JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

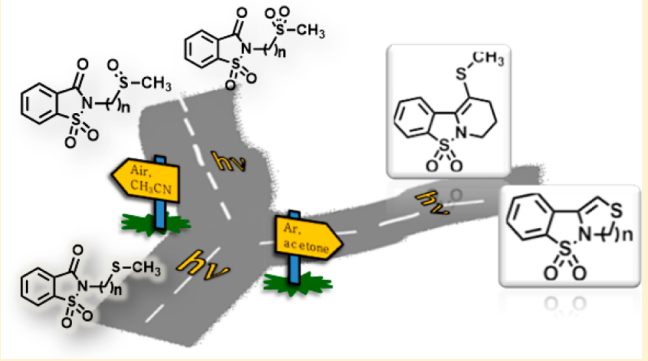
Exploring the Photophysical and Photochemical Properties of *N*-(Thioalkyl)-saccharins as an Alternative Route to the Synthesis of Tricyclic Sultams

Willber D. Castro-Godoy, Gabriela Oksdath-Mansilla,* Juan E. Argüello,* and Alicia B. Peñéñory

INFIQC−CONICET-UNC, Dpto. de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, X5000HUA Córdoba, Argentina

Supporting Information

ABSTRACT: Photocyclization of *N*-(thioalkyl)-saccharin was carried out to obtain different polycyclic sultams in good yields. These photoreactions were efficient under inert atmosphere and acetone triplet-sensitized conditions indicating that the triplet excited state is directly involved in the formation of annulated products. The presence of molecular oxygen changes product distribution, and only photo-oxygenation products (sulfoxides and sulfones) were found. This result is especially valuable since, by simple changing from nitrogen- to oxygen-saturated solvent conditions, the reaction outcome can be tuned from cyclized to sulfur oxidation products. Additionally, steady-state photolysis, electrochemistry, and laser time-resolved spectroscopic studies confirmed that these reactions mainly proceeded by intramolecular electron transfer (ET) between the triplet excited saccharin moiety and sulfur atom.



INTRODUCTION

Sultams are important types of heterocyclic sulfonamide compounds due to their pharmaceutical and industrial importance.[1] Within this context, saccharins play a special role because they already have the sulfonamide functionality in the heterocyclic system. Their derivatives are important pharmaceuticals with a broad spectrum of biological activities and have been used as inhibitors of kinase,[2] human mast cell tryptase[3] and tyrosinase,[4] histone deacetylase,[5] α**1**a and α**1**c adrenergic receptor antagonists,[6] antianxiety and antibacterial agents.[7] More recently it has been shown that saccharin and saccharin-based compounds selectively bind to tumor-associated carbonic anhydrases.[8] Furthermore, saccharin forms salts with different active pharmaceutical ingredients resulting in highly water-soluble saccharinate, which can act as a potent sweetener able to mask the bitter taste of many drugs.[9] In addition, certain substituted saccharin derivatives have been used as intermediates in the preparation of the 4-hydroxy-1,2-benzothiazine 1,1-dioxide (oxicam) ring system, a ring-expanded saccharin derivative with significant anti-inflammatory properties.[10]

Considering the diverse roles of saccharin derivatives, many powerful methodologies have been developed for their synthesis.[11] *N*-substitution and benzene moiety functionalization are significant components of the strategic approach to the saccharin ring system. However, only a limited number of methods describing the synthesis of unsubstituted or substituted fused polycyclic sultams have been reported so far.[12]

On the other hand, synthetic organic photochemistry constitutes a research area with exceptional importance for the development of efficient and selective transformations for the preparation of natural products as well as molecules with high structural complexity.[13] As a general rule, the redox properties of molecules are affected by light absorption where a photoexcited molecule is often a better electron donor or electron acceptor than its ground state. Single electron transfer (SET) between electron donors and acceptors to produce ion-radical intermediates, will be thermodynamically and kinetically favored when redox potentials and excited state-energies are appropriate. Photoinduced electron transfer is a powerful tool for the synthesis of novel organic compounds that may be difficult to obtain by other methods.[14]

The known light-induced reactions of saccharin, *N*-alkylsaccharins and 3,3-disubstituted 2,3-dihydro-1,2-benzisothiazole 1,1-dioxides take place preferentially via homolytic N−S bond cleavage pathways, resulting in formation of benzamide through extrusion of SO_2. For the case of 3,3-disubstituted 2,3-dihydro-1,2-benzisothiazole 1,1-dioxides, a formal oxygen shift from S to N, generating cyclic *N*-hydroxysulfinamides, was also observed.[15] Additionally, the intermolecular photoreaction of saccharin with α-silylamine has demonstrated that photo-

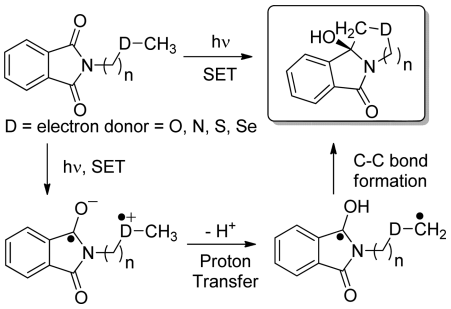
Received: September 3, 2016
Published: December 14, 2016

DOI: 10.1021/acs.joc.6b02171
J. Org. Chem. 2017, 82, 101−108

products are generated via SET pathways in addition to the homolytic N−S bond cleavage process.[16] More recently, the intramolecular photoreaction of *N*-[(trimethylsilyl)alkyl]-saccharins in solution was studied, showing a competitive silyl group transfer, homolysis of the S−N bond and H-abstraction processes, whose relative contribution depends on the reaction conditions.[17] Finally, photoisomerization of saccharin isolated in solid argon has been reported, affording a structural rearrangement when subjected to a narrow-band ultraviolet irradiation.[18]

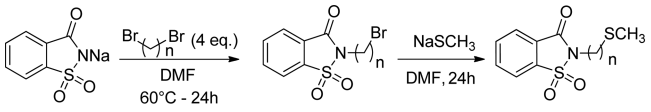
On the other hand, phthalimides are known to participate in different photoreactions including photoreduction, photoaddition, photocyclization, and Norrish type I and II reactions.[19] In particular, photocyclization of *N*-substituted phthalimides can be used in the synthesis of heterocyclic compounds with new rings containing one nitrogen atom,[20] two nitrogen atoms,[21] a nitrogen and an oxygen atom,[22] a nitrogen and a sulfur atom,[23] or a nitrogen and a selenium atom.[24] The key step in these reactions is an ET from the side-chain localized heteroatom to the electronically excited phthalimide chromophore, followed by proton transfer to the ketyl radical anion and combination of the (1,*n*) biradical thus formed (Scheme 1).

Scheme 1. General Mechanism for the Photocyclization of Phthalimide with Different Electron Donors



In contrast to the many reports describing the intramolecular photocyclization of phthalimides, a few studies on the photochemistry of sulfonamide derivatives (e.g., saccharin) and their involvement in SET reactions can be found. Thus, in order to explore new photoinduced SET reactions with synthetic value; we have investigated the photocyclization reactions of *N*-(thioalkyl)-saccharins **1a−c** (Scheme 2). In addition, the photochemical, photophysical and electrochemical properties of these compounds were studied by means of preparative irradiation, cyclic voltammetry, and time-resolved spectroscopy experiments.

Scheme 2. Synthesis of Starting Materials *N*-(Thioalkyl)-saccharins (1a−c)



N-(haloalkyl)-saccharin
(n = 3, 82%)
(n = 4, 79%)
(n = 5, 75%)

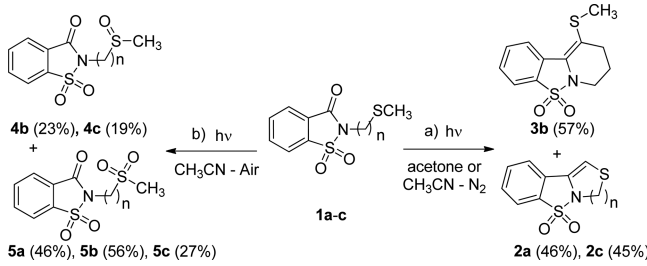
N-(thioalkyl)-saccharin
1a (n = 3) 34%
1b (n = 4) 56%
1c (n = 5) 46%

RESULTS AND DISCUSSION

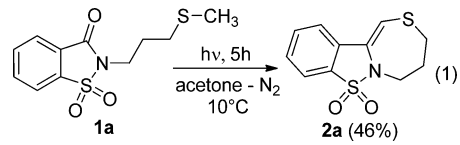
Synthesis of *N*-(Thioalkyl)-saccharins 1a−c. *N*-(thioalkyl)-saccharins were efficiently prepared by reaction of saccharin sodium salt with the corresponding 1,*n*-dihaloalkane. Subsequently, *N*-(haloalkyl)-saccharins were substituted with sodium methyl sulfide in dimethylformamide (DMF) (Scheme 2).

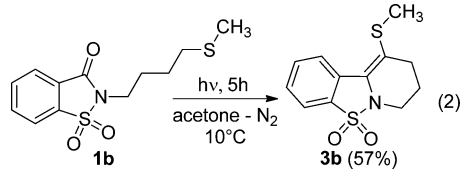
Steady-State Photoreaction of *N*-(Thioalkyl)-saccharins 1a−c. It is known that the photocyclization of *N*-(thioalkyl)-phthalimide systems involving ET process is more efficient from the triplet excited state, whereas the singlet excited state preferentially gives reverse electron transfer (RET).[25] For comparative reasons, photochemical reactions of saccharins under study were carried out in acetonitrile and solvent-sensitized conditions; the effect of the oxygen was also investigated (Scheme 3).

Scheme 3. Photoreaction Pathways for *N*-(Thioalkyl)-saccharins (1a−c)

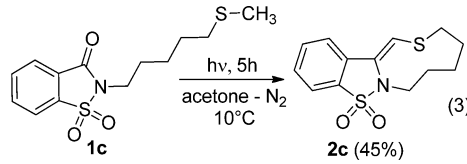


Irradiation of an acetone solution of *N*-(methylthiopropyl)-saccharin **1a** ($n = 3$) at $\lambda = 300$ nm under N_2 atmosphere gave rise to the corresponding annulated endocyclic sulfur-containing product **2a** in 46% isolated yield (eq 1 and entry 1 in Table 1). On the other hand, only the annulated exocyclic sulfur-containing product **3b** was detected in the photolysis of *N*-(methylthiobutyl)-saccharin **1b** ($n = 4$), in 57% isolated yield under the same condition (eq 2 and entry 4 in Table 1).





Additionally, when a solution of *N*-(methylthiopentyl)-saccharin **1c** ($n = 5$) was irradiated, the macrocyclic product **2c** with the sulfur atom in endo position was obtained in 45% isolated yield (eq 3 and entry 7 in Table 1). In all cases, the



DOI: 10.1021/acs.joc.6b02171
J. Org. Chem. 2017, 82, 101−108

Table 1. Photoreaction of *N*-(Thioalkyl)-saccharins 1a−c[a]

entry	compound	solvent	Cvn (%)	product yield (%)[b]			
1	**1a**	Acetone	100	**2a** (46)			
2		CH_3CN	11	**2a** (3)[c]			
3		CH_3CN[d]	78				**5a** (46)
4	**1b**	Acetone	100		**3b** (57)		
5		CH_3CN	21		**3b** (12)[c]		
6		CH_3CN[d]	82			**4b** (23)	**5b** (56)
7	**1c**	Acetone	100	**2c** (45)			
8		CH_3CN	37	**2c** (17)[c]			
9		CH_3CN[d]	50			4c (19)	**5c** (27)

[a]Photolysis was carried out in nitrogen-saturated atmosphere, otherwise indicated, for 5h, at λ = 300 nm in a photochemical reactor, using acetone as solvent at 10 °C, or at λ = 254 nm when CH_3CN was used as solvent. Concentrations of reactant **1a−c** were 2−5 mM. [b]Isolated yields. [c]Yields were determined by CG chromatography based on consumed reactant. [d]Photolysis was carried out in air-saturated atmosphere.

reaction was selective and photocyclized products with concomitant dehydration were observed. Therefore, for n = 3 and 5, sulfur endocyclic products were found, while for n = 4, only the exocyclic-SCH_3 product was observed (Scheme 3, pathway a).

In order to evaluate the difference between singlet and triplet excited state reactivity of *N*-(thioalkyl)-saccharins, the photoreactions of **1a−c** were evaluated under direct excitation conditions (using acetonitrile as solvent). These results were then compared with those of solvent-sensitized (acetone) reactions. Hence, the nitrogen saturated solution of **1a** in CH_3CN was irradiated at λ = 254 nm, giving rise to product **2a** in 3% yield. In exactly the same experimental conditions **1b** afforded the annulated product **3b** and **1c** gave **2c** in only 12% and 17% yields, respectively. In all cases, product distribution was unchanged. However, conversions and product yields were significantly reduced going from solvent-sensitized to direct irradiation conditions, indicating that under the latter conditions another energy wasting competitive process like RET could be evidenced (entries 2, 5, and 8 in Table 1).

Finally, oxygen quenching experiments were performed to obtain more information on the excited state involved in the formation of annulated products, since molecular oxygen is a well-established triplet quencher. For this purpose photochemical reactions were evaluated in CH_3CN solution, under air atmosphere at λ = 254 nm. Thus, oxygen was found to result in a complete quenching of the productions of **2a**,**c** and **3b**. Unexpectedly, under these conditions sulfoxides **4b−c** and sulfones **5a−c** were found as major products. Most likely, saccharin acted as a sensitizer for the photooxygenation reaction where the sulfur atom was oxidized (see the mechanistic discussion below).[26]

Photophysical Study. *Absorption—Fluorescence.* The shape of the UV−visible absorption spectra of compounds **1a−c** is similar to that of *N*-methyl-saccharin, which indicates little, if any, electronic interaction in the ground state. The steady-state fluorescence emission maximum of *N*-methyl-saccharin in CH_3CN is centered at 363 nm, and the excitation spectrum (Figure 1) resembles that of the absorption spectrum. Similar spectra were recorded for *N*-(thioalkyl)-saccharins **1a−c** exhibiting a very weak fluorescence with quantum yield lower than 1×10^{-3}. The singlet energies of E_s = 366−341 kJ mol^{-1} were calculated (Table 2, entry 1−3), which were below the value measured for *N*-methyl-saccharin (390 kJ mol^{-1}, Figure 1, Table 2, entry 4). These results indicate a poor contribution of the singlet excited state on the photophysics of these derivatives which resembles their sulfur phthalimide analogues.[27]

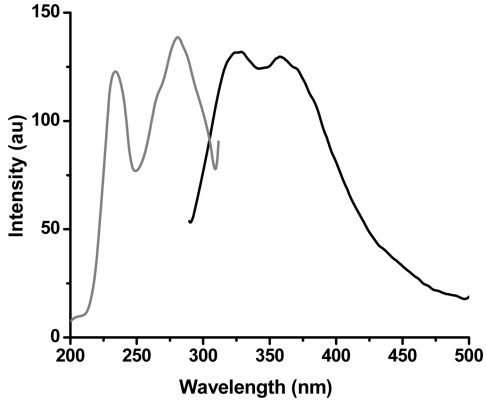


Figure 1. Fluorescence excitation (left, λ_{1f} = 234 and λ_{2f} = 281 nm) and emission (right, λ_{1f} = 326 and λ_{2f} = 363 nm) spectra of *N*-methyl-saccharin in CH_3CN; λ_{exc} = 275 nm.

Table 2. Photophysical Properties of *N*-(Thioalkyl)-saccharins 1a−c, *N*-Methyl-saccharin and *N*-Methyl-phthalimide in CH_3CN

entry	compound	$\lambda_{max\ abs}$	$\lambda_{max\ emm}$	E_{0-0}[a]	E_{0-0}[b]
1	**1a**	254	377	366	
2	**1b**	250	382	341	
3	**1c**	252	381	341	
4	***N*-methyl-saccharin**	253	358	392	334
5[c]	***N*-methyl-phthalimide**	295	420	(334−368)	(286−297)

[a]Singlet excitation energy in kJ mol^{-1}. [b]Triplet excitation energy computed by TD-DFT for *N*-methyl-saccharin in kJ mol^{-1} at the standard 6-31++G(d,p) level of theory, solvent effect considered under the PCM approximation calculation. [c]Values taken from ref 28.

Mediated Excitation. Laser Flash Photolysis was combined with TD-DFT calculations in order to get an approximate value for the triplet energy of the chromophore saccharin. In addition, the comparative method based on energy transfer from known donors (i.e., thioxanthone, benzophenone, and xanthone) and their interaction with *N*-methyl saccharin was studied. Therefore, we investigated the effect of the concentration of *N*-methyl-saccharin on the kinetic trace of laser-generated aromatic ketones used as energy transfer sensitizers. Excitation of thioxanthone (E_T = 265 kJ mol^{-1}), benzophenone (E_T = 289 kJ mol^{-1}), and xanthone (E_T = 310 kJ mol^{-1}) in Ar-saturated acetonitrile, using 355 nm laser pulses, produces the triplet transient characteristic of sensitizers with

DOI: 10.1021/acs.joc.6b02171
J. Org. Chem. 2017, 82, 101−108

λ_{max} equal to 650, 520, and 605 nm, respectively. However, only for xanthone the triplet lifetime becomes shorter with increasing concentration of *N*-methyl-saccharin (Figure 2b).

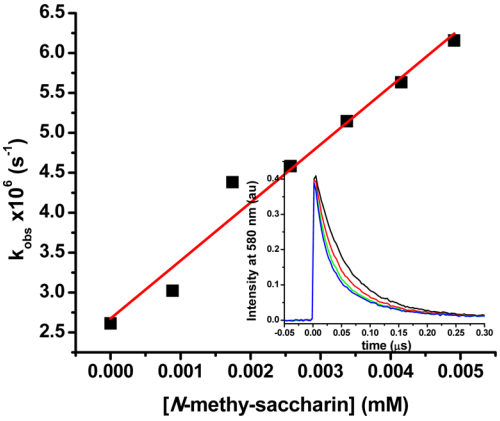


Figure 2. Plot of rate constants of xanthone triplet decay against concentration of *N*-methyl-saccharin to obtain k_q in argon-saturated CH_3CN; λ_{exc} = 355 nm. Inset: Decay traces of the T-T absorption of xanthone (2 mM) measured at 605 nm in the presence of increasing amounts of *N*-methyl-saccharin: 0 mM (—), 1.7 mM (—), 3.4 mM (—), 5 mM (—).

The measured quenching rate constant for the Triplet−Triplet (T-T) energy transfer in acetonitrile at room temperature is 7.3 × 10^8 M^{-1} s^{-1}, significantly lower than the diffusion-controlled limit rate constant (Figure 2a). For thioxanthone and benzophenone no sensitizer effect was observed and the relatively low energy transfer quenching rate constant measured for xanthone indicates that T-T energy transfer is slightly thermodynamically favored. These results point to that the energy level of the reactive triplet excited state of *N*-methyl-saccharin must be higher than 310 kJ mol^{-1} (the triplet energy of xanthone).

There is no report about the energy level of the reactive triplet excited state of *N*-alkyl-saccharin systems. Previously, Yoon et al. have calculated the singlet excited energy of *N*-methyl-saccharin from its longest excitation around 310 nm and supposed that triplet energies are expected not to be much lower than their singlet energies due to the presence of carbonyl and sulfone groups. However, our laser flash photolysis studies suggest that triplet energies are much higher than those expected by Yoon et al. In order to estimate the energy level of the reactive triplet excited state of *N*-alkyl-saccharin systems, TD-DFT calculations were performed using B3LYP exchange-correlation functional together with the standard 6-31++G(d,p) basis set. Zero-point energy corrections (ZPE) were included in the calculations to obtain the Gibbs energy of the stationary points. For these calculations, acetonitrile solvent was described by nonspecific solvent effects within the self-consistent reaction field (SCRF) approach in Tomasi's polarizable continuum model. The computational results gave triplet energy of *N*-methyl-saccharin of 334 kJ mol^{-1} (Table 2, entry 4), which could explain the low quenching rate constant observed for xanthone and any sensitization effect for thioxanthone and benzophenone in the presence of *N*-methyl-saccharin. In order to validate these calculated results, the energy obtained for the analogue *N*-methyl-phthalimide was computed, and the resulting calculated triplet energy was 301 kJ mol^{-1}, close to literature data corresponding to a triplet energy of E_T = 286−297 kJ mol^{-1} (Table 2, entry 5).[28] Hence, it is expected that in photocyclization reactions of **1a−c**, acetone (E_T = 332 kJ mol^{-1}) can efficiently act as a triplet sensitizer. Finally, the T-T transient absorption of saccharin derivatives was also generated by direct excitation (see discussion below).

Direct Excitation. Taking into account that the triplet excited saccharin is involved in photocyclization reaction, it can be deactivated by different routes. In addition to the thermal decay to ground state of **1** (k_d), quenching could also take place via intramolecular electron transfer (k_{ET}) of the sulfur nonbonded electrons to form a radical ion pair followed by proton transfer from the *S*-methyl group or *S*-methylene group.

Nanosecond laser flash photolysis of **1a−c** in CH_3CN irradiating at 266 nm revealed a transient absorption with maxima at 310−320 nm, their lifetimes are in the order of 0.1−0.6 μs. As a typical example, Figure 3a shows the transient absorption spectra and decay traces for *N*-methyl-saccharin. The analysis of the decay signal in the presence of different oxygen concentrations reveals a quenching effect (Figure 3b−d), indicating that this signal can be ascribed to the

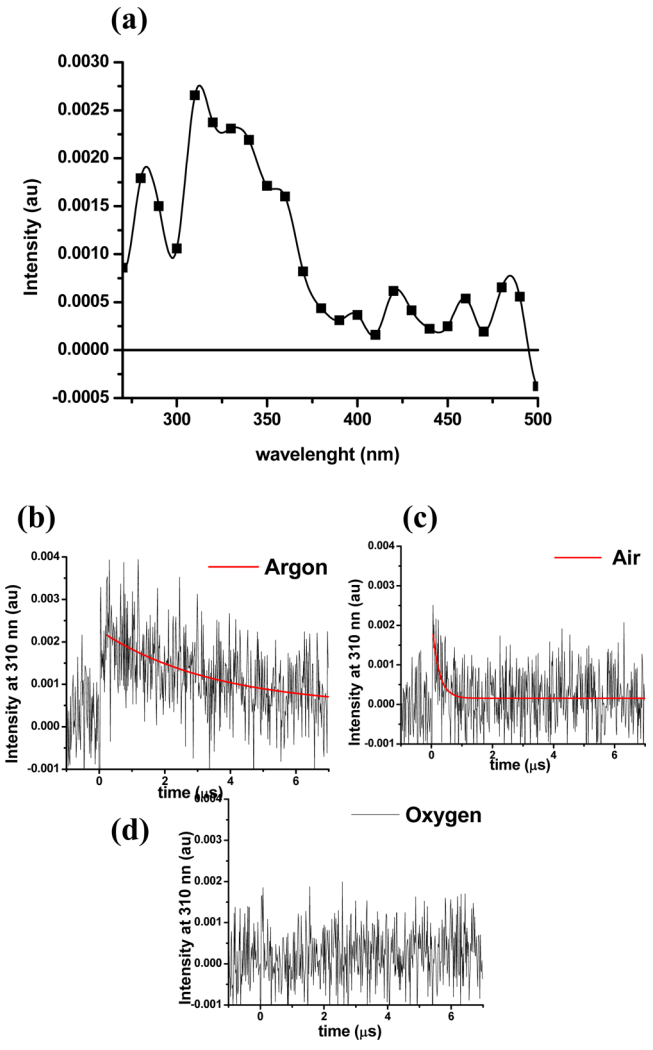


Figure 3. (a) Transient absorption spectra in argon-saturated acetonitrile of *N*-methyl-saccharin 0.3 μs after the 266 nm pulse. (b−d) Decay kinetic at 310 nm in argon, air, and oxygen atmosphere, respectively.

DOI: 10.1021/acs.joc.6b02171
J. Org. Chem. 2017, 82, 101−108

corresponding triplet state of *N*-methyl-saccharin. The results show that the triplet lifetime of **1a−c** is significantly shorter than that of *N*-methyl-saccharin (3.49 μs), which indicates that the presence of donor *S*-alkyl group clearly reduces the lifetime of the transient, which can be rationalized as an increase in the triplet quenching rate constants $k_q(T_1)$. Therefore, the rate constant for non radiative decay ($k_q(T_1)$) of **1a−c** can be estimated from the reciprocal of the triplet lifetime measured for *N*-methyl-saccharin without electron donor group (2.87×10^5 s^{-1}). On the basis of the triplet lifetime (τ_t) measured for *N*-(thioalkyl)-saccharins, $k_q(T_1)$ are estimated using the following equation, $k_q(T_1) = 1/\tau - 1/\tau_0$,[29] and the results find to be 2.8×10^6 s^{-1} (for **1a**), 9.3×10^6 s^{-1} (for **1b**), and 1.4×10^6 s^{-1} (for **1c**) (see Table 3). In all cases the presence of the sulfur atom in the molecules increased 1 order of magnitude the triplet quenching rate constants. These results, together with the electrochemical measurements (see below), would point to an intramolecular electron transfer process for the non radiative deactivation of the triplet state.

Table 3. Kinetic Data Obtained by Laser Flash Photolysis of the Triplet State of 1a−c, Electrochemical Properties, and Calculated Free Gibbs Energies[a]

comp.	T-T $\lambda_{max\ abs}$ (nm)	triplet lifetime τ (μs)	$k_q(T_1)$[b]	$E_{p/2ox}$[c]	E^0_{red}[d]	ΔG^0_{ET} (S_1)[e,f]	ΔG^0_{ET} (T_1)[e,g]
1a	310	0.32	2.8	1.47	−1.65	−15.6	−7.9
1b	310	0.10	9.3	1.39	−1.62	−12.2	−10.4
1c	320	0.59	1.4	1.42	−1.67	−10.3	−8.6

[a]In CH_3CN under argon atmosphere, [**1a−c**] = 0.3−0.5 mM, (λ_{exc} = 266 nm). [b]In 10^6 s^{-1}, obtained by using the expression: $k_q(T_1) = 1/\tau - 1/\tau_0$, where τ_0 is the triplet lifetime of *N*-methyl saccharin, 3.49 μs. [c]Oxidation half wave potential at 0.1 V s^{-1}vs SCE with 0.1 M of $TBATFB_4$ as supporting electrolyte. [d]Reduction potential at 50 V s^{-1}vs SCE with 0.1 M of $TBATFB_4$ as supporting electrolyte. [e]Free Gibbs Energy calculated according Weller equation $\Delta G_{ET} = 23.06\ [E^0(D^+/D) - E^0(A/A^-) + \Delta E_{coul}] - E_{0-0}$ (4), $\Delta E_{coul} = -0.06$ kcal mol^{-1} for acetonitrile.[30] [f]Calculated for the singlet excited state in kcal mol^{-1}. [g]Calculated for the triplet excited state in kcal mol^{-1}.

Electrochemical Measurements. The redox properties of *N*-(thioalkyl)-saccharins **1a−c** were explored by means of cyclic voltammetry experiments with tetrabutylammonium tetrafluoroborate ($TBABF_4$) as supporting electrolyte under argon at room temperature. The cyclic voltammograms of **1a−c** in CH_3CN show an irreversible anodic wave at 1.62 V, oxidation of the R-SCH_3 moiety (see anodic wave in Figure 4). This value is quite in agreement with those previously reported from an analogue *N*-phtaloyl-cysteine.[25] Thus, the oxidation half-wave potential, $E_{p/2}$, of 1.4 V for the oxidation of **1a−c** can be used as a reasonable approximation value for E^0 even though the irreversibility of the process. On the other hand, a cathodic wave centered at −1.67 V is observed. At a low and moderate sweep rate (0.1−2 V s^{-1}), CV displays an irreversible wave, while the system recovers reversibility at a high sweep rate over 50 V s^{-1}, indicating that the saccharin moiety is unstable upon electron injection from the electrode. However, the reduction potential of the saccharin moiety can be extracted from CV at high sweep rates (see Figure 4, current over the square root of the sweep rate vs potential plot). Similar results were observed for thioalkyl saccharins **1a−c**, see SI section, and the results are collected in Table 3.

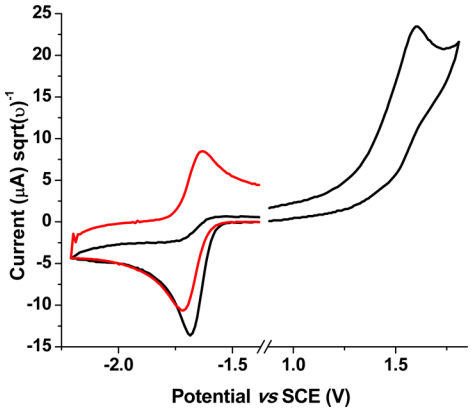


Figure 4. Cyclic voltammogram of **1c** (1.5 mM) in CH_3CN with 0.1 M $TBABF_4$ in argon atmosphere vs SCE at a glassy carbon electrode at room temperature; black line ν = 0.1 V s^{-1}, red line ν = 50 V s^{-1}.

REACTION MECHANISMS

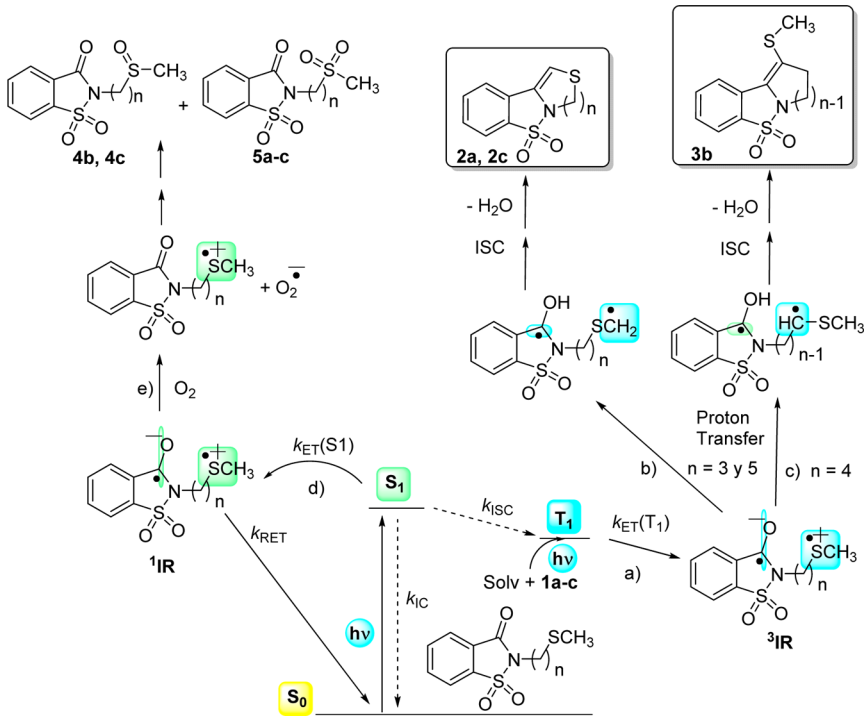
Based on product distribution in photoreactions of *N*-(thioalkyl)-saccharins**1a−c**, laser flash photolysis, and electrochemical studies, possible mechanistic pathways are proposed in Scheme 4.

From the energetic point of view, both singlet and triplet excited states are capable of exergonic intramolecular electron transfer upon photoexcitation of *N*-(thioalkyl)-saccharins **1a−c**. Free energies for electron transfer are −13 and −9 kcal mol^{-1} in average for the first singlet and triplet excited state, respectively, using the Rhem−Weller equation and the results are summarized in Table 3.[30] Under solvent-sensitized conditions the triplet state is selectively populated and, thus, photocyclization occurs more efficiently. The shorter lifetime of ^{3}(**1a−c**)* as compared with the model compound *N*-methyl-saccharin in combination with the highly exergonic Gibbs energies mentioned above, can be considered as evidence of intramolecular ET process, which finally evolves in the formation of annulated products (path a in Scheme 4). Once the radical ions are formed, a proton transfer takes place from neighboring C−H of the thioalkyl radical cation to the ketyl radical anion of saccharin moiety. Interestingly, for saccharins **1a** and **1c**, deprotonation from the terminal methyl group by ketyl radical anion is preferred (path b in Scheme 4).[23] The formed biradical intermediate renders the sulfur containing *endo*-cyclic products **2a** and **2c**, respectively, through a sequence of intersystem crossing, radical-recombination, and dehydration. However, for saccharin **1b**, proton transfer from methylene over methyl competitive positions prevails, mostly giving rise to the sulfur containing *exo*-cyclic product **3b** (path c in Scheme 4). Similar results were observed in the photocyclization of *N*-(thioalkyl)-phthalimide systems.[23c] Nevertheless, in our previous studies, for *N*-(selenoalkyl)-phthalimide analogues, a proton transfer from methylene group was observed with n = 3 and n = 4.[24] These observations suggest that the proton transfer process could be influenced by the nature of donor heteroatom.

The reaction profile looks different when carried out under direct excitation. From an energetic viewpoint, it is clear that ET from the singlet excited state should be more efficient (path d in Scheme 4). Likewise, cyclic products can also be formed by direct excitation. However, a pronounced decrease in conversion is found under these conditions when compared with solvent triplet-sensitized reaction. The low yields found for

DOI: 10.1021/acs.joc.6b02171
J. Org. Chem. 2017, 82, 101−108

Scheme 4. Mechanism Proposed for the Different Photo Products Formation in *N*-Thioalkyl-saccharins (1a−c)



the annulated product of **1a**, **1b**, and **1c** can be attributed to the presence of a competitive process such as reverse electron transfer (RET). Thus, in the case of direct excitation of substrate **1a,b**, RET from the singlet radical ion intermediates must be faster than the deprotonation reaction leading to annulated product. For these reactions the observed cyclized products, although in a lower conversion than that of the solvent-sensitized reactions, can be ascribed to a minor intersystem crossing pathway from S_1 to T_1.

Finally, the formation of sulfoxide and sulfone derivatives of *N*-thioalkyl-saccharins under direct excitation in air atmosphere suggests that, in these conditions, a good electron scavenger like molecular oxygen reacts with the radical ion pair ^{1}IR, giving superoxide radical anion and sulfide radical cation. These radical intermediates finally render the photooxygenation products observed, as already reported for other sensitizers such as 9,10-dicyanoanthracene (path e in Scheme 4).[26] However, a similar route involving the reactive triplet excited state ^{3}IR cannot be ruled out.

CONCLUSIONS

In order to contribute to the photochemistry of sultams, we have explored in detail photochemical, electrochemical, and photophysical properties of *N*-thioalkyl-saccharin systems. For these derivatives, reactivity and chemoselectivity is highly sensitive to photochemical reaction conditions (reaction atmosphere, solvent, and irradiation wavelength). Thus, polycyclic sultams **2** and **3** are favored in the absence of oxygen with an efficient population of the triplet state by solvent sensitization. The presence of molecular oxygen changes the course of the reaction into an efficient photooxygenation of *N*-thioalkyl-saccharins at the sulfur atom level.

The results show that the triplet excited state of saccharins is directly involved in an intramolecular electron transfer process, resulting in an alternative route for the synthesis of new fused polycyclic sultams.

EXPERIMENTAL SECTION

General Methods. Irradiation was conducted in a commercial photoreactor RPR-100 (16 × 3000 Å lamps, λ = 300 ± 10 nm). ^{1}H and ^{13}C NMR spectra were registered on a 400 MHz spectrometer and all spectra were reported in δ (ppm) relative to Me_4Si, with $CDCl_3$ as solvent. Measurements were carried out using the standard pulse sequences. Gas chromatographic analyses were performed on a chromatograph with a flame-ionization detector, on 30 m capillary column of a 0.32 mm x 0.25 μm film thickness, with a 5% phenylpolysiloxane phase. GC-MS analyses were performed on a spectrometer employing a 30 m × 0.25 mm × 0.25 μm with a 5% phenylpolysiloxane phase column. Ionization was achieved by electronic impact (70 eV) and detection setup positive mode. HRMS spectra were recorded on an orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer.

Chemicals. Saccharin sodium salt hydrate, 1,3-dibromopropane, 1,4-dibromobutane, 1,5-dibromopentane, sodium thiomethoxide, thioxanthone, benzophenone, and xanthone were commercially available. Acetonitrile, acetone, dimethylformamide (HPLC grade) were used as purchased without any further purification and stored over molecular sieves (4 Å). Ultrapure water from a Milli-Q station was used. *N*-(haloalkyl)-saccharins were synthesized and purified according to the previously reported procedures.[17,31]

Spectroscopic Measurements. All measurements were carried out under inert atmosphere, in quartz cell, at room temperature. UV−vis spectra were recorded on a UV−vis spectrophotometer and fluorescence spectra were performed in Fluorescence Spectrometer.

Laser Flash Photolysis (LFP). Transient absorption spectra and quenching rate constants were determined using a Nd:YAG laser generating 266 and 355 nm laser pulse (ca. 10 ns pulse duration) as an excitation source. The spectrometer was a commercial setup.

Electrochemistry. The working electrode was a 3 mm-diameter 30 glassy carbon electrode disk carefully polished and ultrasonically rinsed in absolute ethanol before use. The counter electrode was a platinum wire and the reference electrode was an aqueous SCE electrode. All experiments were performed at 20 °C. Cyclic voltammetric data were recorded using a commercial computer-controlled potentiostat.

Computational Details. Theoretical calculations were performed with the GAUSSIAN 09 suite of programs.[32] B3LYP exchange-

DOI: 10.1021/acs.joc.6b02171
J. Org. Chem. 2017, 82, 101−108

correlation functional together with the standard 6-31++G(d,p) basis set. The stationary points were located with the Berny algorithm[33] using redundant internal coordinates. Analytical Hessians were computed to determine the nature of the stationary points (one and zero imaginary frequencies for transition states and minima, respectively)[34] and to calculate unscaled zero-point energies (ZPEs) as well as thermal corrections and entropic effects using the standard statistical mechanic relationships for an ideal gas.[35] The solvent effects on the mechanism have been considered using a self-consistent reaction field method based on the Tomasi's polarizable continuum model. As the solvent used in the experimental work was CH_3CN, we have selected its dielectric constant $\varepsilon = 37.5$.[36] Unless otherwise stated, Gibbs energies have been computed at 298.15 K.

*Representative Experimental Procedure for the Photochemical Reaction of N-(Thioalkyl)-saccharins (**1a–c**).* A solution of **1** in acetone (2−5 mM) was irradiated (λ = 300 nm) in a Pyrex tube for 5 h while purged with a stream of nitrogen and cooled to 10 °C. After removal of the solvent under reduced pressure, the residue was analyzed by CG and purified by column chromatography on silica gel using a mixture of pentane/ethyl acetate (70/30) for **2a**, **2c**, and **3b**, and a mixture of dichlorometane/ethyl acetate (10/90) for **4b**, **4c**, **5a**, **5b**, **5c** as eluent.

Spectral Data of New Compounds. *2-(3-(Methylthio)propyl)-benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**1a**).* (yield 34%, 370.1 mg) Isolated as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.10 (m, 2H), 2.57 (t, J = 6.8 Hz, 2H), 3.86 (t, J = 6.9 Hz, 2H), 7.85 (m, 3H), 8.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 27.5, 31.1, 38.2, 121.0, 125.2, 127.3, 134.4, 134.8, 137.7, 159.0; CG-MS (EI) m/z 271 (M+, 27), 224 (24), 196 (19), 159 (51), 146 (61), 133 (100), 132 (39), 105 (59), 104 (47), 77 (48), 76 (54), 75 (42), 73 (20), 61 (48), 50 (24), 41 (26). HRMS (ESI-TOF) m/z calcd for $C_{11}H_{13}NNaO_3S_2$: 294.02291 found: 294.02297.

*2-(4-(Methylthio)butyl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**1b**).* (yield 56%, 720.5 mg) Isolated as a white solid; mp: 57.4−57.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (q, J = 7.6 Hz, 2H), 1.96 (q, J = 7.5 Hz, 2H), 2.09 (s, 3H), 2.55 (t, J = 7.3 Hz, 2H), 3.80 (t, J = 7.3 Hz, 2H), 7.84 (m, 2H), 7.91 (d, J = 7.0 Hz, 1H), 8.05 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 26.4, 27.6, 33.6, 39.1, 121.1, 125.3, 127.5, 134.5, 134.9, 137.8, 159.1; CG-MS (EI) m/z 285 (M+, 7), 206 (39), 196 (24), 146 (30), 105 (100), 77 (27), 61 (42), 50 (11), 41 (13). HRMS (ESI-TOF) m/z calcd for $C_{12}H_{15}NNaO_3S_2$: 308.03856 found: 308.03898.

*2-(5-(Methylthio)pentyl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**1c**).* (yield 46%, 778.5 mg) Isolated as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (q, 2H), 1.65 (q, 2H), 1.86 (q, 2H), 2.07 (s, 3H), 2.49 (t, J = 7.3 Hz, 2H), 3.76 (t, J = 7.5 Hz, 2H), 7.83 (m, 2H), 7.90 (d, J = 7.1 Hz, 1H), 8.04 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 26.0, 28.1, 28.6, 34.1, 39.3, 121.0, 125.2, 127.5, 134.4, 134.8, 137.8, 159.0; CG-MS (EI) m/z 299 (M+, 12), 252 (15), 220 (51), 196 (30), 184 (16), 146 (38), 132 (22), 114 (13), 105 (100), 77 (35), 68 (33), 61 (71), 41 (26). HRMS (ESI-TOF) m/z calcd for $C_{13}H_{17}NNaO_3S_2$: 322.05421 found: 322.05309.

*4,5-Dihydro-3H-benzo [4,5]isothiazolo[3,2-c][1,4]thiazepine 7,7-Dioxide (**2a**).* (yield 46%, 44.6 mg) Isolated as a white solid; mp: 93.3−94.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (m, 2H), 3.34 (t, J = 6.4 Hz, 2H), 4.16 (t, J = 6.0 Hz, 2H), 6.04 (s, 1H), 7.47 (td, J = 7.0, 1.4 Hz, 1H), 7.56 (m, 2H), 7.75 ($_{app}$d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.8, 33.1, 42.8, 100.5, 120.5, 121.3, 129.3, 130.2, 130.5, 133.1, 134.0; CG-MS (EI) m/z 253 (M+, 100), 161 (49), 188 (16), 134 (27), 117 (25), 103 (13), 89 (18). HRMS (ESI-TOF) m/z calcd for $C_{11}H_{11}NNaO_2S_2$: 276.01234 found: 276.01286.

*(Z)-7,8,9,10,11,12-Hexahydrobenzo[4,5]isothiazolo[2,3-a]-azonine 5,5-Dioxide (**2c**).* (yield 45%, 51.1 mg) Isolated as a white solid; mp: 142.1−142.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.81 (m,2H), 1.94 (m, 4H), 2.75 (dd, J = 5.8, 5.4 Hz, 2H), 3.60 (dd, J = 5.2, 5.2 Hz,2H), 6.16 (s, 1H), 7.59 (m, 2H), 7.69 ($_{br}$d, J = 8.0, Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.15, 30.12, 30.82, 38.39, 41.32, 94.47, 121.08, 121.10, 130.41, 131.16, 131.21, 133.19, 139.01; CG-MS (EI) m/z 281 (M+, 22), 221 (14), 220 (100), 207 (13), 194 (19), 162 (16), 134 (15), 130 (15), 103 (10), 101 (13), 100 (28), 89 (14), 87 (15), 41 (17). HRMS (ESI-TOF) m/z calcd for $C_{13}H_{15}NNaO_2S_2$: 304.04364 found: 304.04281.

*10-(Methylthio)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]-pyridine 5,5-Dioxide (**3b**).* (yield 57%, 54.6 mg) Isolated as a white solid; mp 118.8−119.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.1 (q, 2H), 2.34 (s, 3H), 2.58 (t, J = 6.3 Hz, 2H), 3.60 (dd, J = 6.6, 5.6 Hz, 2H), 7.58 (ddd, J = 7.4, 1.1, 0,4 Hz, 1H), 7.64 ($_{br}$dd, J = 7.4, 0,7 Hz, 1H), 7.82 (d, J = 7.4 Hz, 1H), 8.92 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 25.5, 29.2, 37.8, 113.0, 121.2, 126.9, 129.5, 130.0, 130.3, 132.6, 132.9; CG-MS (EI) m/z 267 (M+, 100), 252 (61), 220 (11), 204 (22), 188 (52), 186 (20), 173 (14), 171 (11), 161 (19), 160 (20), 155 (13), 154 (11), 128 (21), 115 (14), 93 (11). HRMS (ESI-TOF) m/z calcd for $C_{12}H_{13}NNaO_2S_2$: 290.02799 found: 290.02788.

*2-(4-(Methylsulfinyl)butyl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**4b**).* (yield 23%, 2.9 mg) Isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (m, 2H), 2.02 (m, 2H), 2.58 (s, 3H), 2.77 (m, 2H), 3.84 (t, J = 7.0 Hz, 2H), 7.86 (m, 2H), 7.92 (ddd, J = 8.7, 7.3, 1.2 Hz, 1H), 8.06 (dd, J = 7.2, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.95, 27.66, 38.66, 38.72, 53.84, 121.13,125.41, 127.43, 134.57, 135.00, 137.80, 159.18; CG-MS (EI) m/z, 196 (99), 184 (28), 169 (19), 149 (16), 132 (14), 104 (36), 76 (38), 68 (100), 54 (16), 50 (19), 41 (16). HRMS (ESI-TOF) m/z calcd for $C_{12}H_{16}NO_4S_2$: 302.05153 found: 302.05086.

*2-(5-(Methylsulfinyl)pentyl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**4c**).* (yield 19%, 3.1 mg) Isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (m, 2H), 1.88 (m, 4H), 2.56 (s, 3H), 2.71 (m, 2H), 3.80 (t, J = 7.2 Hz, 2H), 7.87 (m, 3H), 8.06 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 26.0, 28.91, 38.7, 39.1, 54.5, 121.1, 125.3, 127.5, 134.5, 135.0, 139.8, 159.2; CG-MS (EI) m/z,196 (58), 184 (37), 169 (14), 166 (12), 132 (13), 105 (16), 104 (28), 77 (27), 68 (100), 50 (11). HRMS (ESI-TOF) m/z calcd for $C_{13}H_{18}NO_4S_2$: 316.06718 found: 316.06751.

*2-(3-(Methylsulfonyl)propyl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**5a**).* (yield 46%, 6.6 mg) Isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (m, 2H), 2.93 (s, 3H), 3.17 (dd, J = 7.70, 10.20 Hz, 2H), 3.97 (t, J = 6.5 Hz, 2H), 7.90 (m, 3H), 8.08 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 37.8, 40.9, 52.2, 121.2, 125.5, 127.2, 134.7, 135.2, 137.7, 159.2; CG-MS (EI) m/z,196 (52), 169 (15), 159 (65), 146 (100), 132 (37), 105 (34), 76 (30), 50 (10), 41 (13). HRMS (ESI-TOF) m/z calcd for $C_{11}H_{14}NO_5S_2$: 304.03079 found: 304.03141.

*2-(4-(Methylsulfonyl)butyl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**5b**).* (yield 56%, 7.5 mg) Isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0 (m, 4H), 2.91 (s, 3H), 3.10 (m, 2H), 3.84 (t, J = 6.4 Hz, 2H), 7.88 (m, 3H), 8.08 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 27.2, 38.4, 40.7, 54.1, 121.2, 125.4, 127.3, 134.6, 135.1, 137.7, 159.3; CG-MS (EI) m/z,196 (39), 169 (10), 146 (100), 132 (23), 105 (21), 77 (23), 76 (21), 55 (12). HRMS (ESI-TOF) m/z calcd for $C_{12}H_{16}NO_5S_2$: 318.04644 found: 318.04654.

*2-(5-(Methylsulfonyl)pentyl)benzo[d]isothiazol-3(2H)-one 1,1-Dioxide (**5c**).* (yield 27%, 4.6 mg) Isolated as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (m, 2H), 1.93 (m, 4H), 2.90 (s, 3H), 3.02 (dd, J = 7.8, 10.6 Hz, 2H), 3.81 (t, J = 7.1 Hz, 2H), 7.88 (m, 3H), 8.06 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 25.6, 27.9, 38.9, 40.7, 54.7, 121.1, 125.4, 127.5, 134.5, 135.0, 137.8, 159.2; CG-MS (EI) m/z,196 (39), 184 (10), 169 (10), 146 (100), 132 (23), 105 (21), 77 (24), 76 (22), 55 (12). HRMS (ESI-TOF) m/z calcd for $C_{13}H_{18}NO_5S_2$: 332.06209 found: 332.06295.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02171.

UV−visible absorption spectra, normalized excitation and florescence spectra, transient spectra obtained upon LFP, cyclic voltammograms, ^{1}H NMR and ^{13}C NMR for

DOI: 10.1021/acs.joc.6b02171
J. Org. Chem. 2017, 82, 101−108

all compounds, theoretical structures, and theoretical energy excitation (PDF)

AUTHOR INFORMATION

Corresponding Authors

*goksdath@fcq.unc.edu.ar.

*jea@fcq.unc.edu.ar.

ORCID

Gabriela Oksdath-Mansilla: 0000-0002-8999-3314

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported in part by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Secretaría de Ciencia y Tecnología (SeCyT), Universidad Nacional de Córdoba (UNC), and Fondo para la Investigación Científica y Tecnológica Argentina (FONCyT). W.C-G. gratefully acknowledges receipt of fellowship from CONICET.

REFERENCES

(1) (a) Majumdar, K. C.; Mondal, S. *Chem. Rev.* **2011**, *111*, 7749−7773. (b) Tang, X.; Li, Z.; Li, Y.; Liu, W.; Yu, P.; Li, L.; Guo, Y.; Yang, C. *Chem. Res. Chin. Univ.* **2015**, *31*, 71−77. (c) Majumdar, S.; Juntunen, J.; Sivendran, S.; Bharti, N.; Sloan, K. B. *Tetrahedron Lett.* **2006**, *47*, 8981−8982. (d) Csakai, A.; Smith, C.; Davis, E.; Martinko, A.; Coulup, S.; Yin, H. *J. Med. Chem.* **2014**, *57*, 5348−5355.

(2) Elsayed, M. S. A.; El-Araby, M. E.; Serya, R. A. T.; El-Khatib, A. H.; Linscheid, M. W.; Abouzid, K. A. M. *Eur. J. Med. Chem.* **2013**, *61*, 122−131.

(3) Combrink, K. D.; Gülgeze, H. B.; Meanwell, N. A.; Pearce, B. C.; Zulan, P.; Bisacchi, G. S.; Roberts, D. G. M.; Stanley, P.; Seiler, S. M. *J. Med. Chem.* **1998**, *41*, 4854−4860.

(4) Gençer, N.; Demir, D.; Sonmez, F.; Kucukislamoglu, M. *Bioorg. Med. Chem.* **2012**, *20*, 2811−2821.

(5) Fu, H.; Han, L.; Hou, X.; Dun, Y.; Wang, L.; Gong, X.; Fang, H. *Bioorg. Med. Chem.* **2015**, *23*, 5774−5781.

(6) Nerenberg, J. B.; Erb, J. M.; Thompson, W. J.; Lee, H.-Y.; Guare, J. P.; Munson, P. M.; Bergman, J. M.; Huff, J. R.; Broten, T. P.; Chang, R. S. L.; Chen, T. B.; O'Malley, S.; Schorn, T. W.; Scott, A. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2467−2472.

(7) Mortazavi, Z. F. A.; Islami, M. R.; Khaleghi, M. *Org. Lett.* **2015**, *17*, 3034−3037.

(8) Mahon, B. P.; Hendon, A. M.; Driscoll, J. M.; Rankin, G. M.; Poulsen, S.-A.; Supuran, C. T.; McKenna, R. *Bioorg. Med. Chem.* **2015**, *23*, 849−854.

(9) Bhatt, P. M.; Ravindra, N. V.; Banerjee, R.; Desiraju, G. R. *Chem. Commun.* **2005**, 1073−1075.

(10) Lombardino, J. G.; Wiseman, E. H.; McLamore, W. M. *J. Med. Chem.* **1971**, *14*, 1171−1175.

(11) (a) Kiselev, G.; Mishnev, A. F.; Ivanova, E. M.; Vozny, I. V.; Žalubovskis, R. *Chem. Heterocycl. Compd.* **2012**, *48*, 1412−1414. (b) Jakopin, Z.; Dolenc, M. S. *Curr. Med. Chem.* **2010**, *17*, 651−671.

(12) Loh, J. K.; Asad, N.; Samarakoon, T. B.; Hanson, P. R. *J. Org. Chem.* **2015**, *80*, 9926−9941.

(13) Bach, T.; Hehn, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000−1045.

(14) (a) Kovarnos, G. J. *Fundamentals of Photoinduced Electron Transfer*; VCH Pub.: New York, 1993. (b) Feldman, K. S.; Gonzalez, I. Y.; Glinkerman, C. M. *J. Org. Chem.* **2015**, *80*, 11849−11862. (c) Albini, A.; Fagnoni, M. *Handbook of Synthetic Photochemistry*; VCH Pub.: New York, 2010.

(15) Döpp, D. *Intr. J. Photochem.* **2001**, *3*, 41−48.

(16) (a) Kamigata, N.; Saegusa, T.; Fujie, S.; Kobayashi, M. *Chem. Lett.* **1979**, *8*, 9−12. (b) Yoon, U. C.; Koh, Y. S.; Kim, H. J.; Jung, D. Y.; Kim, D. U.; Cho, S. J.; Lee, S. J. *Bull. Korean Chem. Soc.* **1994**, *15*, 743−748.

(17) Cho, D. W.; Oh, S. W.; Kim, D. U.; Park, H. J.; Xue, J. Y.; Yoon, U. C.; Mariano, P. S. *Bull. Korean Chem. Soc.* **2010**, *31*, 2453−2458.

(18) Duarte, L.; Reva, I.; Cristiano, M. L. S.; Fausto, R. *J. Org. Chem.* **2013**, *78*, 3271−3275.

(19) (a) Kanaoka, Y. *Acc. Chem. Res.* **1978**, *11*, 407−413. (b) Horvat, M.; Mlinarić-Majerski, K.; Basarić, N. *Croat. Chem. Acta* **2010**, *83*, 179−188. (c) Oelgemöller, M.; Griesbeck, A. G. *J. Photochem. Photobiol., C* **2002**, *3*, 109−127.

(20) Maruyama, K.; Kubo, Y.; Machida, M.; Oda, K.; Kanaoka, Y.; Fukuyama, K. *J. Org. Chem.* **1978**, *43*, 2303−2304.

(21) Coyle, J. D.; Newport, G. L. *J. Chem. Soc., Perkin Trans. 1* **1980**, 93−96.

(22) Sato, Y.; Nakai, H.; Wada, M.; Ogiwara, H.; Mizoguchi, T.; Migita, Y.; Hatanaka, Y.; Kanaoka, Y. *Chem. Pharm. Bull.* **1982**, *30*, 1639−1645.

(23) (a) Sato, Y.; Nakai, H.; Mizoguchi, T.; Hatanaka, Y.; Kanaoka, Y. *J. Am. Chem. Soc.* **1976**, *98*, 2349−2351. (b) Sato, Y.; Nakai, H.; Mizoguchi, T.; Hatanaka, Y.; Kanaoka, Y. *Tetrahedron Lett.* **1976**, *22*, 1889−1890. (c) Sato, Y.; Nakai, H.; Wada, M.; Mizoguchi, T.; Hatanaka, Y.; Migita, Y.; Kanaoka, Y. *Liebigs Ann. Chem.* **1985**, *1985*, 1099−1118. (d) Hatanaka, Y.; Nakai, H.; Wada, M.; Mizoguchi, T.; Kanaoka, Y.; Sato, Y. *Liebigs Ann. Chem.* **1992**, *1992*, 1113−1123.

(24) Oksdath-Mansilla, G.; Heredia, A. A.; Argüello, J. E.; Peñéñory, A. B. *Photochem. Photobiol. Sci.* **2015**, *14*, 726−736.

(25) Griesbeck, A. G.; Hirt, J.; Peters, K.; Peters, E.-M.; von Schnering, H. G. *Chem. - Eur. J.* **1996**, *2*, 1388−1394.

(26) (a) Clennan, E. L.; Liao, C. *J. Am. Chem. Soc.* **2008**, *130*, 4057−4068. (b) Bonesi, S. M.; Manet, I.; Freccero, M.; Fagnoni, M.; Albini, A. *Chem. - Eur. J.* **2006**, *12*, 4844−4857. (c) Baciocchi, E.; Del Giacco, T.; Elisei, F.; Gerini, M. F.; Guerra, M.; Lapi, A.; Liberali, P. *J. Am. Chem. Soc.* **2003**, *125*, 16444−16454.

(27) Görner, H.; Griesbeck, A. G.; Heinrich, T.; Kramer, W.; Oelgemöller, M. *Chem. - Eur. J.* **2001**, *7*, 1530−1538.

(28) Griesbeck, A. G.; Görner, H. *J. Photochem. Photobiol., A* **1999**, *129*, 111−119.

(29) Pérez-Ruiz, R.; Gil, S.; Miranda, M. A. *J. Org. Chem.* **2005**, *70*, 1376−1381.

(30) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259−271.

(31) (a) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's: Texbook of Practical Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 1989; p 780.

(32) Frisch, M. J.; Trucks, G. W.; Schlege, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, M. J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J.; *Gaussian 09*, Revision C.01.; Gaussian, Inc.: Wallingford CT, 2009.

(33) Peng, C. Y.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49−56.

(34) McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625−2633.

(35) Atkins, P. W.; De Paula, J. *Physical Chemistry*, 8th ed.; Oxford University Press: Oxford, 2006.

(36) (a) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117−129. (b) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404−417.

DOI: 10.1021/acs.joc.6b02171
J. Org. Chem. 2017, 82, 101−108