Accepted Manuscript

Synthesis of 4,5,6,7-tetrahydrobenzoxazol-2-ones by a highly regioselective Diels-Alder cycloaddition of *exo*-oxazolidin-2-one dienes with chalcones

Salvador Mastachi-Loza, Tania I. Ramírez-Candelero, Asenet Tapia-Bustamante, Carlos González-Romero, Eduardo Díaz-Torres, Joaquín Tamariz, Rubén A. Toscano, Aydeé Fuentes-Benítes

PII: S0040-4039(19)30364-8
DOI: https://doi.org/10.1016/j.tetlet.2019.04.027
Reference: TETL 50742

To appear in: *Tetrahedron Letters*

Received Date: 10 February 2019
Revised Date: 10 April 2019
Accepted Date: 15 April 2019

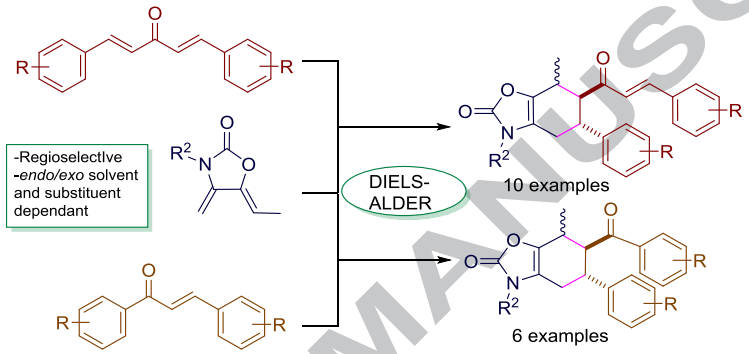
Please cite this article as: Mastachi-Loza, S., Ramírez-Candelero, T.I., Tapia-Bustamante, A., González-Romero, C., Díaz-Torres, E., Tamariz, J., Toscano, R.A., Fuentes-Benítes, A., Synthesis of 4,5,6,7-tetrahydrobenzoxazol-2-ones by a highly regioselective Diels-Alder cycloaddition of *exo*-oxazolidin-2-one dienes with chalcones, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.04.027

Graphical Abstract

Synthesis of 4,5,6,7-tetrahydrobenzoxazol-2-ones by a highly regioselective Diels-Alder cycloaddition of *exo*-oxazolidin-2-one dienes with chalcones.

Leave this area blank for abstract info.

Salvador Mastachi-Loza, Tania I. Ramírez-Candelero, Asenet Tapia-Bustamante, Carlos González-Romero, Eduardo Díaz-Torres, Joaquín Tamariz, Rubén A. Toscano and Aydeé Fuentes-Benítes.



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of 4,5,6,7-tetrahydrobenzoxazol-2-ones by a highly regioselective Diels-Alder cycloaddition of *exo*-oxazolidin-2-one dienes with chalcones.

Salvador Mastachi-Loza,[a] Tania I. Ramírez-Candelero,[a] Asenet Tapia-Bustamante,[a] Carlos González-Romero,[a] Eduardo Díaz-Torres,[a] Joaquín Tamariz,[b] Rubén A. Toscano [c] and Aydeé Fuentes-Benítes.*[a]

[a] *Facultad de Química, Universidad Autónoma del Estado de México, Paseo Tollocan y Colón S/N, 50000, Toluca, México.*
**E-mail: mpagfuentesb@uaemex.mx*
[b] *Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala S/N, 11340, CDMX, México.*
[c] *Instituto de Química, Universidad Nacional Autónoma de México, Circuito exterior, C.U. Coyoacán, 04510, CDMX, México*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Diels-Alder Reaction
Chalcone
Cyclization
Tetrahydrobenzoxazol-2-one
Benzoxazolone

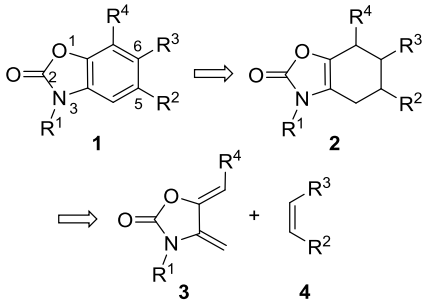
ABSTRACT

The synthesis of novel of 4,5,6,7-tetrahydrobenzoxazol-2-ones is herein reported. They were obtained in moderate to good yields by a highly regio- and stereoselective Diels-Alder cycloaddition of N-substituted exo-oxazolidin-2-one dienes with chalcones or bis-chalcones as dienophiles.

1. Introduction.

Benzoxazolones (BOAs) are biological important molecules isolated from many plants. The relevance of this heterocyclic framework for medicinal chemistry is evidenced by the descriptions over the last 30 years.[1] of its extensive bioactivity in natural and synthetic derivatives. Considered a privileged scaffold, BOAs display bioisosterism and have pharmacologial properties similar to a variety of molecules (e.g., phenylurethanes, cathecol derivatives and coumarins) with which they share structural resemblance.[2] Some of these properties are associated with the changes in substituents at the C_5 and C_6 positions of the skeleton.[3,4] Biological studies have demostrated that BOAs exhibit antibacterial,[5] antifungal, [6] analgesic, [7] anti-inflammatory, [8] anticonvulsant,[9] dopaminergic,[10] and reverse transcriptase inhibition activity.[11]

These heterocycles are usually synthesized by a condensation reaction of *o*-aminophenols with urea (as the classic procedure), or less commonly with 1,1'-carbonyldiimidazole,[12] ethyl cloroformate or phosgene.[13] Other methods involve Beckmann[14] or Lossen rearrangements[12] or a reaction between *N*-alkyl-*N*-arylhydroxylamine and trichloroacethyl chloride.[15] For instance, *N*-substituted benzoxazol-2-ones **1** can be prepared from the aromatization of 4,5,6,7-tetrahydrobenzoxazolones **2**, which are easily generated through a Diels-Alder addition between dienes **3** and diverse dienophiles **4** (Scheme 1).[16–18]



Scheme 1. Retrosynthesis for *N*-substituted benzoxazol-2-ones.

On the other hand, chalcones are a group of compounds of great interest because of their wide scope of biological activity.[19] They are characterized by a scaffold formed by two benzene rings attached to a 2-propen-1-one chain moiety. *Trans* isomer **5** is the most common configuration found in nature.[20,21] This family of compounds has structural diversity, exemplified by *bis*-chalcones 1,5-diarylpenta-1,4-dien-3-ones derivatives **6** that share several biological properties with chalcones **5** (Figure 1).

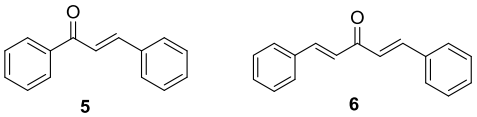


Figure 1. Core structure of chalcones **5** and *bis*-chalcones **6**.

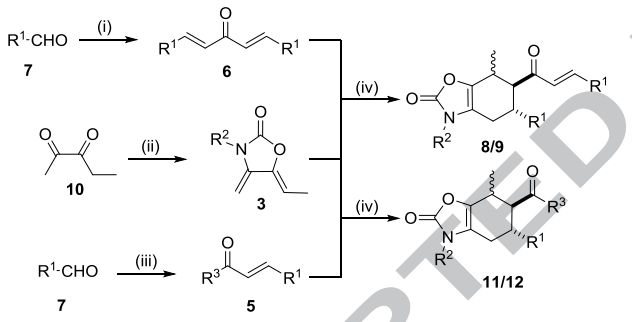
Due to the conjugated double bond to a carbonyl group and to a delocalized π-electron system of both benzene rings, chalcones exhibit low redox potential that allows them to undergo electron transfer reactions.[22] Consequently their diverse applications include their involvement in Diels- Alder rections either as dienophiles,[23–25] or as dienes[26] (the latter for hetero-Diels-Alder cycloadditions).

We herein present the synthesis of novel 5,6-substituted 4,5,6,7-tetrahydrobenzoxazol-2-ones **8, 9, 11** and **12** obtained by a Diels-Alder cycloaddition of *N*-substituted *exo*-oxazolidin-2-one dienes **3a-c** with chalcones **5a-g** and *bis*-chalcones **6a-f** (Scheme 2).

2. Results and Discussion.

A template (with its file name ending on .dot, rather than on .doc) in Word® is a "mold" that formats documents based on it. If you click 'New' on the 'File' menu, what you see and open are in fact templates. To use the *Tetrahedron Letters* template you should first save it with the other templates. To do this, click on 'New' on the 'File' menu, choose the 'General' tab and paste the template there. To create a new document, select the template, choose the Create New Document option, and double-click on the template icon. Save the document.

Dienes **3a-c** were synthesized by following the reported condensation reaction,[18,27] in this case with 2,3-pentanedione (**10**) and the corresponding arylisocyanate, in the presence of triethylamine as the base.



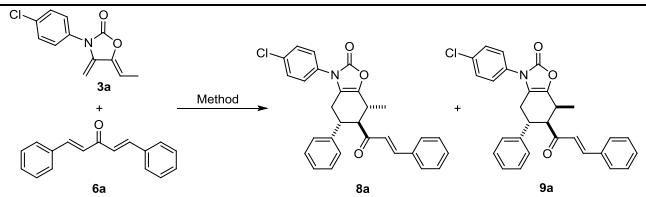
Scheme 2. Synthesis of tetrahydrobenzoxazol-2-ones. Reagents and conditions: i) acetone, NaOH aq. 10%, EtOH, rt; ii) R^1-NCO, triethylamine, Li_2CO_3, toluene; iii) R^3-$COCH_3$, NaOH aq. 10%, EtOH, rt; iv) MW, 180 °C or conventional heating (180 °C).

The preparation of the chalcone derivatives **5a-g** and *bis*-chalcones **6a-f** was carried out with the Claisen-Schmidt condensation.[28–31] By adding equimolar amounts of the corresponding ketone and aldehyde to a 10% aqueous solution of NaOH in ethanol as the solvent, the desired products were provided in good yields. Chalcones **5a-g** were afforded by the condensation reaction between acetone and the series of benzaldehydes **7**, and *bis*-chalcones **6a-g** by the reaction of acetophenone derivatives with benzaldehydes **7**.

Once having dienes and dienophiles on hand, three methods for evaluating Diels-Alder cycloaddition were tested by using equimolar amounts of compounds **3a** and **6a** (Table 1). Method A consisted of refluxing the reaction mixture in a water/methanol solution (entry 1), while method B and C involved heating at 180 °C with different energy sources (entries 2-3). The latter methods furnished higher yields and required shorter reaction times.

It is striking that in all reaction conditions employed, the cycloadditions proceeded with high regioselectivity, exclusively yielding the *ortho* isomers (relative to methyl and enone functional groups). However, the *endo*/exo stereoselectivity was lower, showing an inverse ratio when changing the polarity of the solvent. Thus, the *endo* isomer **9a** was the major isomer and displayed a greater selectivity with a polar mixture of solvents (method A), while the *exo* isomer **8a** was the main adduct (though in lower isomeric ratio) with toluene acting as the solvent.

Table 1. Methods for the Diels-Alder cycloaddition of **3a** with **6a**.

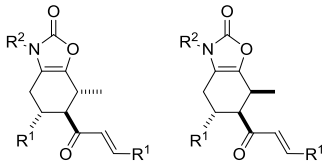


Method	Conditions [a]	Time (h)	Ratio 8/9 [b]	Yield (%)[c]
A	MeOH/H_2O (9:1)[d] reflux	72	22:78	25
B	toluene, 180 °C	24	65:35	86
C	toluene, 180 °C (MW)	0.5	63:37	79

[a]With **3a** (0.85 mmol) and **6a** (0.85 mmol). [b]Determined by ^{1}H NMR. [c]For the diastereoisomeric mixture. [d] Other mixtures were tested with no better results.

Following the reaction conditions established in methods A-C, the series of 4,5,6,7-tetrahydrobenzoxazol-2-ones **8/9** was prepared by utilizing *N*-substituted *exo*-heterocyclic dienes **3a-c** and *bis*-chalcones **6a-f** (Table 2). A change in *exo*/*endo* selectivity was observed with *ortho* substituents in the aromatic ring at C_5, even when toluene was used as the solvent (adducts **8**/**9-i**, **j** and **k**).

Table 2. Synthesized *exo*/*endo* tetrahydrobenzoxazol-2-ones **8** and **9**.



Adducts	Method	R^1	R^2	Ratio 8/9[a]	Yield (%)[b]
8b, 9b	C	phenyl	4-methoxyphenyl	50:50	85
8c, 9c	A	phenyl	phenyl	35:65	28
8d, 9d	B	4-methoxyphenyl	4-chlorophenyl	62:38	86
8e, 9e	B	4-methoxyphenyl	4-methoxyphenyl	63:37	91
8f, 9f	B	4-methoxyphenyl	phenyl	59:41	67
8g, 9g	C	2-thienyl	4-methoxyphenyl	50:50	86
8h, 9h	B	2-thienyl	4-chlorophenyl	55:45	72
8i, 9i	B	2-chorophenyl	phenyl	38:62	95
8j, 9j	B	2,3-dimethoxyphenyl	4-methoxyphenyl	15:85	91

8k,9k	B	2,6-dichlorophenyl	4-methoxyphenyl	<1:99	72

[a] Determined by ^{1}H NMR. [b] For the diastereoisomeric mixture.

Elucidation of the relative configuration of compounds **8**/**9** was achieved by 2D ^{1}H NMR experiments (COSY and NOESY), assigning the signals for the H_4-H_7 protons in the cyclohexene moiety. In the case of **8h** (Figure 2a), for example, the relative configuration of the C_7 methyl group was ascertained through the measurement of the coupling constants of the H_6 proton, the signal of which (3.12 ppm) is a large-sized doublet of doublet (*dd*, J = 11.2, 9.5 Hz). Hence, H_6 has *axial-axial* couplings with H_5 and H_7, meaning that the C_7 methyl, C_5 thiophenyl and C_6 thiophenylacryloyl groups adopt an *equatorial* conformation. This relative configuration was supported by a NOESY experiment, revealing cross peak/diagonal peak signals of H_7 with H_5 that indicate a spatial *syn-axial* relationship, leaving the C_5 thiophenyl and the C_7 methyl groups in a *syn-equatorial* relative configuration (Figure 2b).

For the isomer **9h**, the signal of the H_6 proton (3.74 ppm) is a *dd* (J = 10.7, 5.6 Hz), suggesting an *axial-axial* relationship with proton H_5 and *axial-equatorial* relationship with H_7. Therefore, the C_7 methyl group adopts an axial conformation. This was confirmed as the NOESY experiment shows cross peak/diagonal peak signals for a dipolar interaction of the C_7 methyl group with H_5, reflecting a spatial *syn-axial* relationship between them.

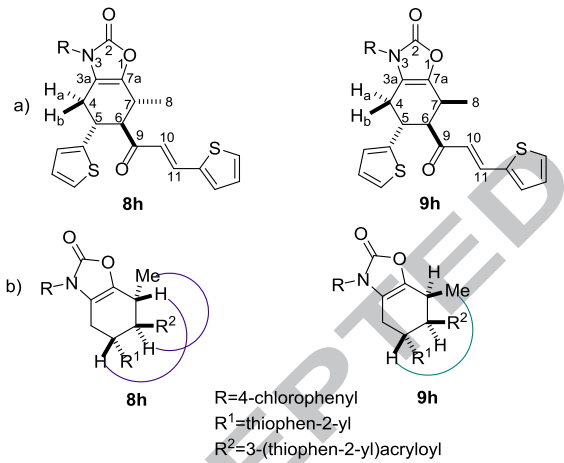


Figure 2. a) Structures for compounds **8h** and **9h** b) NOESY correlations for compounds **8h** and **9h**.

This structural assignment was further supported by an X-ray diffraction crystallographic analysis of the major diastereoisomer **9i** (Figure 3), in which the C_7 methyl group showed a *syn* relationship to the C_6 cinnamoyl and an *anti* relationship to the C_5 aryl groups.

All compounds in the **8**/**9** series displayed similar chemical shifts and NMR patterns of multiplicity, as well as NOESY spatial relationships. . For compound **9k**, however, the chemical shifts of protons H_5 (4.41 ppm) and H_6 (4.84 ppm) underwent a stronger deshielding effect than that observed for other compounds (ca. 3.50 and 3.70 ppm). This behavior may be accounted for by a plausible restricted rotation of the C_5 aryl ring, leaving the chlorine atoms close to those protons as suggested by ^{1}H NMR. In such a case, the paramagnetic anisotropic effect of the chlorine atoms attached at the C_{19} and C_{23} atoms would alter the magnetic environment of the protons at C_5 and C_6 (Figure 4). As a consequence of the restricted rotation of the C_5 aryl ring, the aromatic protons H_{20} and H_{22} would become magnetically nonequivalent, as was indeed shown by their signals with a significant Δδ for H_{20} (7.16 ppm, dd, J = 8.1, 1.0 Hz), H_{22} (7.34 ppm, dd, J = 8.1, 1.0 Hz) and H_{21} (7.06 ppm, t, J = 8.1 Hz). This possibility is supported by the fact that the aromatic B ring protons H_{14} and H_{16} are magnetically equivalent (7.35 ppm, d, J = 8.1 Hz), as is H_{15} (7.20 ppm, t, J = 8.1 Hz), indicating a C_{11}-C_{12} free bond rotation.

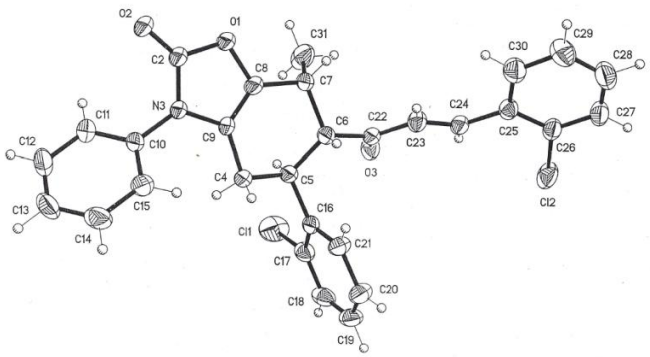


Figure 3. ORTEP plot for **9i**.

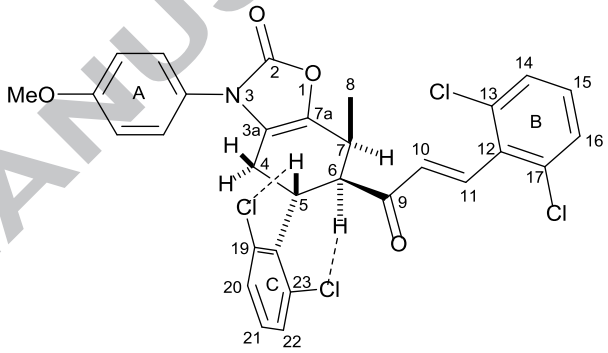
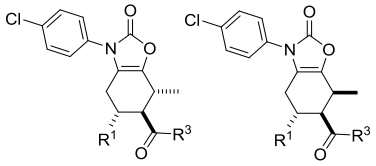


Figure 4. Compound **9k.**

Chalcones **5a-g** were also evaluated as dienophiles in the Diels-Alder reaction with diene **3a** under the conditions of method B (Table 1, entry 3), to afford a series of tetrahydrobenzoxazol-2-ones **11**/**12** (Table 3). Interestingly, there was a preference of these compounds for the *endo* versus *exo* adduct, except with adducts **11**/**12c,d**. The latter compounds have a 4-methoxyphenyl group in R^1 with *endo*/*exo* ratios close to 1:1, revealing no clear preference for either of the isomers. General *endo* preference could be explained by the change of the cinnamoyl group at C_6, present in compounds **8**/**9**, thus changing the steric repulsive effects and secondary orbital interactions between diene and dienophile in the transition state during the formation of compounds **11**/**12**.[32]

The reaction led to results analogous to those for **8**/**9**. The products were characterized by 2D ^{1}H NMR analysis (COSY and NOESY) as a mixture of diastereoisomers **11**/**12**. The reaction was regioselective, leading only to *ortho* isomers (with the acyl group at C_6). The relative configuration of the adducts was established by examining the H_6 proton signal, which displayed coupling constants and multiplicity similar to those found with the same proton in **8**/**9**. The NOESY experiment gave an analogous finding regarding the *syn* spatial interactions. The structure of the adducts was also confirmed by an X-ray diffraction crystallography analysis for the minor diastereoisomer **11a** (Figure 5).

Table 3. Synthesized *exo*/*endo* tetrahydrobenzoxazol-2-ones **11**/**12**.



11 **12**

Adducts	R^1	R^3	Ratio **11**/**12**[a]	Yield (%)[b]
11a, 12a	4-methylthiophenyl	4-methylphenyl	12:88	45
11b, 12b	2,4-dichlorophenyl	4-methylphenyl	13:87	83
11c, 12c	4-methoxyphenyl	4-methylphenyl	54:46	61
11d, 12d	4-methoxyphenyl	phenyl	53:47	46
11e, 12e	phenyl	phenyl	45:55	62
11f, 12f	4-methylthiophenyl	4-chlorophenyl	23:74	56
11g, 12g	2,4-dichlorophenyl	3-methoxyphenyl	<1:99	93

[a] Determined by ^{1}H NMR. [b] For the diastereoisomeric mixture.

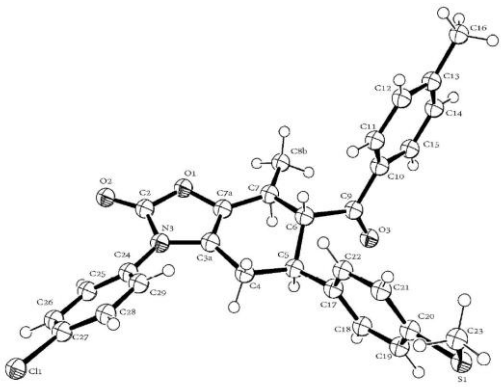


Figure 5 ORTEP plot for **11a**.

3. Conclusions.

The synthesis is herein described, for the series of 5,6-substituted 4,5,6,7-tetrahydrobenzoxazol-2-ones **8**/**9** and **11**/**12** via a highly regioselective Diels-Alder cycloaddition. The *endo/exo* stereoselectivity of compounds **8**/**9** was dependent on the solvent, polarity and substituents. An *endo* preference existed when using the solvent with the strongest polarity and an *exo* preference with the nonpolar solvent, except for the adducts bearing C_6-2,4-dichlorophenyl, C_6-2-chlorophenyl or C_6-2,3-dimethoxyphenyl substituents. On the other hand, compounds **11**/**12** showed *endo* preference with the nonpolar solvent. The adduct structures and relative configuration were established through NMR spectroscopic and X-ray diffraction analyses. Synthetic applications of these novel compounds are currently underway, and the results will be reported in due time.

4. Acknowledgments.

Financial support from UAEMéx (project No.4512/2018/CI) and CONACyT (postgraduate scholarship grant No. 401195) is gratefully acknowledged. J.T. is thankful to the SIP/IPN (grant 20180198) and CONACYT (grant 178319) for financial support. The authors would like to thank Dr. Davir González-Calderón, M. en C. Nieves Zavala-Segovia, and Lizbeth Triana-Cruz (CCIQS UAEMéx–UNAM), Instituto de Química UNAM as well as Luis Velasco, Javier Pérez, Hector Rios, María I. Chavez, Beatriz Quiroz and Mario Alfredo Garcia Carrillo for technical assistance. J.T. is a fellow of the EDI-IPN and COFAA-IPN programs.

5. References and notes.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk). CCDC registry number for **8i/9i**: 1033700. CCDC registry number for **11a**: 1882393.

1. Aichaoui H, Guenadil F, Kapanda CN, Lambert DM, McCurdy CR, Poupaert JH. Med Chem Res. 2008; 18: 467–476.
2. Poupaert J, Carato P, Colacino E. Curr Med Chem. 2005; 12: 877–885.
3. Tang L, Ban SR, Feng XE, Lin WH, Li QS. Chin Chem Lett. 2010; 21: 63–66.
4. Friebe A, Vilich V, Hennig L, Kluge M, Sicker D. Appl Environ Microbiol. 1998; 64: 2386–2391.
5. Soyer Z, Eraç B. J Pharmacol Sci. 2007; 32: 167–171.
6. Kaplancikli ZA, Turan-Zitouni G, Revial G, Guven K. Arch Pharm Res. 2004; 27: 1081–1085.
7. Gökhan N, Erdoğan H, Durlu NT, Demirdamar R. Il Farm. 1999; 54: 112–115.
8. Gökhan-Kelekçi N, Köksal M, Ünüvar S, Aktay G, Erdoğan H. J Enzyme Inhib Med Chem. 2009; 24: 29–37.
9. Ucar H, Van derpoorten K, Cacciaguerra S, Spampinato S, Stables JP, Depovere P, Isa M, Masereel B, Delarge J, Poupaert JH. J Med Chem. 1998; 41: 1138–1145.
10. Weinstock J, Gaitanopoulos DE, Stringer OD, Franz RG, Hieble JP, Kinter LB, Mann WA, Flaim KE, Gessner G. J Med Chem. 1987; 30: 1166–1176.
11. Deng B-L, Cullen MD, Zhou Z, Hartman TL, Buckheit Jr. RW, Pannecouque C, Clercq ED, Fanwick PE, Cushman M. Bioorg Med Chem. 2006; 14: 2366–2374.
12. Gerova MS, Stateva SR, Radonova EM, Kalenderska RB, Rusew RI, Nikolova RP, Chanev CD, Shivachev BL, Apostolova MD, Petrov OI. Eur J Med Chem. 2016; 120: 121–133.
13. Piomelli, D., Pizzirani, D., Bach, A., Scarpelli, R., Melzig, L., Mor, M.United States, US20170182009A1 2017.
14. Kalcheva V, Lozanova K, Simov D, Terent'ev PB. Chem Heterocycl Compd. 1985; 21: 985–987.
15. Ram RN, Soni VK. J Org Chem. 2013; 78: 11935–11947.
16. Bautista R, Bernal P, Montiel L, Delgado F, Tamariz J. Synthesis. 2011; 6: 929–933.
17. González-Romero C, Bernal P, Jiménez F, Cruz MC, Fuentes-Benites A, Benavides A, Bautista R, Tamariz J. Pure Appl Chem. 2007; 79: 181–191.
18. Mandal AB, Gómez A, Trujillo G, Méndez F, Jiménez HA, Rosales MJ, Martínez R, Delgado F, Tamariz J. J Org Chem. 1997; 62: 4105–4115.
19. Nowakowska Z. Eur J Med Chem. 2007; 42: 125–137.
20. Srinivasan B, Johnson TE, Lad R, Xing C. J Med Chem. 2009; 52: 7228–7235.
21. Bazzaro M, Anchoori RK, Mudiam MKR, Issaenko O, Kumar S, Karanam B, Lin Z, Isaksson Vogel R, Gavioli R, Destro F, Ferretti V, Roden RBS, Khan SR. J Med Chem. 2011; 54: 449–456.
22. Patil CB, Mahajan SK, Katti SA. ChemInform. 2010; 41: i.
23. Corbett JL, Weavers RT. Synth Commun. 2008; 38: 489–498.
24. Büldt LA, Wenger OS. Chem Sci. 2017; 8: 7359–7367.
25. Nasir SB, Tee JT, Rahman NA, Chee CF. In Flavonoids - From Biosynthesis to Human Health; G. C. Justino, Ed.; InTech, 2017;
26. Lv H, Mo J, Fang X, Chi YR. Org Lett. 2011; 13: 5366–5369.
27. Fuentes A, Martínez-Palou R, Jiménez-Vázquez HA, Delgado F, Reyes A, Tamariz J. Monatshefte Für Chem. 2005; 136: 177–192.
28. Palaniappan A, Udhayakumar R, Srinivasan S, Raju C. J Chem Pharm Res. 2012; 4: 2385.
29. Awasthi SK, Mishra N, Kumar B, Sharma M, Bhattacharya A, Mishra LC, Bhasin VK. Med Chem Res. 2009; 18: 407–420.
30. Sebti S, Solhy A, Tahir R, Boulaajaj S, Mayoral JA, Fraile JM, Kossir A, Oumimoun H. Tetrahedron Lett. 2001; 42: 7953–7955.
31. Rayees Ahmad M, Girija Sastry V, Bano N, Anwar S. Arab J Chem. 2016; 9: S931–S935.
32. Fringuelli F, Taticchi A. The Diels-Alder Reaction: Selected Practical Methods, John Wiley & Sons, 2002.

Highlights

- Synthesis of novel 4,5,6,7-tetrahydrobenzoxazol-2-ones
- Highly regioselective Diels-Alder cycloaddition
- The *endo/exo* stereoselectivity of synthetized compounds was dependent on the solvent, polarity and substituents.