, , J.P. Bonte, P. Depreux, D.H. Caignard, M. Millan, A. Newman-Tancredi, P. Renard, M.C. Rettori, "Preparation of piperazinylmethylbenzothiazolinones, -benzoxazolinones, -benzoxazinones, and related compounds as central nervous system agents", *European Patent,* **1998**, EP 841330.

[4]. *H. Ucar, K. Van Derpoorten, S. Cacciaguerra, S. Spampinato, J.P. Stables, P. Depovere, M. Isa, B. Masereel, J. Delarge, J.H. Poupaert*, "Synthesis and Anticonvulsant Activity of 2(3*H*)-Benzoxazolone and 2(3*H*)-Benzothiazolone Derivatives", Journal of Medicinal Chemistry, **vol. 41**, 1998, pp 1138-1145

[5]. *J.H. Poupaert, P. Carato, E. Colacino, S. Yous*, "2(3*H*)-Benzoxazolone and bioisosters as

"Privileged Scaffold" in the design of pharmacological probes", Current Medicinal Chemistry, **vol. 12**, 2005, pp 877-885

[6]. *F. Guenadil, H. Aichaoui, C. N. Kapanda, D. M. Lambert, Ch. R. McCurdy, J. H. Poupaert*, "Design and synthesis of 3-acyl-2(3H)-benzoxazolone and 3-acyl-2(3H)-benzothiazolone derivatives", Monatshefte für Chemie, **vol. 142**, 2011, pp. 67-80

[7]. *L. Yingjun, Li. Chunyan, J. Kun, S. Shuqin, Z. Xiaoxia*, "Synthesis and Biological Activities of Novel Benzoxazolinone/Benzothiazolone Derivatives Containing Oxadiazole Moiety", Acta Chimica Sinica, **vol. 70**, no. 2, 2012, pp 151-160

[8]. *G. Zheng, T. Chen, X. Peng, Sh. Long*, "Synthesis, Anti-Inflammatory, and Analgesic Activities of Derivatives of 4-Hydroxy-2-benzoxazolone", Journal of Chemistry, **vol. 1**, 2015, pp 29-37

[9]. *M. S. Gerova, F. E. Svetoslavov, B. L. Shivachev, R. P. Nikolova, O. I. Petrov*, "Synthesis of 4-acetyl-2(3*H*)-benzothiazolone: Sulfur bioisostere of benzoxazolone allelochemicals", Phosphorus, sulfur and silicon, **vol. 192**, no. 8, 2017, pp 905-910

[10]. *G. Romeo, O. Prezzavento, S. Intagliata, V. Pittalà, M. N. Modica, A. Marrazzo, R. Turnaturi ,C. Parenti, S. Chiechio, E. Arena, A. Campisi, G. Sposito, L. Salerno,* "Synthesis, *in vitro* and *in vivo* characterization of new benzoxazole and benzothiazole-based sigma receptor ligands", European journal of medicinal chemistry, vol. 174, 2019, pp 226-235

[11]. *S. Bilginera, H. I. Gula, F. S. Erdala, H. Sakagamib, S. Leventc, I. Gulcind, C. T. Supurane*, "Synthesis, cytotoxicities, and carbonic anhydrase inhibition potential of 6-(3-aryl-2-propenoyl)-2(3H)-benzoxazolones", Journal of enzyme inhibition and medicinal chemistry, **vol. 34**, no. 1, 2019, pp 1722-1729

[12]. F. Guenadil, "$FeCl_3$-DMF complex as efficient catalyst for the synthesis of 6-acyl-2(3*H*)-benzoxazolones and 6-acyl-2(3*H*)-benzothiazolones", Bulletin of the Chemical Society of Ethiopia, **vol. 33**, no. 3, 2019, pp 579-585

[13]. V. Esmail, M. Somayeh, A. Morteza, *H. Akram, O. Parisa*, "Convenient and Robust Metal-Free Synthesis of Benzazole-2-Ones Through the Reaction of Aniline Derivatives and

Sodium Cyanate in Aqueous Medium", Iranian journal of chemistry and chemical engineering, **vol. 39**, no. 5, 2020, pp 11-19

[14]. *W. J. Close, B. D. Tiffany, M. A. Spielman*, "The Analgesic Activity of Some Benzoxazolone Derivatives", Journal of the American chemical society, **vol. 71**, no. 4, 1949, pp. 1265–1268

[15]. *C. Safak, H. Erdogan, E. Palaska, R. Sunal, S. Duru,* "Synthesis of 3-(2-pyridylethyl) benzoxazolinone derivatives: potent analgesic and antiinflammatory compounds inhibiting prostaglandin E2", Journal of medicinal chemistry, **vol. 35**, 1992, pp. 1296–1299

[16]. *D.S. Doğruer, S. Unlü, M.F. Sahin, E. Yeşilada*, "Anti-nociceptive and antiinflammatory activity of some (2-benzoxazolinone-3-yl and 2-benzothiazolone-3-yl)acetic acid derivatives". Il Farmaco**, vol. 53**, 1998, pp. 80–84

[17]. *S. Ünlüa, T. Önkola, Y. Dündara, B. Ökçelika, E. Küpelib, E. Ye¸Siladab, N. Noyanalpana, M. F. Sahin,* "Synthesis and Analgesic and Anti-inflammatory Activity of Some New (6-Acyl-2-benzoxazolinone and 6-Acyl-2-benzothiazolinone Derivatives with Acetic Acid and Propanoic Acid Residues", Archiv der Pharmazie**, vol. 336**, 2003, pp 353-361

[18]. *B. L. Deng, M. D. Cullen, Z. Zhou, T. L. Hartman, R. W. BuckheitJr, Ch. Pannecouque, E. De Clercq, Ph. E. Fanwick, M. Cushman,* "Synthesis and anti-HIV activity of new alkenyldiarylmethane (ADAM) non-nucleoside reverse transcriptase inhibitors (NNRTIs) incorporating benzoxazolone and benzisoxazole rings" Bioorganic & Medicinal Chemistry , **vol. 14**, no. 7, 2006, pp. 2366–2374.

[19]. *Y. Dündar, B. Çakir, M. F. Sahin*, " Synthesis of 2(3H)-benzothiazolinone derivatives as analgesic and anti-inflammatory agents", Turkish journal of pharmaceutical sciences**, vol. 3**, no. 2, 2006, pp 51-60

[20]. *M. Koksal, N. G. Kelekci, G. O. Mercanoglu, H. Erdogan*, "Synthesis and Evaluation of Analgesic, Anti-Inflammatory and Antioxidant Activities of New 6-Acyl-3-alkyl-5-methyl-2(3H) -benzoxazolones", Arzneimittelforschung, vol. 58, no. 8, 2008, pp 398-404

[21]. *N. Gökhan-Kelekçi, M. Köksal, S. Ünüvar, G. Aktay, H. Erdoğan*, "Synthesis and characterization of some new 2(*3H*)-benzoxazolones with analgesic and antiinflammatory activities", Journal of Enzyme Inhibition and Medicinal Chemistry, **vol. 24**, no. 1, 2008, pp 29-37

[22]. *Y. Mulazim, C. Berber, H. Erdogan, M. H. Ozkan, B. Kesanli*, "Synthesis and analgesic activities of some new 5-chloro-2(3H)-benzoxazolone derivatives", The Euro Biotech Journal, **vol. 1**, 2017, pp. 235–240

[23]. T. Hashihayata, H. Mandai, T. Mukaiyama, "6-Nitro-2-benzothiazolyl α-Glucoside and α-Mannoside in β-Selective Glycosylations", Bulletin of the Chemical Society of Japan, **vol. 77**, n.1, 2004, pp 169-178

[24]- *K. Seddiki, W. Yahia, M. Liacha, A. Defant, D. Sighel, I. Mancini*, "Microwave-assisted synthesis of new imide- and formamide-derivatives of 2(3H)-benzoxazolinones and 2(3H)-benzothiazolinones", Arkivoc**, vol. 4**, 2017, pp 315-329

[25]. *P. Carato, K. Cherry, N. Lebegue, P. Berthelot, S. Yous,* "Synthesis of 6-Cycloalkylcarbonyl-2(3H)-benzothiazolones via 6-Tributyltin Intermediates", Heterocycles, **vol. 71**, no.9, 2007, pp. 2041-2047

[26]. *G. Mairesse, J.C Boivin, D.J. Thomas, M.C. Bermann, J.P. Bonte, D. Lesieur,* "Structure de la benzoyl-6 dihydro-2,3 benzoxazole-1,3 one-2, C14H9NO3", Acta Crystallographica section C, **vol. 40**, 1984, pp 1019-1020

[27] *S. Yous, JH. Poupaert, I. Lesieur, P. Depreux, D. Lesieur,* " AlCl3-DMF Reagent in the Friedel-Crafts Reaction. Application to the Acylation Reaction of 2(3H)-Benzothiazolones" Journal of Organic Chemistry, **vol. 59**, no. 6, 1994, pp 1574-1576

[28] *H. Aichaoui, D. Lesieur, J.P. Henichart,* "A convenient and efficient method for the preparation of 6-acyl-2(3H)-benzoxazolones", Journal of Heterocyclic Chemistry, **vol. 29**, no. 6, 1994, pp 171-175

[29]. *H. Chabane, Y. Adjeroud, M. Liacha*, " Convenient synthesis and characterization of some novel benzothiazolone-based Schiff bases as potential pharmaceutically active agents", Journal of organic communication, **vol. 10**, no. 1, 2017, pp 24-31

[30]- *Y. Adjeroud, H. Chabane, M. Liacha*, " Comparative study of conventional and microwave-assisted synthesis of novel-6-(arylideneamino)benzo[d]oxazol-2(3*H*)-ones with potential antibacterial activity", Romanian Journal of Chemistry, **vol. 61**, no. 2, 2016, pp 111-17

[31] *M. Doumas, S. Rouillon, N. Venisse, C. Nadeau, P.P. Eugene, A. Farce. Ph. Chavatte, A. Dupuis, V. Migeot, P. Carato*, "Chlorinated and brominated bisphenol A derivatives: Synthesis, characterization and determination in water samples", Chemosphere, **vol. 213,** 2018, pp. 434-442