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ARTICLE TYPE

Photochemistry of *N*-(selenoalkyl)-Phthalimides. Formation of *N*, Se-heterocyclic systems

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A variety of *N*-(selenomethyl)alkyl-phthalimides (alkyl = $-(\text{CH}_2)_n-$; $n = 2-5$, **1a**, **b**, **d**, **e**) and *N*-(selenobenzyl)propyl phthalimide (**1c**) were synthesized and their photochemistry studied at $\lambda = 300$ nm. Steady-state photolysis and laser time-resolved spectroscopic studies confirmed that these reactions proceeded by direct or acetone-sensitized excitation followed by intramolecular electron transfer (ET) between the phthalimide moiety and Se atom. Two main pathways are possible after ET: proton transfer to the ketyl radical anion from the $\text{CH}_3\text{Se}^{++}$ or the $-\text{CH}_2\text{Se}^{+-}$ moieties, yielding the corresponding biradicals. Collapse of these biradicals yields cyclization products with the respectively *endo* or *exo* selenium-containing heterocycles. Competition between both proton transfers depends on the chain length of the alkyl spacer between the phthalimide and Se groups as well as the size of the cycle being formed.

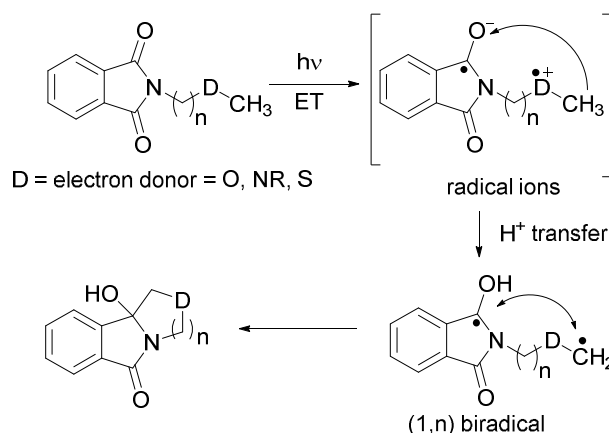
Introduction

Photoinduced electron transfer (PET) is a process in which photoexcited molecules can act as strong oxidizing or reducing species. Electronically excited molecules are often better electron donors or electron acceptors than their ground states. In the last two decades, PET reactions have been of particular interest to organic chemists concerned with the synthesis of novel organic compounds that may be difficult to synthesize by other routes. After being oxidized or reduced by a photosensitizer, an organic substrate can be transformed into a reactive intermediate which may undergo further reaction.¹

Probably, the most active area of organic photochemistry has been the study of systems possessing a carbonyl moiety. Excited carbonyl chromophores of ketones, aldehydes, amides or imides are good electron acceptors that oxidize alkenes, amines, thioethers or carboxylates. These reactions are applied to the synthesis of heterocyclic compounds when the acceptor and donor are linked *via* a tether.²

This concept has been shown for an imide such as phthalimide. In the presence of electron donors, the electronically excited phthalimide could also undergo electron transfer processes acting as electron acceptor. The photochemical reactivity of the phthalimide chromophore is rather broad in its scope. In the excited state, this chromophore undergoes intra- and intermolecular hydrogen atom abstraction from suitable donor sites, which results in photoreduction, cleavage or cyclization products. In the presence of good electron donors, phthalimide in the excited state does not abstract H-atoms but rather undergoes a single electron transfer (SET).³ Thus, different spacer-linked donor-acceptor couples of the phthalimide (acceptor)-heteroatom

donor (O, N, S) have been studied.⁴ These reactions involve an electron transfer from the side-chain localized heteroatom to the electronically excited phthalimide chromophore. The radical ion pair thus formed has acidic hydrogens at the α -position of the radical cation site and proton transfer to the ketyl radical anion may occur. Finally, the (1,*n*) biradical formed can combine to render heterocyclic ring systems in good yields (Scheme 1).



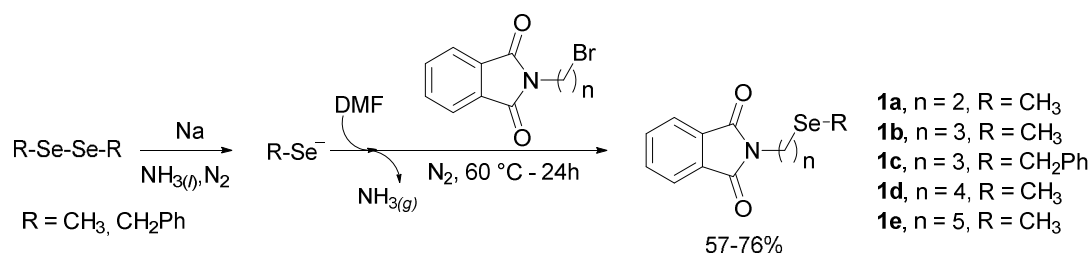
Scheme 1 Photocyclization reaction of phthalimide with donor substituents

Currently, there are reports on photocyclization reactions of *N*-substituted phthalimides with other electron-donor groups such as alkenyl,⁵ electron-rich arenes,⁶ carboxylates,⁷ and trimethyl silyl and tributyl stannyl-terminated phthalimido polyether,⁸ leading to new heterocycles. However, to the best of our knowledge, there are not any reports for the synthesis of selenacycles by employing this methodology.

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ARTICLE TYPE

Scheme 2 Synthesis of starting materials *N*-(selenoalkyl)-phthalimides (**1a-e**)

Early selenium chemistry involved the synthesis of simple aliphatic compounds such as selenols (RSeH), selenides (RSeR) and diselenides (RSeSeR); however, when several new reactions leading to novel compounds with unusual properties were discovered, that selenium chemistry began to attract more general interest.⁹

Although selenium belongs to the same group in the periodic table as that of sulphur, they both differ in several physical, chemical and physiological properties. For instance, replacing cysteine (Cys) for selenocysteine (Sec) in the active site of enzymes increases the catalytic activity by several hundred folds.¹⁰

Since then, there has been a growing interest in the synthesis of organoselenium compounds due to their use in bioorganic chemistry, enzymology and medicine. These compounds exhibit various types of biological activities including antitumor, anti-inflammatory, antibacterial and antifungal. Many selenium-containing compounds with biological activity are heterocycles, and their syntheses represent an important challenge for organoselenium chemists.¹¹

In this study, we report the synthesis of *N*-(selenoalkyl)-phthalimides **1a-e** (Scheme 2) and further aspects concerning the scope and limitations for the synthesis of new organoselenium tricyclic ring systems. The photochemistry of these compounds is described, evaluating the efficiency of the photochemical reaction as a function of the distance between the donor and electron acceptor as well as the stability of the radical intermediates. The photochemical properties of the phthalimide derivatives **1a-e** are also studied by time-resolved spectroscopic techniques determining thermodynamic and kinetic parameters which allow elucidation of the reaction mechanism.

Results and Discussion

Synthesis of *N*-(selenoalkyl)-phthalimides (**1a-e**).

Nowadays, organoselenium reagents are employed in many synthetic transformations due to their wide availability and easy manipulation. The selenium group can be introduced into an organic substrate *via* both nucleophilic and electrophilic reagents. Specifically, *N*-phenylselenophthalimide has been used as a versatile and useful carrier of the PhSe group.¹² More recently, a

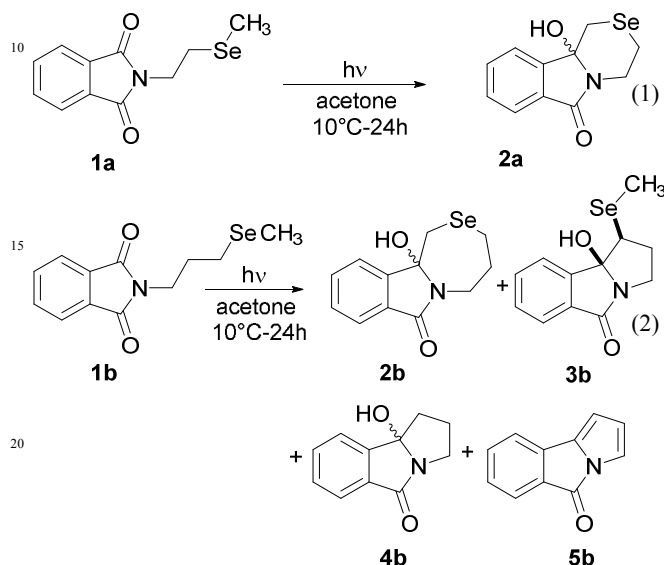
mild activation of *N*-(phenylselenomethyl)-phthalimide by iodonium ion in the presence of alcohols to give the corresponding *O*-phthalimidomethyl derivatives (Pim-ethers) was reported, making this approach a new and efficient method for alcohol protection.¹³ On the other hand, organoselenium anions are powerful nucleophiles usually prepared *in situ* because of their air-sensitive condition.^{9a}

The selenium derivatives (**1a-e**) used in this study were synthesized in good yields according to the sequence shown in Scheme 2. First, *N*-(haloalkyl)-phthalimides were prepared by reaction of the corresponding 1,*n*-dihaloalkane with potassium phthalimide; subsequently, the selenium group was introduced by substitution with the alkaneselenate anion obtained by *in situ* reduction of the dialkyl diselenide with sodium in liquid ammonia under inert atmosphere.^{14,15}

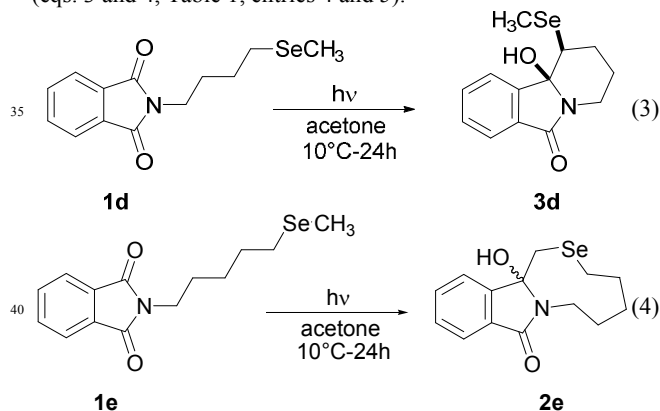
Photocyclization reactions of **1a-e**, steady-state photolysis.

Phthalimides **1a-e** were irradiated in acetone as solvent under similar conditions as *N*-(thioalkyl)-phthalimide analogues (irradiation at $\lambda = 300$ nm, under N_2 atmosphere).^{4a-f} Table 1 summarizes both, conversion and yield of the photo products. Photochemistry of **1a** gave mainly rise to the annulated product **2a** in 29% isolated yield after 24 h of irradiation (eq 1, Table 1 entry 1). On the other hand, four different products could be detected in the photolysis of phthalimide **1b** (eq 2, Table 1, entry 2). In this case two annulated products **2b** and **3b**, which contained selenium, were formed in only 8% and 5% isolated yields, *endo*- and *exo*-cyclic derivatives relative to Se, respectively. However, the main product **4b** was obtained in 30% isolated yield, together with a small amount of **5b** (2% yield). Both, **4b** and **5b**, lost the selenium atom during the reaction course (eq 2). Diastereoisomerically pure **3b** was isolated from the reaction mixture by column chromatography. The structural assignment of the isolated diastereomer **3b** was based on their ¹H NMR and ¹³C NMR spectra, using NOESY experiments to establish the relative stereochemistry of the Se-CH₃ group. The data were consistent with the methyl group at position 1 *cis* to the OH group at position 9. The presence of a single diastereomer may come from a strong interaction between the selenium and the oxygen atoms as was reported in the literature.¹⁶ In contrast to

these results, irradiation of phthalimide **1c** which contains the seleno-benzyl group led to decomposition, and no cyclization product was observed, dibenzyl being obtained as only isolable product (Table 1, entry 3). This result was ascribed to homolysis of **1c** as shown by the control reaction of the benzyl phenyl selenide model. Thus, when a solution of benzyl phenyl selenide was irradiated under the same conditions, dibenzyl and Ph₂Se₂ were obtained as products.



The photoreactions of **1d** and **1e** under similar conditions produced a complex product mixture and only 9% and 5% of the heterocyclic compounds **3d** and **2e**, respectively, were detected. Similarly to **3b**, the spectroscopic data for compound **3d** were consistent with the *cis* relative configuration between the seleno methyl and the OH groups. In addition, it can be seen that the efficiency in the cyclization reaction decreases with chain length (eqs. 3 and 4, Table 1, entries 4 and 5).



The photocyclization products may tentatively be rationalized as an intramolecular electron transfer reaction followed by proton transfer from the carbon adjacent to selenium radical cation to the ketyl radical anion giving a biradical which finally collapses in the photoproducts observed. It is known that photocyclization of *N*-(thioalkyl)-phthalimide derivatives proceeds through an electron transfer process.^{3,4a-f} On the other hand, it has been reported that organoselenium compounds can be easily oxidized

by excited 1,4-dicyanonaphthalene where a SET was invoked,¹⁷ therefore, it is expected that *N*-(selenoalkyl)-phthalimides are capable of participating in a PET process.

In this photoreaction, a competition of the two active positions adjacent to the selenium atom for the propylene-linked substrate **1b** was observed, in contrast with the sulphur analogue which mainly furnishes product by proton transfer from the more acidic *S*-methyl group.^{4a}

Table 1: Photocyclization of *N*-(selenoalkyl)-phthalimides (**1**).^a

Substrate	n	cvn (%) ^b	Product (%) ^c
1a	2	100	2a (29)
1b	3	90	2b (8), 3b (5), 4b (30), 5b (2)
1c	3	100	(PhCH ₂) ₂ ^d
1d	4	40	3d (9)
1e	5	68	2e (5)

^aThe photolysis was carried out in inert atmosphere for 24h, at λ = 300nm in a photochemical reactor, using acetone as solvent at 10°C. [1] = 2-5mM. ^bConversion (cvn) yield based on substrate consumption. ^cIsolated yields. ^dOnly product observed.

In order to discriminate between the reactivity of singlet or triplet state of *Se*-methyl substituted phthalimides, the photocyclization of **1b** was evaluated under both direct excitation (acetonitrile) and solvent-sensitization (acetone) conditions. Furthermore, the influence of aprotic solvent in the photolysis was assessed using toluene as solvent. The results are compiled in Table 2.

Table 2: Photoreaction of *N*-[(methylseleno)-propyl]-phthalimide **1b**.^a

Solvent	cvn (%) ^b	Product (%) ^c			
		2b	3b	4b	5b
1 acetonitrile	53	3	4	3	1
2 Acetone	90	8	5	30	2
3 acetone ^d	33	6	13	1	1
4 Toluene	95	11	8	26	29

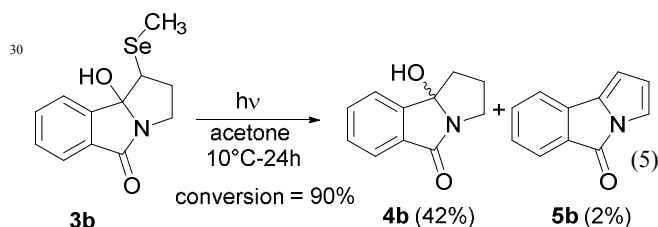
^aThe photolysis was carried out in inert atmosphere for 24h, at λ = 300nm in a photochemical reactor at 10°C. [1b] = 2-5mM. ^bConversion (cvn) yield based on substrate consumption. ^cIsolated yields. ^d[1b] = 12mM.

Irradiation of **1b** acetonitrile solution gave similar product distributions but in a lesser conversion when compared with acetone (Table 2, entries 1 and 2, respectively). At higher concentration of **1b** using acetone as solvent, a lower conversion was also observed. The yield of cyclic product **4b** dropped and a slightly increase of **3b** was observed (Table 2, entry 3). Finally when toluene was used as solvent the photoreaction of **1b** took place with a good conversion. The main products observed were **4b** and **5b** in a 26% and 29% isolated yield respectively (Table 2, entry 4).

These results suggest that the cyclic products could be formed by direct excitation or triplet-sensitization by acetone. Interestingly, the photocyclization in apolar solvent was also

efficient where ET processes with radical ions as intermediaries are unlikely. However, a number of examples have been reported where intramolecular ET reactions have shown to be efficient even in non polar solvent such as benzene.¹⁸ Thus, it can be noted that the effect of the solvent polarity in this type of reactions is less pronounced than expected and there is not a clear cut-off on the reactivity going from polar to non polar solvents. In addition, toluene could also act in these reactions as a sensitizer, like acetone, since it is able to absorb light in our experimental conditions and its intersystem crossing quantum yield is also efficient.¹⁹

As mentioned above, when the photolysis takes place at low conversion, an increase in the yield of selenium including product **3b** is found together with a marked decrease in the amount of **4b**. This observation indicates that the non-containing selenium heterocyclic compound **4b** is a secondary photoproduct. In order to probe this, the photolysis of the isolated **3b** was carried out in the same reaction conditions (eq. 5). The irradiation of **3b** cleanly delivers in a 42% yield the cyclic product **4b** and 2% of **5b**. The irradiation of the isolated **4b** was also conducted in order to check the possible route of formation of **5b**. In this case, the reaction was performed in toluene as solvent because, under these conditions, **5b** was obtained in a higher yield. However, **4b** was recovered unchanged (96% of mass recovering) and no trace of **5b** was observed. These results support the fact that the formation of both cyclic products **4b** and **5b** comes from a different decomposition pathway of the primary product **3b**, probably due to a photo-homolytic fragmentation of SeCH₃ and OH groups.



To gain insight into the reaction mechanism, steady-state absorption and emission together with laser flash photolysis measurements were performed. All the experiments were compared with *N*-methyl-phthalimide, compound without the selenium atom in its structure and used as a reference to evaluate quantitatively the effect of the inclusion of the heteroatom in the photophysical properties of *N*-(selenoalkyl)-phthalimides (Figure S1 in the Supporting information). The shape of the UV-visible absorption spectra of compounds **1a-e** is similar to that of *N*-methyl-phthalimide. This result indicates little, if any, electronic interaction in the ground state. For **1a-d**, steady-state fluorescence spectra were acquired. *N*-(selenoalkyl)-phthalimides exhibit a very weak fluorescence with quantum yield lower than 1×10^{-3} , indicating a poor contribution of the excited singlet state on the photochemistry of these compounds. Similar results were observed for the sulphur analogues (Figure S2 in the Supporting information).²⁰

Mediated Excitation: Energy Transfer

The triplet energy transfer to phthalimide **1b** was studied by laser flash photolysis in the presence of different aromatic ketones namely: thioxanthone ($E_T = 265 \text{ kJ mol}^{-1}$), benzophenone ($E_T = 289 \text{ kJ mol}^{-1}$), 4, 4'-dimethoxy-benzophenone ($E_T = 292 \text{ kJ mol}^{-1}$) and xanthone ($E_T = 310 \text{ kJ mol}^{-1}$) as energy transfer sensitizers.¹⁷ In all cases the triplet lifetime of the sensitizers become shorter with the increasing concentration of **1b**. Thus, the measured quenching rate constants range 10^8 - $10^{10} \text{ M}^{-1} \text{ s}^{-1}$ in acetonitrile as indicated in Table 3.

Table 3: Rate constant k_q for the energy transfer reaction between sensitizers and **1b** in acetonitrile.^a

Sensitizer	E_T^b	λ_{max}^c	$k_q(\text{T}_1)^d$
1 Thioxanthone	265	650	0.035
2 Benzophenone	289	520	0.83
3 4,4'-Dimethoxybenzophenone	292	350	0.53
4 Xanthone	310	605	1.76

^aIn argon-saturated solution at room temperature, $\lambda_{\text{exc}} = 355 \text{ nm}$.
^b $E_T/\text{kJ mol}^{-1}$. ^c $\lambda_{\text{max}}/\text{nm}$ observed for the T-T absorption of the ketones. ^d $k_q/10^{10} \text{ M}^{-1} \text{ s}^{-1}$

The possibility of an ET or hydrogen atom transfer between the sensitizers and **1b** was disregarded since after the laser pulse, formation of the ketyl radical anion or ketyl radical of the sensitizer was not observed (Figure S1, Supporting information). Thus, the quenching was ascribed to an energy transfer process to the phthalimide-type acceptor molecule from the triplet state of high energy sensitizers. The quenching rate constants in acetonitrile at room temperature are close to the diffusion-controlled limit, except for the reaction with thioxanthone where this rate constant is significantly lower. These results are in agreement with literature data for *N*-phthalimides corresponding to a triplet energy of $E_T = 286$ - 297 kJ mol^{-1} .²¹ Therefore, it is expected that in photocyclization reactions, the solvent acetone ($E_T = 332 \text{ kJ mol}^{-1}$)¹⁷ can efficiently act as a triplet sensitizer.

Direct Excitation: Triplet Formation and Decay

A ground-state bleaching trace was obtained after short laser pulse excitation of **1b** in Argon saturated acetonitrile. The 266-nm laser flash photolysis revealed one transient whose absorption spectrum is close to the ground-state absorption around 290 nm (Figure S1 in the Supporting information and Figure 1a). The analysis of the bleaching signal in the presence of different oxygen concentration reveals a quenching effect, indicating that the bleaching signal can be ascribed to the corresponding triplet state of phthalimide **1b** (Figure 1b). The analysis was based in the ground-state recovering kinetics, as expected for a triplet excited state; the kinetics is accelerated by the presence of molecular oxygen. In argon atmosphere, this transient decay rapidly with a lifetime of $0.047 \mu\text{s}$ compared to *N*-methyl-phthalimide whose lifetime is $2.47 \mu\text{s}$, determined under the same experimental conditions.

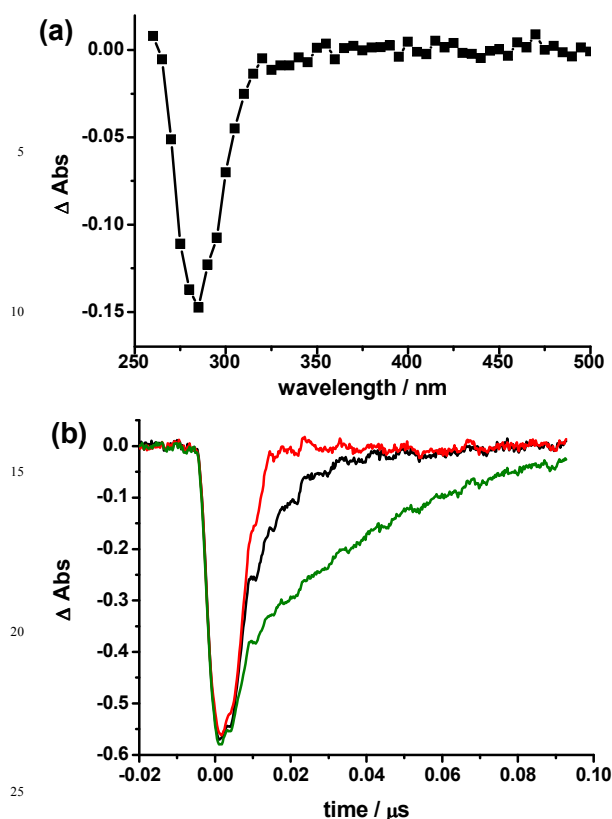
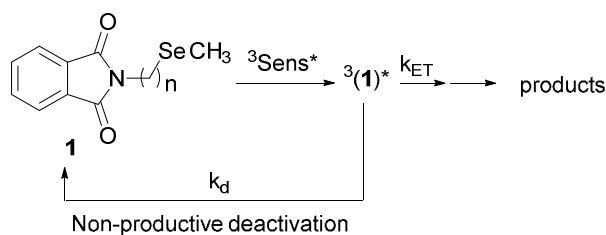


Fig. 1 (a) Transient Absorption spectrum in argon-saturated acetonitrile solution of **1b**, 0.2 mM, obtained at 0.05 μs after the 266 nm laser pulse. (b) Temporal profile recorded at 300 nm for **1b** under Argon (green), aerated (black) and oxygen atmosphere (red).

Intramolecular Electron Transfer

The photochemical processes proposed for **1** are outlined in Scheme 3. Under sensitization condition the triplet state $^3(1)^*$ can be deactivated by several routes. It can decay thermally to ground state **1** with total rate constants k_d or may be quenched via an electron transfer process with a rate constant of k_{ET} giving the cyclic products.



Scheme 3 Deactivation mechanism from triplet state of **1**

By comparing the triplet state decays of *N*-methyl-phthalimide and phthalimide **1b** substituted by an electron atom donor such as selenium, it is noticeable that the presence of the seleno-alkyl group clearly reduces the lifetime of the transient, indicating the participation of an electron transfer process. Therefore, the rate constant for the non-productive decay (k_d) of **1b** can be assumed as the k_d value derived from the lifetime ($\tau_{t,0} = 2.47 \mu\text{s}$) of non-reactive *N*-methyl-phthalimide ($1/\tau_{t,0} = 4.05 \times 10^5 \text{ s}^{-1}$). Based on

the triplet lifetime (τ_t) measured for compound **1b**, the rate constant for the electron transfer (k_{ET}) can be calculated from the expression in eq. 6, where k_q can be estimated as $2.09 \times 10^7 \text{ s}^{-1}$, from the reciprocal of the triplet lifetime measured for **1b** and *N*-methyl-phthalimide as a model of a compound lacking the donor in the molecular moiety.²²

$$\frac{1}{\tau_t} - \frac{1}{\tau_{t,0}} = k_q (T_1) \quad (6)$$

On the other hand, free energy changes associated with electron transfer from both the singlet and triplet state, ΔG_{ET}^0 , from **1b** were estimated using the Gibbs free energy relationship (eq. 7).²³

$$\Delta G_{ET} = 23.06 [E^0(D^+/D) - E^0(A/A^-) + \Delta E_{coul}] - E_{0-0} \quad (7)$$

The redox properties of phthalimide **1b** were explored by means of electrochemical experiments. The cyclic voltammogram of **1b** in acetonitrile with tetrabutylammonium tetrafluoroborate (TBABF₄) as the supporting electrolyte at room temperature under argon shows an anodic wave at 1.3 V (oxidation of R-SeCH₃ moiety) and a cathodic one centred at -1.47 V. Within the limit of experimental uncertainty, the former electrochemical reaction is to be considered irreversible, while the latter is reversible (reduction of the phthalimide moiety) (Figure 2). The irreversibility on the oxidation remained the same up to the maximum sweep rate accessible (100 V s^{-1}). The oxidation half-wave potential, $E_{p/2}$, of 1.19 V for the oxidation of **1b** can be used as a reasonable approximation value for the E^0 value because of the irreversibility of the process. Under the same condition, for the model compound *N*-methyl-phthalimide, only the cathodic wave is observed (Figure S4 in the Supporting information). Those values are in quite good agreement with those reported for the model substrates dibutylselenide (peak potential at 1.65 V vs. SCE)²⁴ and *N*-methyl-phthalimide (-1.37 V in DMF and 1.47 V in MeCN both vs SCE).^{25,26}

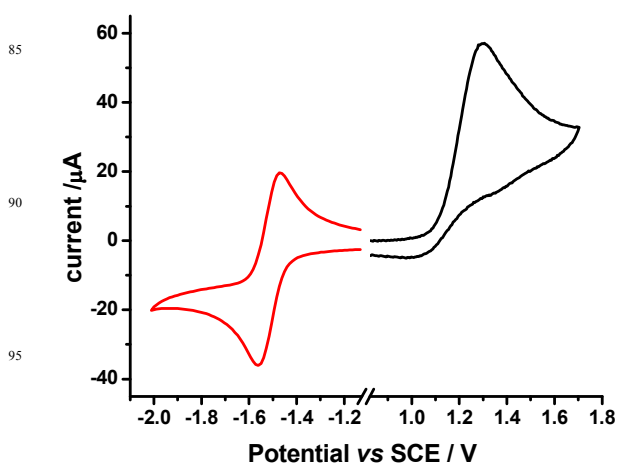


Fig. 2 Cyclic voltammogram of **1b** (1.6 mM) in acetonitrile with 0.1M TBABF₄ in argon atmosphere vs SCE at a glassy carbon electrode at room temperature, $\nu = 0.1 \text{ V s}^{-1}$.

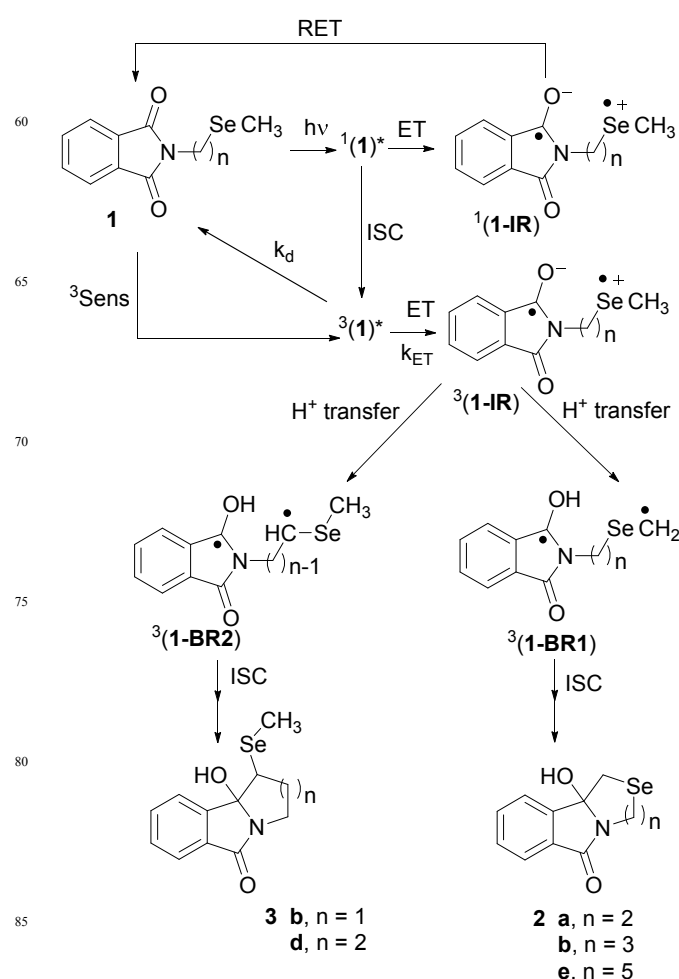
In addition, the singlet and triplet energies [$E_{0-0}(S_1) = 87.95$ kcal mol⁻¹, $E_{0-0}(T_1) = 70.98$ kcal mol⁻¹] for *N*-methyl-phthalimide have already been reported.²⁷ By fitting the above data in eq 7, the following free energy changes resulted: $\Delta G_{ET}(S_1) = -25.2$ kcal mol⁻¹ and $\Delta G_{ET}(T_1) = -8.2$ kcal mol⁻¹. This means that the electron transfer from the singlet excited state should be even more efficient. However, a decrease in conversion under direct irradiation compared with the triplet-sensitizer reaction was observed (Table 2, entries 1 and 2, respectively). Similar results were found with thioalkyl-phthalimide derivatives.²⁸

Proposed Reaction Mechanism

Considering the above results from the sensitizer experiments in steady-state and time resolved experiments, we can propose the following reaction mechanism (Scheme 4). Cyclic products can be formed either by direct excitation or solvent-sensitization. From an energetic point of view, electron transfer from the singlet excited state is more efficient. However, the lower conversion observed in the reactions can be attributed to the presence of a very fast competitive process such as reverse electron transfer (RET); however, a low population of the single excited state by non radiative process such as internal conversion or intersystem crossing cannot be ruled out.

In the presence of a triplet sensitizer, an efficient population of the triplet state from *N*-(selenoalkyl)-phthalimide is possible. Under these conditions the reaction proved more efficient and an intramolecular electron transfer process to give the radical ion pair as intermediates can occur. The shorter lifetime of the triplet state of **1b** compared with the model compound *N*-methylphthalimide can be considered a piece of evidence taken from the time-resolved experiments. Subsequently, a proton transfer takes place from the radical-cation of the selenium group to the ketyl radical anion in ³(**1-IR**). For phthalimide **1b**, two competitive proton transfer pathways are possible from adjacent carbons, δ -CH₂ and ϕ -CH₃ positions. Thus, deprotonation at the terminal methyl group (ϕ -CH₃) by the ketyl radical anion gives the biradical intermediate ³(**1-BR1**) which, subsequently, through intersystem crossing and radical-recombination, renders the *endo*-cyclic product **2b**. Yet, proton transfer from the methylene group (δ -CH₂) generates the corresponding biradical intermediate ³(**1-BR2**) which, following the same sequence, gives the *exo*-cyclic product **3b** observed. As stated above, **4b** and **5b** are secondary photoproducts arising from **3b**, probably due to photo-homolytic fragmentation of C-SeCH₃ and C-OH bonds.

A similar reaction scenario can be stated for the other *N*-(selenoalkyl)-phthalimides which, for compounds **1a** and **1e**, only deprotonation of the methyl group was found, obtaining six and nine member *endo*-cyclic selenium-containing products isolable as **2a** and **2e**, respectively. However, for derivative **1d**, only deprotonation of the methylenic group was found, giving the *exo*-cyclic selenium-containing product **3d**. As a general trend, six and five membered ring products are preferred, possibly given by a kinetic control, favouring a six and five member transition state geometry in the proton transfer step. For compound **1e**, ϵ methylenic protons are far from selenium atom and not acidic enough for a good deprotonation reaction.



Scheme 4 Mechanism proposed for the formation of photocyclization products

Conclusions

The photocyclization reactions of substituted *N*-phthalimides are of great synthetic interest and lead to the construction of a variety of cyclic compounds, six-, seven- and even nine-member selenacycles. It is noteworthy that these scaffolds are difficult to obtain by conventional procedures. In addition, the azabicycles obtained are benzofused analogues to bioactive pyrrolizidine and indolizidine alkaloids, within this context, the reported photochemical procedure being here a useful alternative to the currently available multistep syntheses. The ability of selenium as an electron donor group in intramolecular electron transfer reactions was evaluated, it being an additional contribution to the study of the phthalimide system. The mechanistic analysis in steady-state and with time-resolved and electrochemical techniques allowed us to evidence that electron transfer processes are involved in the photocyclization of *N*-selenoalkylphthalimides.

As mentioned, new heterocyclic selenium-bearing compounds were synthesized. Moreover, the high degree of competing reaction pathways suggests that the photochemistry of selenium-containing phthalimide compounds offers an interesting source of new synthetic developments taking into account that studies in this line are in early stages.

Experimental

General Methods

Irradiation was conducted in a Rayonet photoreactor RPR-100 (16 x 3000 Å lamps, $\lambda = 300 \pm 10$ nm). ^1H , ^{77}Se and ^{13}C NMR spectra were registered on a Bruker AC-400 (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 Agilent 5890 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. GS-MS analyses were performed on a Shimadzu GC-MS QP 5050 spectrometer employing a 30 m x 0.25 mm x 0.25 μm with a 5% phenylpolysiloxane phase column. Ionization was achieved by electronic impact (70eV) and detection set up positive mode. HRMS spectra were recorded on a GCT Premier orthogonal acceleration time-of-flight (oa-TOF) GC mass spectrometer.

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:** Transient absorption spectra and quenching were determined using a Continuum-Surelite I Nd:YAG laser generating 266 nm and 355 nm laser pulse (10 mJ per pulse, ca 10 ns pulse duration) as excitation source. The spectrometer was a commercial Applied Photophysics, LKS80. All the kinetics determinations were performed at 25 ± 1 °C.

Electrochemistry: The working electrode was a 3 mm-diameter glassy carbon electrode disk (Tokai) 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, AUTOLAB PGSTAT20, ECO-Chemie.

Chemicals: Phthalimide, *N*-(2-chloroethyl)-phthalimide, 1,3-dibromopropane, 1,5-dibromopentane, dimethyldiselenide, KOH, Na, benzophenone, 4,4-dimethoxy-benzophenone, xanthone and thioxanthone were purchased from Sigma-Aldrich Chemicals Co. Acetonitrile, acetone, dimethylformamide (Merck HPLC grade) were used as purchased without any further purification and stored over molecular sieves (4Å). Toluene was distilled after refluxing with Na/benzophenone and stored over nitrogen atmosphere. Water was filtered Milli-Q purity.

The *N*-(haloalkyl)-phthalimides were synthesized and purified according to the previously reported procedures.^{14, 15} Products 9b-hydroxy-2,3-dihydro-1H-pyrrolo[2,1-a]isoindol-5(9bH)-one (**4b**)²⁹ and 5H-pyrrolo[2,1-a]isoindol-5-one (**5b**)³⁰ are known and exhibited physical properties identical to those reported in the literature.

General procedure for the synthesis of selenoalkyl phthalimide derivatives (1a-e), (Scheme 2): Into a three-necked, 250-mL, round-bottomed flask equipped with a cold-finger condenser charged with dry ice-ethanol, a nitrogen inlet and a magnetic

stirrer was condensed 150 mL of ammonia previously dried with Na metal under nitrogen. The dialkyl diselenide (0.5 mmol) was added and then 2 equiv. of Na metal in small pieces, waiting for bleaching between each addition. After the last addition, the ammonia was allowed to evaporate and 25 mL of DMF was introduced together with *N*-(haloalkyl)-phthalimide (1 mmol). The crude reaction was dissolved in water and then extracted with diethyl ether. The product was further purified by column chromatography using a mixture of petroleum ether and ethylic ether as the eluent.

N-(2-Selenomethyl)ethyl)-phthalimide (**1a**): (yield 65%) ^1H NMR (400 MHz, CDCl_3): $\delta = 2.07$ (s, 3H), 2.83 (t, $J = 7.2$ Hz, 2H), 3.95 (t, $J = 7.2$ Hz, 2H), 7.73 (dd, $J = 5.6, 3.2$ Hz, 2H), 7.85 (dd, $J = 5.6, 3.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 4.2, 22.7, 37.4, 123.3, 132.0, 134.0, 168.1$; ^{77}Se NMR (76 MHz, CDCl_3): $\delta = 61.5$. GC-MS (EI) m/z 269 (M^+ , 39), 174 (86), 160 (82), 130 (36), 122 (100), 76 (47). HRMS (ESI-TOF) m/z calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_2\text{Se}$: 270.0028 [$\text{M}+\text{H}$]⁺, found: 270.0030.

N-(3-Selenomethyl)propyl)-phthalimide (**1b**): (yield 76%) ^1H NMR (400 MHz, CDCl_3): $\delta = 2.00$ (s, 3H), 2.05 (q, $J = 7.0$ Hz, 2H), 2.56 (t, $J = 7.0$ Hz, 2H), 3.79 (t, $J = 7.0$ Hz, 2H), 7.72 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.85 (dd, $J = 5.4, 3.1$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 4.0, 21.8, 28.9, 38.0, 123.2, 132.1, 133.9, 168.3$; ^{77}Se NMR (76 MHz, CDCl_3): $\delta = 80.2$. GC-MS (EI) m/z 283 (M^+ , 12), 188 (100), 169 (15), 160 (85), 148 (8), 130 (33), 104 (18), 77 (24), 76 (24), 41 (35). HRMS (ESI-TOF) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_2\text{Se}$: 284.0185 [$\text{M}+\text{H}$]⁺, found: 284.0195.

N-(3-Selenobenzyl)propyl)-phthalimide (**1c**): (yield 63%) ^1H NMR (400 MHz, CDCl_3): $\delta = 1.98$ (q, $J = 7.2, 2\text{H}$), 2.46 (t, $J = 8.0$ Hz, 2H), 3.73 (t, $J = 7.2$ Hz, 2H), 3.78 (s, 2H), 7.11-7.26 (m, 5H), 7.72 (dd, $J = 5.6\text{Hz}, 3.2$ Hz, 2H), 7.84 (dd, $J = 5.6, 3.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 20.3, 26.9, 29.1, 38.0, 123.2, 126.7, 128.5, 128.8, 132.1, 134.0, 139.0, 168.3$; ^{77}Se NMR (76 MHz, CDCl_3): $\delta = 255.3$. GC-MS (EI) m/z 359 (M^+ , 4), 268 (5), 188 (22), 160 (13), 91 (100), 65 (15). HRMS (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{17}\text{NNaO}_2\text{Se}$: 382.0317 [$\text{M}+\text{Na}$]⁺, found: 382.0325.

N-(4-Selenomethyl)butyl)-phthalimide (**1d**): (yield 65%) ^1H NMR (400 MHz, CDCl_3): $\delta = 1.67 - 1.76$ (m, 2H) 1.77 - 1.82 (m, 2H), 1.98 (s, 3H), 2.58 (t, $J = 7.2$ Hz, 2H), 3.72 (t, $J = 7.0$ Hz, 2H), 7.72 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.85 (dd, $J = 5.5, 3.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 4.1, 24.6, 27.4, 28.7, 37.4, 123.2, 132.1, 133.9, 168.4$; ^{77}Se NMR (76 MHz, CDCl_3): $\delta = 77.5$. GC-MS (EI) m/z 297 (M^+ , 7), 202 (32), 160 (100), 130 (12), 77 (10). HRMS (ESI-TOF) m/z calcd for $\text{C}_{13}\text{H}_{15}\text{NNaO}_2\text{Se}$: 320.0161 [$\text{M}+\text{Na}$]⁺, found: 320.0167.

N-(5-selenomethyl)pentyl)-phthalimide (**1e**): (yield 57%) ^1H NMR (400 MHz, CDCl_3): $\delta = 1.41-1.49$ (m, 2H), 1.67-1.75 (m, 4H), 1.97 (s, 3H), 2.53 (t, $J = 7.3$ Hz, 2H), 3.69 (t, $J = 7.3$ Hz, 2H), 7.68 (dd, $J = 5.4, 3.04$ Hz, 2H), 7.81 (dd, $J = 5.4, 3.04$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 4.0, 25.1, 27.0, 28.1, 29.7, 37.8, 123.2, 132.1, 133.9, 168.4$; ^{77}Se NMR (76 MHz, CDCl_3): $\delta = 77.0$. GC-MS (EI) m/z 311 (M^+ , 12), 216 (53), 160

(100), 148 (13), 130 (24), 104 (10), 77 (15). **HRMS (ESI-TOF)** m/z calcd for $C_{14}H_{18}NO_2Se$: 312.0498 $[M+H]^+$, found: 312.0505.

General procedure for the photocyclization of selenoalkyl phthalimides derivatives (1a-e): A solution of **1** in acetone (2-5 mM) was irradiated ($\lambda = 300$ nm) in a Pyrex tube for 24 h while purged with a stream of nitrogen and cooled to nr. 10 °C. After removal of the solvent under reduced pressure, the residue was purified by column chromatography and analyzed by GC.

10b-hydroxy-1,3,4,10b-tetrahydro-6H-[1,4]selenazinof[3,4-a]isoindol-6-one (2a): 1H NMR (400 MHz, $CDCl_3$): $\delta = 2.57$ (dt, $J = 14.4, 2.4$ Hz, 1H), 2.75 (td, $J = 12.4, 3.2$ Hz, 1H), 2.89 (d, $J = 12.4$ Hz, 1H), 3.15 (d, $J = 12.4$ Hz, 1H), 3.45 (ddd, $J = 14.2, 12.4, 3.2$ Hz, 1H), 4.37 (s, 1H), 4.68 (dt, $J = 14.4, 2.8$ Hz, 1H), 7.51-7.55 (m, 1H), 7.58-7.64 (m, 2H), 7.81-7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.9, 30.5, 37.8, 82.9, 121.6, 123.9, 130.1, 131.2, 132.3, 145.7, 165.1$; ^{77}Se NMR (76 MHz, $CDCl_3$): $\delta = 74.7$. **GC-MS (EI)** m/z 253 (24), 251 ($[M-H_2O]^+$, 100), 249 (11), 238 (23), 236 (93), 234 (54), 170 (47), 159 (10), 129 (41), 115 (61), 102 (41), 89 (29), 75 (49). **HRMS (ESI-TOF)** m/z calcd for $C_{11}H_{11}NNaO_2Se$: 291.9848 $[M+Na]^+$, found: 291.9859.

11b-hydroxy-1,4,5,11b-tetrahydro-3H,7H-[1,4]selenazepino[3,4-a]isoindol-7-one (2b): 1H NMR (400 MHz, $CDCl_3$): $\delta = 2.09$ (q, $J = 14.4$ Hz, 2H), 2.64-2.67 (m, 2H), 3.09 (m, 1H), 3.15 (d, $J = 14$ Hz, 1H), 3.40 (d, $J = 14$ Hz, 1H), 3.50 (d, $J = 14.8$ Hz, 1H), 4.33 (s, 1H), 7.42-7.46 (m, 1H), 7.51-7.54 (m, 1H), 7.57-7.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.6, 28.4, 34.1, 38.6, 92.2, 121.7, 123.0, 129.7, 131.5, 132.6, 146.3, 168.2$; ^{77}Se NMR (76 MHz, $CDCl_3$): $\delta = 156.9$. **GC-MS (EI)** m/z 265 ($[M-H_2O]^+$, 75), 263 (40), 236 (45), 184 (100), 129 (21), 115 (10), 102 (26). **HRMS (ESI-TOF)** m/z calcd for $C_{12}H_{14}NO_2Se$: 284.0185 $[M+H]^+$, found: 284.0204.

9b-hydroxy-1-(selenomethyl)-1,2,3,9b-tetrahydro-5H-pyrrolo[2,1-a]isoindol-5-one (3b): 1H NMR (400 MHz, $CDCl_3$): $\delta = 2.03$ (s, 3H), 2.74 (m, 2H), 2.83 (m, 1H), 3.34 (d, $J = 1.4$ Hz, 1H), 3.44 (ddd, $J = 11.3, 5.7, 4.2$ Hz, 1H), 3.66 (dt, $J = 11.3, 8.5$ Hz, 1H), 7.50 (td, $J = 7.5, 1.2$ Hz, 1H), 7.59 (td, $J = 7.5, 1.2$ Hz, 1H), 7.67 (dt, $J = 7.5, 1.2$ Hz, 1H), 7.81 (dt, $J = 7.5, 1.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 4.7, 35.7, 41.1, 44.6, 95.5, 122.8, 123.8, 130.2, 131.7, 132.8, 145.9, 169.8$; ^{77}Se NMR (76 MHz, $CDCl_3$): $\delta = 88.5$. **GC-MS (EI)** m/z 265 ($[M-H_2O]^+$, 100), 263 (61), 250 (98), 169 (85), 142 (23), 115 (79). **HRMS (ESI-TOF)** m/z calcd for $C_{12}H_{13}NNaO_2Se$: 306.0004 $[M+Na]^+$, found: 306.0030.

10b-hydroxy-1-(selenomethyl)-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-6(2H)-one (3d): 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.52 - 1.37$ (m, 1H), 1.84 - 1.75 (m, 1H), 2.05 (s, 3H), 2.21 - 2.12 (m, 1H), 2.33 (qd, $J = 13.0, 3.7$ Hz, 1H), 2.49 (dd, $J = 13.0, 4.0$ Hz, 1H), 3.00 (td, $J = 13.0, 3.4$ Hz, 1H), 3.73 (d, $J = 1.6$ Hz, 1H), 4.04 (dd, $J = 13.0, 4.9$ Hz, 1H), 7.39 (td, $J = 7.5, 0.9$ Hz, 1H), 7.53 (m, 2H), 8.28 (d, $J = 7.6$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 4.3, 27.1, 29.6, 35.5, 46.2, 88.5, 123.1, 124.5,$

129.6, 130.8, 131.6, 147.1, 164.9. ^{77}Se NMR (76 MHz, $CDCl_3$): $\delta = 159.3$. **GC-MS (EI)** m/z 279 ($[M-H_2O]^+$, 100), 264 (99), 234 (19), 184 (69), 182 (99), 172 (39), 154 (26), 130 (26), 129 (28), 128 (39), 127 (42), 102 (41). **HRMS (ESI-TOF)** m/z calcd for $C_{13}H_{16}NNaO_2Se$: 320.0161 $[M+Na]^+$, found: 320.0174.

13b-hydroxy-1,4,5,6,7,13b-hexahydro-3H,9H-[1,4]selenazonino[3,4-a]isoindol-9-one (2e): 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.49 - 1.57$ (m, 2H), 1.66 - 1.74 (m, 1H), 1.78 - 1.86 (m, 2H), 2.03 - 2.15 (m, 1H), 2.52 - 2.58 (m, 1H), 2.63 - 2.69 (m, 1H), 3.28 (d, $J = 14.1$ Hz, 1H), 3.41 (m, 2H), 3.58 - 3.64 (m, 1H), 3.53 (s, 1H), 7.41 - 7.44 (m, 2H), 7.54 - 7.58 (m, 1H), 7.60 - 7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.1, 24.4, 24.8, 26.8, 29.4, 38.0, 91.0, 121.3, 123.1, 129.9, 131.5, 132.4, 146.5, 169.0$; ^{77}Se NMR (76 MHz, $CDCl_3$): $\delta = 117.5$. **GC-MS (EI)** m/z 293 ($[M-H_2O]^+$, 17), 236 (12), 212 (14), 198 (16), 184 (88), 158 (100), 146 (33), 130 (20), 115 (13), 102 (29), 89 (21). **HRMS (ESI-TOF)** m/z calcd for $C_{14}H_{17}NNaO_2Se$: 334.0317 $[M+Na]^+$, found: 334.0343.

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Notes and references

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