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FULL PAPER

Intramolecular hydroamination of selenoalkynes to 2-selenylindole in absence of catalyst

Felipe L. Coelho, Eduarda S. Gil, Paulo F. B. Gonçalves, Leandra F. Campo and Paulo H. Schneider*

Abstract: In this work, a series of 2-chalcogenylindoles were synthesized by an efficient new methodology, starting from chalcogenoalkynes, including an inedited tellurium indole derivative. For the first time, these 2-substituted chalcogenylindoles were obtained in the absence of metal catalyst or base, under thermal conditions only. In addition, the results described herein represent a methodology with inverse regioselectivity for the chalcogen functionalisation of indoles.

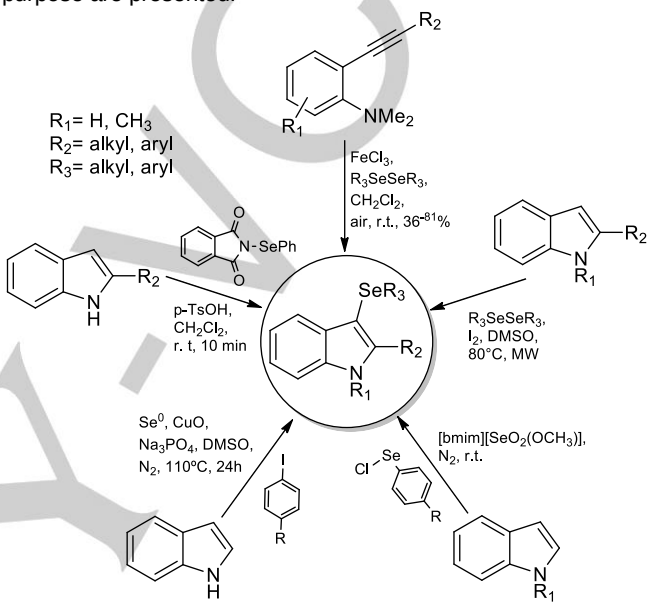
Introduction

Annually, the Njarddarson group reports the most prescribed pharmaceutical products. In the latest published list, almost 50% of the 200 compounds listed are N-containing hetorocycles.[1] This number reinforces the importance and applicability of nitrogen-containing heterocycles in biological and pharmacological areas. In this context, the indole ring is one of the most widely distributed heterocycles in nature, ranging from tryptophan to vincristine or more complex analogues.[2] Described as 'privileged structures', since they are capable of binding to many receptors with high affinity and selectivity, substituted indoles play important roles in, for example, modulation of oxidative stress, intestinal inflammation and hormone secretion in animals, as well as in controlling plant defence systems or growth and insect behaviour.[3-4]

Since the last century, synthesis and functionalisation of indoles remains the focus of many synthetic organic chemists. Numerous methods for the preparation of these compounds have been developed, of which the highlighted improvements involve starting material availability and functional group tolerance allied to milder conditions.[5] For over 100 years, classical Fischer indole synthesis has been a useful protocol for a variety of substituted derivatives, even at the gram scale.[5] The condensation of aryl hydrazines with ketones has been gradually substituted by other methods.[5]

Reactions that have emerged in the last decades involve cyclisation of o-alkynylanilines and derivatives,[6a] reductive cyclisations of nitrocompounds,[6b] Larock heteroannulation[6c] and more specific reactions, such as Nenitzescu[6d] and Madelung reactions.[6e] Usually, these methods require metal catalysis or the use of strong bases, such as t-BuOK, to promote the cyclisation.[6f]

On the other hand, concerning selenium-functionalised indoles, few methods have been developed or applied to the synthesis of these compounds. In Figure 1, some important protocols for this purpose are presented.[7]



Scheme 1. General protocols for indole functionalisation with selenium moiety.

It is important to mention that the developed protocols usually present the necessity for an electrophilic selenium reagent, previously prepared for derivatisation. The reaction conditions generally involve metal catalysis or oxidasing reagents. Moreover, all describe the functionalisation of the 3-position, furnishing 3-selenylindoles. To the best of our knowledge, there is only one protocol where the authors identified a 2-substituted selenylindole as a by-product in a coupling reaction between arylselenocyanate and 2-ethynylaniline catalysed by $Cu(OAc)_2$ and Ag_2CO_3, in attempt to synthesise chalcogenoalkynes.[8]

Given the reactivity of the indole ring, and the well-established conditions in functionalisation reactions for the synthesis of 3-selenylindoles, there is clearly a lack of development of new strategies for functionalisation in position 2. With this criterion in mind, and in consonance with our continuing interest in the synthesis of organoselenium compounds,[9] we designed a selenium-containing precursor, considering a subsequent cyclisation step for an indole construction in which the functionalised position was pre-defined. Based on protocols established for cyclisation of 2-(phenylethynyl)anilines, which afford 2-phenyl-1*H*-indoles, we chose appropriate selenylalkyne derivatives for the preparation of 2-selenylindoles.

Chalcogenoalkynes, in general, have been already employed as precursors in many chemical transformation reactions, including electrophilic cyclisation,[10] electrocyclisation,[11]

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10.1002/chem.201901667

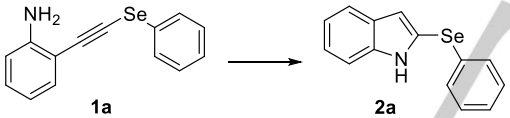
acidic hydrolysis,[12] hydroalumination,[13] hydrohalogenation[14] and hydroboration.[15] Likewise, organoselenium groups constitute a very interesting reactive site since the carbon–chalcogen bond can be readily replaced by carbon–hydrogen,[16] carbon–lithium,[17] allowing a series of reactions with different kind of electrophiles and carbon–carbon bonds.[18]

In this context, this work presents an innovative application of these compounds in the intramolecular hydroamination of *o*-chalcogenoalkyne anilines for the synthesis of 2-selenylindoles. In fact, we envisioned the possibility that the chalcogen atom plays a crucial role on the reaction pathway.

Results and Discussion

Our study began by attempting to find a cyclisation methodology starting from 2-((phenylselanyl)ethynyl) aniline (**1a**). To prove our concept on a thermal cyclisation, we started our studies by reproducing some methodologies from the literature, in which several transition metal catalysts were selected, proposing the formation of a six-membered complex, which could increase the intramolecular hydroamination reaction associated with selenium assistance.[19] The results obtained are summarised in Table 1. For silver and indium catalysts (entries 1, 4 and 5) no reaction was observed and starting material was recovered at the end of the reaction. The use of palladium and copper (entries 2 and 7) led to decomposition of **1a** to diphenyldiselenide and 2-ethynylaniline.

Table 1. Reaction optimization of thermal intramolecular hydroamination.[a,b]



1a **2a**

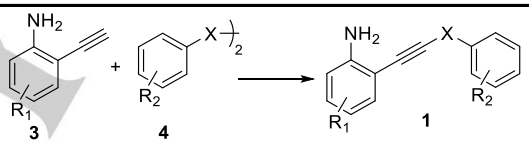
#	Catalyst	Solvent	Time/ Temperature	Yield
1	$AgNO_3$	MeCN	8h / 60 °C	-
2	$PdCl_2(PPh_3)_2$	MeCN	4h / 70 °C	-
3	$NaAuCl_4$	EtOH	18h / 70 °C	35% [c]
4	$InCl_3$	DMSO	8h / 60 °C	-
5	$InBr_3$	DMSO	8h / 60 °C	-
6	$AuCl_3$	EtOH	6h / 70 °C	-
7	Cu nano	DMSO	6h / 80 °C	-
8	-	Toluene	18h / 110 °C	90% [d]

[a] Catalyst load = 10 mol %. [b] All reactions were also evaluated at room temperature. [c] by GC-MS. [d] Isolated yield.

When gold catalysts, such as $NaAuCl_4$ or $AuCl_3$ (entries 3 and 6) were used, a complex mixture of side products was formed, and in case of $NaAuCl_4$, a 35% yield of the desired product could be identified by GC-MS. Back to our initial point, an alternative strategy to circumvent these problems of (*i*) feasibility of carbon–selenium bond cleavage, (*ii*) inactivation of catalyst, probably by effective coordination with amino groups and (*iii*) side-product formation, could be a thermal cyclisation. In this context, refluxing 2-((phenylselanyl)ethynyl)aniline (**1a**) in toluene afforded the desired 2-selenylindole **2a** in 90% yield. More important, this developed method proceeded in the absence of any metal catalyst or strong base and required high temperature only. An additional reaction using potassium *tert*-butoxide in *N*-methylpyrrolidone was performed. The addition of base to the reaction medium instantly caused a colour change, and decomposition of starting materials was observed by TLC.

Having developed this method for the preparation of 2-substituted selenylindoles, other examples of chalcogenoalkyne analogues were synthesised to evaluate the extension of this thermal cyclisation, Table 2. The derivatives **1b**–**1m**, presented in Table 2, comprise a series of compounds in which it was intended to verify the influence of donating and withdrawing groups, steric effects, chalcogen exchange and moreover, substituents both in alkyne and selenide moieties. It is worth mentioning that all chalcogenoalkynes (**1b–1m**) are new compounds, and their synthesis required a methodology study.

Table 2. Synthesis of chalcogenoalkynes compounds (**1a-1m**) and synthetic methodologies applied.



3 **4** **1**

	X	R_1	R_2	Method	Yield (%)
1a	Se	H	H	1	88
1b	Se	H	4-CH_3	1	84
1c	Se	H	4-Cl	1	91
1d	Se	H	3-CF_3	1	85
1e	Se	H	4-OCH_3	1	77
1f	Se	H	2-CH_3	1	63
1g	Se	H	C_4H_9	1	42
1h	S	H	H	2	89
1i	Te	H	H	2	49
1j	Se	4'-CH_3	H	3	70
1k	Se	4'-Br	H	3	45
1l	Se	4'-CN	H	3	53
1m	Se	4'-NC_4H_8	H	3	89

Method 1: DMSO (2 mL), terminal alkyne (1.0 mmol), diorganyl dichalcogenide (0.5 mmol), CsCO3 (650 mg, 1.0 mmol), 3,5-dimethyl-1-((phenylselanyl)methyl)-1H-pyrazole (13 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol). Method 2: CH2Cl2 (1.5 mL), terminal alkyne (1.0 mmol), diorganyl dichalcogenide (0.5 mmol) and AgNO3 (10 mol %). Method 3: DMSO (3.0

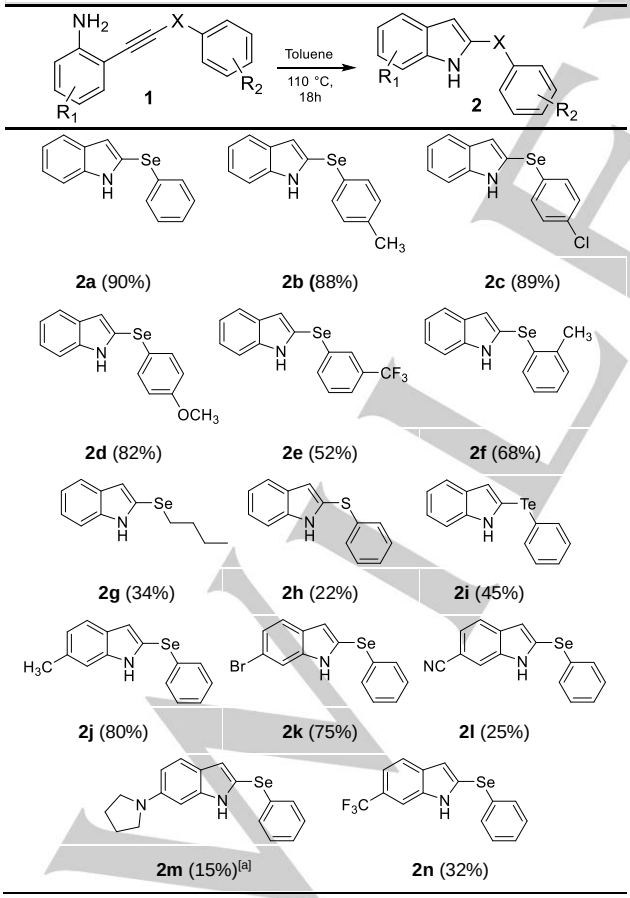
10.1002/chem.201901667

mL), terminal alkyne (1.0 mmol), diorganyl dichalcogenide (0.5 mmol), CsCO3 (650 mg, 1.0 mmol) and InCl3 (0.1 mmol).

For the synthesis of the chalcogenoalkynes, we chose three well-established methods from the literature, which involved, besides phenylacetylene (3) and dichalcogenide (4) derivatives, copper complexes with caesium carbonate (method 1), silver nitrate (method 2) or indium chloride with caesium carbonate (method 3) (for detailed protocols for the synthesis of 1b–1m, see Supporting Information). The choice of each method was according to the best product yield. All the chalcogenoalkynes were obtained in good to excellent yields (45–91%).

Having synthesised all the starting materials, the scope of thermal cyclisation was investigated. In general, thermal cyclisation tolerated diverse substitution patterns and a broad spectrum of substituents attached to the phenyl ring of both the selenide and the alkyne. The desired products were isolated in good to excellent yields. For instance, functional groups attached to the phenyl ring of the diselenide, such as donating groups (**2b** and **2d**), as well as withdrawing groups (**2**c and **2e**) did not significantly affect product yield. Despite low yield for **2g**, with an alkyl chain, the result is very positive taking into account the low stability of substrate **1g**. Additionally, the methodology is also efficient, when considering steric environment, in case of *o*-methylated compound **2f**.

Table 3. Substrate scope of intramolecular cyclization.



2a (90%) **2b** (88%) **2c** (89%)

2d (82%) **2e** (52%) **2f** (68%)

2g (34%) **2h** (22%) **2i** (45%)

2j (80%) **2k** (75%) **2l** (25%)

2m (15%)[a] **2n** (32%)

Reaction conditions: **1a-m** (0.5 mmol), toluene (5 mL), reflux for 18 h. [a] Reaction with 5 mol % $NaAuCl_4$.

Different groups attached to the phenyl group of the alkyne were also tolerated. For strong withdrawing or donating groups, the efficiency of thermal cyclisation was less. For instance, the substrate containing *N*-pyrrolidinyl group (**2m**) underwent reaction only after addition of gold catalyst ($NaAuCl_4$). For this example, no reaction was observed even when heating the reaction mixture at reflux for 72 h. Very importantly, tellurium and sulfur indole derivatives were also obtained by this methodology, especially taking into account that the tellurium derivative is described for the first time in the literature. This result clearly represents an important methodology for the synthesis of tellurium-containing indoles.

Noteworthy, although chalcogenylindoles containing sulphur and tellurium could be prepared by this presented methodology, selenium derivatives achieved considerably better yields. Thus, to further comprehend the mechanism of the reaction and the influence of the chalcogen atom in the reaction pathway of chalcogenoacetyene cyclisation, a computational study was carried out. First, for the choosen selenoalkyne **1a**, as model substrate, the optimized geometry and electrostatic surface potential (Figure 1) shows a twisted structure in which a higher electronic density is presented by carbon C10 in comparison with carbon C11, -0.1057 and -0.0243 respectively.

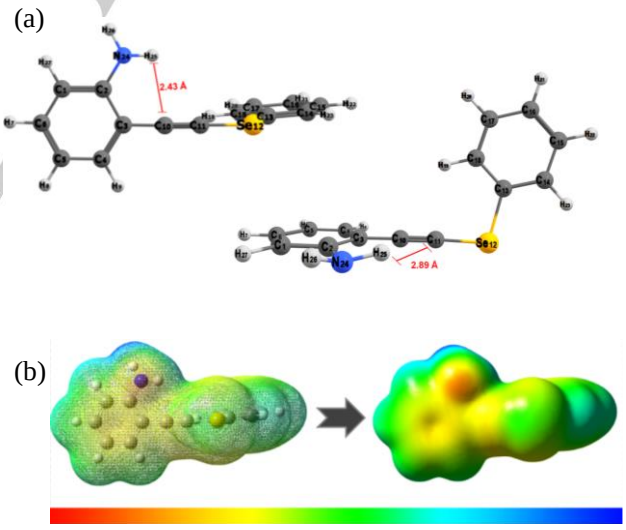


Figure 1. (a) Optimized geometry of selenoalkyne 1a calculated at the CAM-B3LYP/6-31G level. (b) Electrostatic surface potentials (ESP) for 1a (electronic density grows from blue to red).

The computed reaction profile for selenoalkyne cyclisation involves an initial step of hydrogen transfer from amino group to carbon C10. This step is proposed since no transition state was found involving direct nucleophilic attack of nitrogen to the carbon C11 without previously protonation. The transition state TS1 presents a high energy barrier, in agreement with thermal

10.1002/chem.201901667

conditions. Important to mention, that in case of hydrogen transfer to carbon C11, an equilibrium structure was found, comprised by a six-membered intramolecular hydrogen interaction. Thus, the vinyl cation intermediary is stabilized by selenium via orbitalar interaction between lone pair on chalcogen and σ*-(antibonding) C10-C11. After conformational stabilization (TS2), the intramolecular nucleophilic attack of nitrogen to carbon C11 takes place, generating the indole product in an exergonic process.

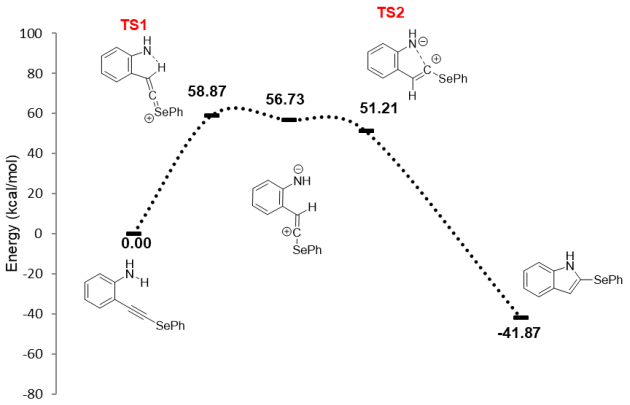


Figure 2. Computed reaction profile (CAM-B3LYP/6-31G(d)) for the cyclisation of selenoalkyne to indole. The energy of selenoalkyne is taken as reference (0 kcal.mol^{-1}).

The reasons why this reaction occurs preferentially with selenium than sulfur was investigated, including also a comparison with oxygen. The NBO analysis of the reactant and analogue molecules with sulfur and oxygen instead of selenium were performed to predict the most important donor−acceptor interactions for the studied systems. The interacting orbitals and the second-order perturbation energies E(2) of these interactions are shown in Table 3. The interaction between the lone pairs and the σ*(antibonding) C10−C11 orbitals n(X)→σ*(C10-C11) (X = O, S, Se) are stronger for the molecule with selenium, when compared to the analogues with sulfur and oxygen. On the other hand, the interactions between the lone pairs of the chalcogens with the π*(antibonding) C10−C11 orbitals n(X)→π*(C10-C11) are stronger for oxygen than for sulfur and selenium. Considering these two interactions, the molecule with oxygen can donate more electronic density to the C10-C11 bond than the other two molecules. Because of this, the C10-C11 bond is stronger for the oxygen analogue. Thus, the interaction of carbons 10 and 11 with hydrogen 25 is more difficult for oxygen analogue than for the sulfur and selenium analogues, *i.e*, the formation of TS1 is less favorable for these two molecules. Additionally, the molecule with selenium donates less electronic density to the C10-C11 bond than the other two molecules, showing that C10-C11 bond is weaker for this molecule. Thus, the interaction of carbons 10 and 11 with hydrogen 25 is easier for the selenium analogue than for the sulfur and oxygen analogues, *i.e*, the formation of TS1 is more favorable for the molecule with selenium.

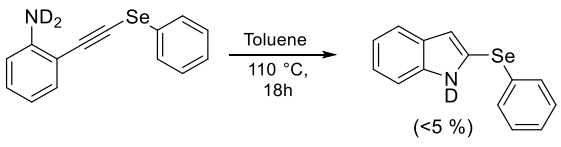
In addition, to furnish additional evidences for the reaction mechanism, and taking into account the experimental results, where we observed a dramatical reduction in the reaction yield for the sulfur derivatives, some additional theoretical

Table 4. Interacting orbitals of molecule 1a and its analogues with sulfur and oxygen and the second-order perturbation energies E(2) of these interactions.

Interaction	E(2)
n(Se)→σ*(C10-C11)	8.96 kcal.mol^{-1}
n(Se)→π*(C10-C11)	28.24 kcal.mol^{-1}
n(S)→σ*(C10-C11)	8.22 kcal.mol^{-1}
n(S)→π*(C10-C11)	33.49 kcal.mol^{-1}
n(O)→σ*(C10-C11)	5.65 kcal.mol^{-1}
n(O)→π*(C10-C11)	37.99 kcal.mol^{-1}

experiments were performed. The energy barrier for the formation of TS1, that comprise the proton transfer from NH_2, was calculated with an alkyl group attached to the sulfur, which could make S-alkyne more basic and a trifluoromethyl group in *para* position of NH_2 to increase acidity the NH_2 (see Electronic Supplementary Information). In both cases, a decrease in the energy barrier could occur and facilitate the reaction. However, the calculated energy barriers showed a slight decrease in energy, 2 and 4 Kcal/mol, respectively, which would not influence significantly the reaction. Indeed, in the case, of trifluoromethyl substituent, the respective selenylindole **2n** was obtained with 32 % yield similar to that observed for cyano derivative (example **2n**, Table 3).

Finally, we propose a cyclisation of the deuterated selenoalkyne **1a** to provide some information about the isotope effect in the proposed protocol. Employing the same reaction parameters, a significant reaction inhibition was observed supporting the proposed mechanism. Probably, the migration of the deuterium atom was not as effective as hydrogen and the TS1 specie, from deuterated selenoalkyne, is not accessed, precluding the product achievement.



Scheme 2. Isotopic effect experiment in selenoalkyne thermal cyclisation.

Conclusions

In summary, we report for the first time a successful intramolecular hydroamination reaction of chalcogenoalkynes to 2-substituted chalcogenylindoles in the absence of any catalyst or basic conditions. A broad range of derivatives were obtained in moderate to high yields. This report presents a methodology with inverse regioselectivity for chalcogen functionalisation of indoles. In addition, we could also synthesise the unpublished tellurium indole derivative. The change from selenium to tellurium and sulfur analogues leads us to conclude that the selenium moiety assists the reaction, making the use of catalyst unnecessary.

Experimental Section

General: For general experimental details, characterisation data, and ^{1}H and ^{13}C NMR spectra for novel compounds, see the Supporting Information.

General protocol for preparation of chalcogenalkyne (1a-1m)

Method 1: To a round-bottom flask was added as follow: DMSO (2 mL), respective terminal alkyne (1.0 mmol), corresponding diorganyl dichalcogenide (0.5 mmol), $CsCO_3$ (650 mg, 1.0 mmol), 3,5-dimethyl-1-((phenylselanyl)methyl)-1*H*-pyrazole (13 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol). Reaction mixture was stirred for 25 minutes at room temperature. Crude was diluted with water, extracted with AcOEt (3x25 mL), dried and purified by column chromatography (Hex:AcOEt, 1:99).

Method 2: To a round-bottom flask was added as follow: CH_2Cl_2 (1.5 mL), terminal alkyne (1.0 mmol), corresponding diorganyl dichalcogenide (0.5 mmol) and $AgNO_3$ (10 mol %). The mixture was stirred at 25 °C until complete consumption of terminal alkyne (by TLC). After that, the solvent was evaporated and the crude product was purified by column chromatography on silica gel using a hexane or a mixture of hexane/ethyl acetate as the eluent to afford the desired products.

Method 3: To a round-bottom flask was added as follow: DMSO (3.0 mL), respective terminal alkyne (1.0 mmol), corresponding diorganyl dichalcogenide (0.5 mmol), $CsCO_3$ (650 mg, 1.0 mmol) and InCl3 (0.1 mmol). The reaction vessel was placed in an oil bath at 80 °C and stirred for appropriated time (by TLC). After reaction, the resulting mixture was cooled to room temperature, dilute in Et_2O and washed with brine (3 x 15 mL), water (3 x 15 mL), and dried over Na_2SO_4. Purification carried out by column chromatography (Hex:AcOEt, 1:99).

General procedures for selenylindoles synthesis

In a 10 mL Schlenk tube, a solution of correnponding chalcogenalkyne (0.5 mmol) in toluene (5 mL) was refluxed for 18 hours. After this, solvent was removed under reduced pressure and crude was purified by column chromatography on silica gel using hexane/ethyl acetate (5:95) as the eluent to afford the desired products.

Theoretical calculations

The reaction coordinate for the formation of molecule **5a** from molecule **4a** was inspected by DFT calculations using the functional CAM-B3LYP.[20] The basis set used was the 6-31G(d). All species were fully optimized and their final structures were tested by vibrational analysis in order to verify the existence of transition state TS (presents an imaginary frequency) or equilibrium structure. The solvent effect was considered in all the calculations using PCM (polarizable continuum model) and the solvent considered was toluene.[21] Charges from electrostatic potential using a grid based method (ChelpG) were computed, as well the electrostatic potential surfaces (ESP).[22] Natural Bond Orbital (NBO) analysis were performed in order to elucidate the factors responsible for stabilization of this molecule.[23]All the calculations were performed using Gaussian 16 package.[24] The electrostatic surface potentials were rendering using GaussView 5.0 program.[25]

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Keywords: Selenium • Indoles • Chalcogenoalkynes • Thermal Cyclisation • DFT study

[1] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Ed.* **2010**, *87(12)*, 1348-1349.

[2] R. Vicente, *Org. Biomol. Chem.*, **2011**, *9*, 6469-6480.

[3] D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103,* 893-930.

[4] J-H. Lee, T. K. Wood, J. Lee, *Trends in Microbiol.*, **2015**, *23(11)*, 707-718.

[5] G. Gribble, *J. Chem. Soc*., *Perkin Trans.* **2000**, *1*, 1045–1075.

[6] (a) A. L. Rodriguez, C. Koradin, W. Dohle, P. Knochel, *Angew. Chem., Int. Ed.* **2000**, *39*, 2488-2490. (b) L. Ackermann, *Org. Lett.* **2005**, *7*, 439-442. (b) I. Choi, H. Chung, J. W. Park, Y. K. Chung, *Org. Lett.* **2016**, *18 (21)*, 5508–5511. (c) M. Shen, G. Li, B. Z. Lu, A. Hossain, F. Roschangar, V. Farina, C. H.Senanayake, *Org. Lett.* **2004**, *6 (22)*, 4129–4132. (d) S. Shefali, S. K. Srivastava, S. M. Husbands, J. W. Lewis, *J. Med. Chem.* **2005**, *48*, 635-638. (e) E. F. Da Settimo, F. Simorini, S. Taliani, *J. Med. Chem.* **2008**, *51,* 5798–5806. (f) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875-2911.

[7] (a) A. Sperança, B. Godoi, P. H. Menezes, G. Zeni, *Synlett* **2013**, *24*, 1125–1132. (b) E. G. Zimmermann, S. Thurow, C. S. Freitas, S. R. Mendes, G. Perin, D. Alves, R. G. Jacob, E. J. Lenardão, *Molecules* **2013**, *18*, 4081-4090. (c) X. Zhao, Z. Yu, T. Xu, P. Wu, H. Yu, *Org. Lett.* **2007**, *9(25)*, 5263-5266. (d) J. B. Azeredo, M. Godoi, G. M. Martins, C. C. Silveira, A. L. Braga, *J. Org. Chem.* **2014**, *79*, 4125−4130. (f) D. Luo, G. Wu, H. Yang, M. Liu, W. Gao, X. Huang, X. Chen, H. Wu, *J. Org. Chem.* **2016**, *81*, 4485−4493.

[8] N. Mukherjee, D. Kundu, B. C. Ranu, *Adv. Synth. Catal.* **2017**, *359*, 329-338

[9] (a) D. S. Rampon, F. S. Rodembusch, R. Lourega, P. F. B. Gonçalves, A. A. Merlo, P. H.Schneider, *J. Braz. Chem. Soc.* **2010**, *21*, 2100-2107. (b) C. S. Radatz, D. Alves, P. H. Schneider, *Tetrahedron* **2013**, *28*, 1316-1321. (c) T. E. Frizon, D. S. Rampon, H. Gallardo, A. A. Merlo, P. H. Schneider, O. E. D. Rodrigues, A. L. Braga, *Liq. Cryst*. **2012**, *39*, 769-777. (e) D. S. Rampon, P. H. Schneider, *J. Org. Chem.*, **2014**, *79*, 5987-5992. (f) C. S. Radatz, D. S. Rampon, R. A. Balaguez, D. Alves, P.H. Schneider, *Eur. J. Org. Chem.* **2014**, 31, 6945-6952.

[10] F. Manarin, J. A. Roehrs, R. M. Gay, R. Brandão, P. H. Menezes, C. W. Nogueira, G. Zeni, *J. Org. Chem.* **2009**, *74*, 2153–2162.

[11] W. Lim, Y. H. Rhee, *Eur. J. Org. Chem.* **2013**, *3*, 460–464.

[12] M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, C. Santi, R. Terlizzi, *Eur. J. Org. Chem.* **2004**, *16*, 3447-3458.

[13] M. I. Al-Hassan, *Synth. Commun.* **2001**, *31(19)*, 3027–3030.
[14] J. V. Comasseto, P. H. Menezes, H. A. Stefani, G. Zeni, A. L. Braga, *Tetrahedron* **1996**, *52(29)*, 9687-9702.
[15] D. Y. Yang, X. Huang *J. Organomet. Chem.* **1997**, *543*, 165-169.
[16] M. Sevrin, D. Vanende, A. Krief, *Tetrahedron Lett.* **1976**, *17,* 2643-2646.
[17] (a) A. Krief, J. Bousbaa, *Tetrahedron Lett*. **1997**, *38*, 6291-6294. (b) I. D. Kostas, C. G. Screttas, *J. Org. Chem.* **1997**, *62*, 5575-5577.
[18] (a) C. C. Silveira, A. L. Braga, A. S. Vieira, G. Zeni, *J. Org. Chem.* **2003**, *68*, 662-665. (b) A. L. Stein, F. N. Bilheri, G. Zeni *Chem. Commun.* **2015**, *51*, 15522-15525. (c) A. V. Martynov, V. A. Potapov, S. V. Amosova, N. A. Makhaeva, I. P. Beletskaya, L. Hevesi, *J. Organomet. Chem.* **2003**, *674*, 101-103. (d) G. Zeni, C. W. Nogueira, J. M. Pena, C. Pilissão, P. H. Menezes, A. L. Braga, J. B. T. Rocha, *Synlett* **2003**, *4*, 579-581.
[19] For indole synthesis from 2-ethylaniline derivatives: (a) A. L. Rodriguez, C. Koradin, W. Dohle, P. Knochel, *Angew.Chem., Int. Ed.* **2000**, *39*, 2488. (b) N. Sakai, K. Annaka, T. Konakahara, *Org. Lett.* **2004**, *6*, 1527. (c) B. C. J. Van Esseveldt, F. L. van Delft, J. M. M. Smits, R. de Gelder, H. E. Schoemaker, F. P. J. T. Rutjes, *Adv. Synth. Catal.* **2004**, *346*, 823. (d) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, L. M. Parisi, *J. Org. Chem.* **2005**, *70*, 6213. (e) A. Arcadi, E. Pietropaolo, A. Alvino, V. Michelet, *Org. Lett.* **2013**, *15*, 2766–2769.
[20] T. Yanai, D. Tew, N. Handy, *Chem. Phys. Lett.* **2004**, *393*, 51-57.
[21] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999-3094.
[22] C. M. Breneman, K. B. Wiberg, *J. Comput. Chem.* **1990**, *11*, 361-373.
[23] F. Weinhold, C. R. Landis, *Chem. Educ. Res. Pract.* **2001**, *2*, 91-104.
[24] Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
[25] GaussView, Version 5, Dennington, R. Keith, T. A. Millam, J. M. Semichem Inc., Shawnee Mission, KS, 2009.

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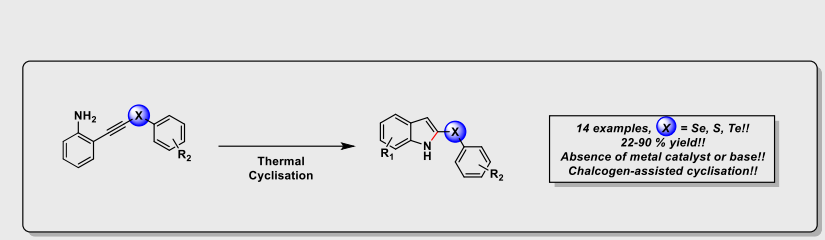

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Page No. – Page No.

Intramolecular hydroamination of selenoalkynes to 2-selenylindole in absence of catalyst