Insights on the synthesis and stereochemistry of benzoxazoles obtained from ketene dithioacetals

Maxwel E. Bille (G),[1] Ana Júlia Ferrugini Souza (G),[1] Rodrigo S. Correa (PQ),[2] Julliane Yoneda (PQ),[1] Diego Pereira Sangi (PQ) [1]*

[1] Departamento de Química, Instituto de Ciências Exatas, Universidade Federal Fluminense. [2] Departamento de Química, Instituto de Ciências Exatas e Biológicas, Universidade Federal de Ouro Preto. *dpsangi@id.uff.br

RESUMO (Times New Roman, tam 12)

Benzoxazoles are a very interesting class of heterocyclic compounds, due their important applications in biological sciences. Ketene dithioacetals are substrates to double vinylic substitution allowing the synthesis of some heterocycles, including benzoxazoles. An experimental and theoretical study was carried out to investigate benzoxazole synthesis via ketene dithioacetals, understanding the scope of the method and stereochemistry aspects. The single-crystal X-ray diffraction for compound **15** confirms the composition and stereochemistry, in which an *E*-isomer configuration is observed.

Keywords: Ketene dithioacetals, Benzoxazoles, Synthesis, X-ray diffraction, Theoretical calculations.

Introduction

N-heterocyclic compounds are renowned for their broad spectrum of biological activities, attributed to their relative conformational stability and charge distribution, which contribute to enhancing pharmacodynamic properties. Benzoxazoles are among the oldest *N*-heterocyclic compound classes, consisting of a bicyclic structure formed by the union of a benzene and an oxazolidine. They constitute an important class of chemical entities in life sciences, regarded as privileged structures for their ability to serve as ligands for various biological targets. Figure 1 presents some drugs containing benzoxazole scaffolds in their structure (1-3).

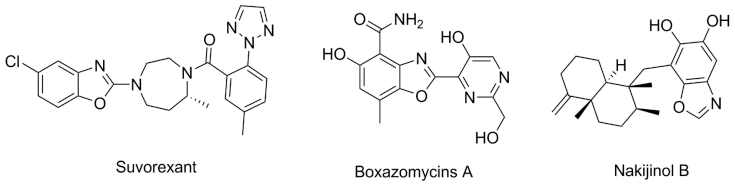

Figure 1. Examples of drugs containing benzoxazole heterocycles.

Ketene dithioacetals are important building blocks on organic synthesis, facilitating the obtaining of many different heterocyclic compounds as benzoxazoles that are synthesized by double vinylic substitution (4,5). In the present report we carried experimental and theoretical studies about vinylic substitution on ketene dithioacetals, in order to produce 2-substituted benzoxazole derivatives, understanding the scope of the method and to gain insights about structural and stereochemistry aspects.

Experimental

General procedure for the synthesis of benzoxazole derivatives

In a microwave-compatible glass vessel, polarized dithioacetal (**1**-**7**) (1 mmol) and 2-aminophenols (1 mmol) were suspended in ethanol (3 mL). The mixture was irradiated with microwaves for 60 minutes, maintaining a temperature of 110 °C with constant stirring.

At the end of the reaction, the solvent was evaporated, and the products described below were obtained in pure form after chromatography column and recrystallization.

The data from the infrared spectroscopy, mass spectrometry and nuclear magnetic resonance spectra of hydrogen (^{1}H NMR) and carbon (^{13}C NMR) that were used to identify the synthesized compounds are as follows.

Molecular Modeling

The structures of the ketene dithioacetals were constructed using the *Spartan'10* software[13] and optimized with Merck Molecular Force Field (MMFF). The optimized structures were submitted to a conformational analysis, using the Austin Method 1 (AM1) Hamiltonian at *Spartan*. The lowest-energy conformer for each compound was submitted to a full geometry optimization by using B3LYP/6-311++G(d,p) level of theory in *Gaussian 16W* program[14]. The physicochemical descriptors as The energy gap ($\Delta E = E_{LUMO} - E_{HOMO}$), chemical potential ($\mu$), chemical hardness ($\eta$), global softness (S), absolute electronegativity (χ), electrophilicity index (ω) and nucleophilicity index (N) were calculated from the optimized structures.

Benzoxazole derivatives structures with double bonds inside and outside the ring were constructed and optimized with the AM1 method in the *Gaussian 16W* program. After that, the N-C=C-R dihedral angle was scanned in steps of 30° with density functional theory at B3LYP/6-31G(d,p) level. The Gibbs free energy of the most stable conformer of each structure was obtained after its optimization and frequency calculation at B3LYP/6-311++G(*d*,*p*) level of theory in the same program.

Results and Discussion

Using 2-aminophenols as nucleophiles it could be possible to produce benzoxazole derivatives, by double vinylic substitution of the methylsulfanyl groups (Fig. 3). However, only dithioacetals **1**, **4** and **6** reacted to produce the benzoxazoles (**8**-**16**).

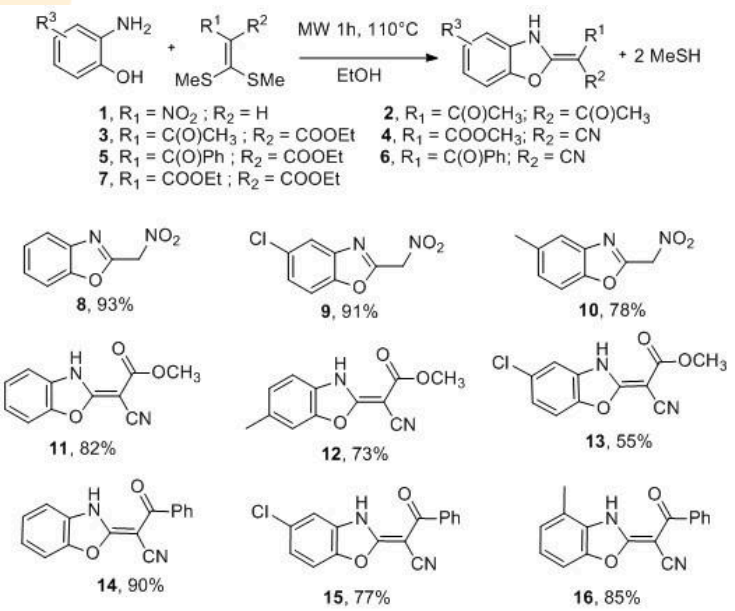

Figure 2. Synthesis of benzoxazole derivatives (**8-16**).

These results lead to three questions: (i) Why didn´t ketene dithioacetals **2**, **3**, **5** and **7** react?; (ii) Why are benzoxazoles **8-10** aromatic while in derivatives **11-16** the double bond resonates with electron withdrawing groups?; (iii) In case of derivatives **11-16**, what stereoisomers E or Z are produced effectively?. Crystallographic X-ray diffraction and computational calculations were carried out in an attempt to understand these issues.

Global reactivity descriptors can elucidate the overall structure, reactivity, and bonding of molecular motifs. Literature data show that these physicochemical descriptors can be related to reactivity of organic compounds. Considering this, some reactivity descriptors, such as energy gap (ΔE), chemical potential (μ), chemical hardness (η), global softness (S), absolute electronegativity (χ), electrophilicity index (N) and nucleophilicity index (ω), were calculated in order to rationalize why ketene dithioacetals **2**, **3**, **5** and **7** didn´t react. The results are in Table 1.

Table 1. Calculated global reactivity descriptors for ketene dithioacetals (**1-7**).

	ΔE	μ	η	S	χ	ω	N
1	**4.1984**	**-4.8816**	**4.1984**	**0.2382**	**4.8816**	**2.8379**	**2.5092**
2	4.8262	-4.0915	4.8262	0.2072	4.0915	1.7343	2.9854
3	4.3280	-4.3616	4.3280	0.2311	4.3616	2.1977	2.9644
4	**4.3182**	**-4.6435**	**4.3182**	**0.2316**	**4.6435**	**2.4967**	**2.6874**
5	4.4170	-4.2025	4.4170	0.2264	4.2025	1.9993	3.0790
6	**4.0779**	**-4.7247**	**4.0779**	**0.2452**	**4.7247**	**2.7371**	**2.7263**
7	5.1707	-4.0439	5.1707	0.1934	4.0439	1.5813	2.8608

The results on Table 1 allows a good rationalization for the experimentally observed reactivity. Larger energy gaps ($\Delta E = E_{LUMO} - E_{HOMO}$), higher hardness (η) and lower softness (ω) correspond to lower reactivity. As compounds **1**, **4** and **6** present the lower values of gap and hardness, combined with higher softness, they are the more reactive ones.

Concerning on the question of aromaticity of benzoxazoles **8-10**, which is not observed for **11-16**, relative stabilities were calculated for compounds **8**, **11** and **14** with the double bond inside and outside the ring, after scanning the N-C=C-R dihedral angle in steps of 30°. The energies were computed for the most stable conformations and are presented in Table 2.

Table 2. Relative energies and standard Gibbs free energies for benzoxazoles **8**, **11** and **14** with the double bond inside (**A**) and outside (**B**) the ring calculated at B3LYP/6-311++G(*d*,*p*) level of theory.

	8A	**8B**	**11A**	**11B**	**14A**	**14B**
E_{rel} (kcal mol^{-1})	0	4.9	10.6	0	11.1	0
$G°_{rel}$ (kcal mol^{-1})	0	2.1	8.8	0	9.7	0

The aromaticity of benzoxazoles **8-10**, represented by compound **8**, is observed experimentally because the form **8A** (with the double bond inside the ring) is more stable than **8B**, unlike compounds **11** and **14**, for which the **B** form, with the double bond outside the ring, is the most stable one according to B3LYP/6-311++G(*d*,*p*) calculations.

Ketene dithioacetals **4** and **6** resulted in derivatives **11-16**, interestingly, all of them in one unique stereoisomer. In order to understanding this, we recently used DFT calculations to demonstrate that the rotational barriers are 20 (Z → E) to 35 (E → Z) kcal mol^{-1}, which prevents fast, free rotation at room temperature, and the *E* isomer is the single form observed experimentally because it is 6 - 8 kcal mol^{-1} more stable than the *Z* isomer (6).

To support theoretical calculations, single crystals of compound **15** were obtained and analyzed by single-crystal X-ray diffraction (Figure 4). The crystal structure reveals a well-resolved monoclinic crystal system in the $P2_1/n$ space group, with good-quality refinement, corroborating with E isomer.

Conclusions

Ketene dithioacetals **1**, **4** and **6** demonstrated to be good substrates to synthesize benzoxazoles as demonstrated by their calculated reactivity descriptors, which indicated higher softness, lower hardness and lower energy gap, giving them higher reactivity among the other ketene dithioacetals studied. The DFT calculations corroborate with exo double bond to structures **11-16** once that the resonance outside of the ring brings more stability than the aromaticity according to calculated relative energies. Crystal structure of **15** confirms the *E*-isomer stereochemistry, as expected according to the experimental and theoretical studies.

Acknowledgements

To the Fluminense Federal University for the support

References

1. D. P. Sangi. *Química Nova,* **2016**, 39(8), 995-1006.
2. C. S. Demmer, L. Bunch. *Eur. J. Med. Chem.* **2015**, 97: 778-785.
3. M. E. Welsch; S. A. Snyder; B. R. Stockwell, *Curr Opin Chem Biol.* **2010**, 14(3):347-61.
4. L Huang, J. Wu, J. Hu, Y. Bi, D. Huang. *Tetrahedron Lett.* **2020**, 61: 151363.
5. L. Baliza et. al. *Chem Biol Drug Design,* **2024**, 104: e14581.
6. M. P. Freitas et al. *An. Acad. Bras. Ciênc.* **2024** 96(3) e20240156.