Visible light-promoted synthesis of 2-aryl-(3-organoselanyl)thieno[2,3-b]pyridines

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ABSTRACT
We describe a simple and environment-friendly visible light-promoted protocol to access 2-aryl-(3-organoselanyl)thieno[2,3-b]pyridines, through the selenocyclization of 3-(arylethynyl)-2-(alkylthio)pyridines in the presence of diorganyl diselenides as selenium source. The Se-based reactive species were generated in situ by the homolytic Se-Se bond cleavage using blue LED in an O₂ atmosphere at room temperature. The protocol was suitable for a wide range of substrates bearing different substituents, allowing the synthesis of twenty-one thieno[2,3-b]pyridines in good to excellent yields (57–99%).

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Introduction
The Green Chemistry Principle #6, the design for energy efficiency, warns about the economic and environmental impact of the energy-intensive processes in the chemical industry. To minimize this negative impact of the chemical activity, it is necessary to look for alternative, more efficient energy sources, combined with the development of synthetic procedures conducted at room temperature and pressure (1–8). Over the past few decades, electromagnetic irradiation (microwave, UV, and visible-light), sonochemistry, and mechanochemistry have played a pivotal role in achieving this audacious goal by promoting many chemical transformations to prepare valuable compounds (9–14). In this context, the photochemistry has been consolidated as an important field of the synthetic organic chemistry, being characterized as a clean and low-energy demand method able to promote chemical reactions, mainly through TM- and dye-based photocatalysis, disclosing an initial single electron transfer (SET) process (15–21).

Heterocycles are recognized as a very important class of natural and synthetic compounds which play an important role in the manufacturing and pharmaceutical industries (22–28). This importance is evident considering that around 60% of the approved small-molecule drugs registered in the U.S. FDA database are composed of at least one heterocycle unit (29–31). A representative example of this class of compounds is the thieno[2,3-b]pyridine derivatives, which have attracted interest due to their activities against some pathologies, including inflammatory processes and cancer (32–45). Two outstanding examples are compound A, a drug candidate against the hepatitis C virus (HCV) (46) and the derivative B, an anti-HIV agent (Scheme 1)(47,48).

Organoselenium compounds are largely known for their usefulness as intermediates in organic synthesis, in addition to their catalytic ability (49–54). Moreover, through the molecular hybridization with heterocyclic compounds, organoselenium moieties can generate bioactive molecules with multitarget and boosted
pharmacological activities (55–58). Some remarkable examples are the 3-selanylindole derivative C (59–63) which has been exhaustively investigated against mood and neurodegenerative diseases, and the 4-selanylquinoline derivative D, which presents a powerful anti-inflammatory activity superior to that of Meloxicam, a worldwide marketed drug for the treatment of inflammatory processes (Scheme 1) (64).

Very recently, to study the synthetic viability of joining these bioactive molecular cores (thieno[2,3-b]pyridines and organoselenium), we reported a synthetic strategy to construct 2-aryl-(3-organochalcogenyl)thieno[2,3-b]pyridines 3, through a thermal electrophilic chalcogenocyclization of 3-(arylethynyl)-2-(alkylthio)pyridines 1, promoted by Oxone® and diorganyldichalcogenides 2 (Scheme 2) (65).

Scheme 1. Bioactive thieno[2,3-b]pyridines and organoselenium derivatives.

Scheme 2. Our achievements in the synthesis of 2-aryl-(3-organoselanyl)thieno[2,3-b]pyridines 3.
In the last decade, visible light-promoted strategies have disclosed a new era in the chemistry of organoseelenium compounds, by delivering simple and efficient protocols to construct Se-based structures, just using inexpensive light-emitting diodes (LEDs) or commercial CFL bulbs, triggering radical oxidative processes (12).

Thus, as part of our continuing efforts to develop new environment-friendly protocols to construct important structures from a biological point of view, we present herein a simple and efficient strategy to access 2-aryl(3-organoselanyl)thieno[2,3-b]pyridines 3, through the visible light-promoted selenocyclization of 3-(phenylethynyl)-2-(propylthio)pyridine derivatives 1, using diorganyl diselenides 2 in O2 (Scheme 2).

Results and discussion

To set the best reaction conditions and based on our recent works (65,66), we elected 3-(phenylethynyl)-2-(propylthio)pyridine 1a as the standard substrate to perform the visible-light-promoted selenocyclization, using different chip LEDs (50 W) as light source, to prepare 2-phenyl-3-(phenylselanyl)thieno[2,3-b]pyridines 3, through the visible light-promoted selenocyclization of 3-(phenylethynyl)-2-(propylthio)pyridine derivatives 1, using diorganyl diselenides 2 as the product.

Initially, substrate 1a (0.15 mmol) reacted in the presence of EtOH, under blue light irradiation (λ ~ 460-470 nm, peak at 470 nm), with different amounts of diphenyl diselenide 2a. By employing 0.075 mmol of 2a (1.0 equiv), the desired product 3a was obtained at 80% after 24 h, while increasing the amount of 2a to 0.09 mmol (1.2 equiv) did not cause a remarkable change in the reaction yield (Table 1, entries 1-2). Surprisingly, when 0.11 mmol (1.5 equiv) of PhSeSePh 2a was employed, the reaction time was drastically reduced, and the desired product 3a was isolated in 90% yield after 2 h (Table 1, entry 3).

Based on this result, a brief study of the reaction medium was conducted, using several polar aprotic solvents and hexanes (Table 1, entries 4–8). Among the tested solvents, DMSO presented the worst performance, with the desired product 3a being obtained in just 5% yield after 24 h. On the other hand, reactions performed using acetone, THF, MeCN, and hexanes yielded 3a successfully (92–98%) in short reaction times (1.25-2 h). We elected hexanes as the best solvent for the reaction, affording 3a in 98% yield after 1 h (Table 1, entry 8).

After this, experiments were performed using white and green lights (LED chip, 50 W), and in both cases, the reaction time slightly increased, while a decrease in the reaction yield was observed (Table 1, entries 9 and 10). We have performed one experiment outdoor, under sunlight, and in this case, the expected product 3a was obtained in 60% yield after 8 h of reaction (Table 1, entry 11). In contrast, no reaction was observed in the dark, and after 24 h the starting materials 1a and 2a were recovered, confirming the pivotal role of the visible light as the energy source (Table 1, entry 12).

Table 1. Optimization of the reaction.a

| Entry | 2a (mmol) | Visible light | Solvent | Time (h) | Yield (%) b |
|-------|-----------|---------------|---------|----------|-------------|
| 1     | 0.075     | blue LED     | EtOH    | 24       | 80          |
| 2     | 0.09      | blue LED     | EtOH    | 24       | 84          |
| 3     | 0.11      | blue LED     | EtOH    | 2        | 90          |
| 4     | 0.11      | blue LED     | acetone | 1.25     | 93          |
| 5     | 0.11      | blue LED     | THF     | 1.25     | 92          |
| 6     | 0.11      | blue LED     | DMSO    | 24       | 5           |
| 7     | 0.11      | blue LED     | MeCN    | 1.25     | 97          |
| 8     | 0.11      | blue LED     | hexanes | 1        | 98          |
| 9     | 0.11      | white LED    | hexanes | 2        | 86          |
| 10    | 0.11      | green LED    | hexanes | 3        | 75          |
| 11    | 0.11      | sunlight     | hexanes | 8        | 60          |
| 12d   | 0.11      | sunlight     | hexanes | 24       | -           |
| 13d   | 0.11      | blue LED     | hexanes | 0.5      | 98          |

aA round-bottomed flask were added 3-(phenylethynyl)-2-(propylthio)pyridine 1a (0.15 mmol), diphenyl diselenide 2a and solvent (2.0 mL). The resulting mixture was stirred under visible-light irradiation (LED chip, 50 W) at room temperature, under open-air condition, during the tabulated time.

bYields obtained after column chromatography.

cThe reaction was carried out under dark conditions.

dThe reaction was performed under an O2 atmosphere (in a balloon).
Finally, the reaction was performed under an O₂ atmosphere (in a balloon), and the reaction time was satisfactorily halved, yielding 3a in 98% after 0.5 h (Table 1, entry 13).

Based on these outcomes, the best reaction condition was set as irradiating a mixture of the substrates 1a (0.15 mmol) and 2a-o (0.11 mmol) in hexanes as solvent (2.0 mL) under an O₂ atmosphere with blue LED (50 W) for 0.5 h (Table 1, entry 13).

With the best condition in hand, the reaction scope was evaluated to explore the applicability of our protocol to other substrates. The detailed experimental procedure for the reaction is described in the Supporting Information, page S3. First, the scope of diorganyl diselenides 2a-o was evaluated in the reaction with the alkyne 1a (Table 2). When para-substituted diaryl diselenides bearing electron-donating (R = 4-MeC₆H₄ 2b; R = 4-MeOC₆H₄ 2c) or electron-withdrawing groups (R = 4-FC₆H₄ 2d; R = 4-ClC₆H₄ 2e) were used, the expected products 3b-e were accessed in 86-99% yield, after 24-36 h of reaction. It is worth mentioning that among them, bis(4-fluorophenyl)diselenide 2d was the less reactive, affording 3-[(4-fluorophenyl)selenyl]-2-phenylthieno[2,3-b]pyridine 3d in 86% yield after 36 h.

Surprisingly, ortho-substituted diphenyl diselenides 2f (R = 2-MeC₆H₄), 2g (R = 2-MeOC₆H₄), and 2h (R = 2-ClC₆H₄) reacted smoothly with the substrate 1a,
reducing the reaction time remarkably in comparison with the para-substituted ones (0.5 h for 2f, 6 h for 2g and 4 h for 2h), and yielding the respective products 3f-h also in an excellent yield range of 96–99%. Satisfactorily, diaryl diselenide 2i, bearing the strong electron-withdrawing CF3 group at the meta-position, reacted efficiently to yield the product 3i in 91% after 7 h. An equally excellent outcome was obtained starting from the bulky and electron-rich dimesityl diselenide 2j, which gave the product 3j in 98% yield after 3 h. Unfortunately, dibutyl diselenide 2k was not a suitable substrate in the reaction with 1a, and only trace amounts of the product 3k could be detected, even after 72 h of reaction (Table 2).

Additionally, the behavior of other aromatic diselenides 2 as substrate in the transformation was evaluated. bis(1-naphthyl)diselenide 2l and bis(2-thienyl)diselenide 2m reacted with 1a to afford the respective products 3l and 3m in 70% and 57% yield, after 72 and 24 h, respectively. 2,2’-dipyridyl diselenide 2n failed to yield the respective product 3n, even after 72 h of reaction. Interestingly, bis[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]diselenide 2o, derived from glycerol, reacted successfully under our conditions to give the product 3o in 77% yield after 7 h.

Then, we evaluated the behavior of differently substituted 3-(arylethynyl)-2-(propylthio)pyridine derivatives

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**Table 3. Scope of the reaction of 3-(arylethynyl)-2-(propylthio)pyridines 1b-i with 2a.**

| Compounds | Yield (%) | Time (h) |
|-----------|-----------|----------|
| 3p        | 96%       | 0.5      |
| 3q        | 88%       | 1        |
| 3r        | 96%       | 0.5      |
| 3s        | 85%       | 1        |
| 3t        | 89%       | 0.5      |
| 3u        | 91%       | 0.5      |
| 3v        | 90%       | 0.5      |
| 3w        | 91%       | 0.5      |

*a* In a round-bottomed flask were added the 3-(arylethynyl)-2-(propylthio)pyridine 1b-i (0.15 mmol), diphenyl diselenide 2a (0.11 mmol) and hexanes (2.0 mL). The atmosphere was saturated with O2 (in a balloon). The resulting mixture was irradiated with blue light (LED chip, 50 W) at room temperature for the tabulated time (monitored by TLC).

*b* Yields obtained after column chromatography. See Supporting information for details.

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**Scheme 3. Gram-scale experiment.**
1b-i in the reaction with diphenyl diselenide 2a under the optimal conditions (Table 3).

The reaction was not sensitive to the electronic effect of substituents in the para- and ortho-positions at the pendant phenyl ring of the triple bond. Thus, the p-tolyl 1b (R^1 = 4-MeC_6H_4) and p-chloro-phenyl 1d (R^1 = 4-ClC_6H_4) derivatives were good substrates, giving the expected products 3p and 3r both in 96% yield after 0.5 h. Steric hindrance effects, however, could be noticed, and o-tolyl 1c (R^1 = 2-MeC_6H_4) and o-chloro-phenyl 1e (R^1 = 2-ClC_6H_4) derivatives were converted to 3q and 3s in slightly lower yields of 88% and 85%, respectively after 1.0 h of reaction. Additionally, the 1-naphthyl derivative 1f reacted effectively with 2a to afford the expected product 3t in 89% yield after 0.5 h. Then, the effect of methyl substituents in the pyridyl ring at the positions C5 (1g) and C6 (1h) was evaluated, and the respective products 3u and 3v were obtained in 91% and 90% yield after 0.5 h. The high selectivity of the reaction could be demonstrated using 3,5-bis(phenylethynyl)-2-(propylthio)pyridine 1i as starting alkynyl counterpart, affording exclusively 3w in 91% yield after 0.5 h, with the phenylalkynyl group at C5 remaining intact and able for new modifications (Table 3). Supporting information shows the spectral data and melting points of all the prepared compounds (pages S3-S12).

To evaluate the robustness and scalability of our protocol, a gram-scale experiment was carried out, increasing the reaction scale 20 times, from 0.15 to 3.0 mmol, in the reaction of 1a with 2a. Product 3a was obtained in 99% yield (1.09 g), after 1 h, proving the protocol applicability (Scheme 3).

To support a mechanism proposal, some control experiments were designed and carried out. Initially, a solution of substrate 1a was irradiated in the absence of diphenyl diselenide 2a. After irradiation for 0.5 h, no cyclization product was observed, with 1a recovered (Scheme 4, Eq. A). The reaction between 1a and 2a was observed under a nitrogen atmosphere (N_2, in a balloon). After 24 h of irradiation, the substrate 1a was converted to 3a in 70% yield (Scheme 4, Eq. B). Both results confirm that the selenium species is crucial to disclosing the annulation process, which can be accelerated and enhanced by O_2, even if the reaction may occur in its absence. The reaction was conducted in the presence of radical scavengers, TEMPO and hydroquinone, and the reaction efficiency was completely suppressed (Scheme 4, Eq. C). Finally, S-benzyl alkyne

Scheme 4. Control experiments around the reaction mechanism.
1j was employed as substrate instead of 1a and besides the product 3a (95% yield), benzaldehyde could be detected by GC-MS as a by-product (Scheme 4, Eq. D).

Based on these results, and literature reports (12,65), a plausible reaction mechanism was proposed for the transformation. The reaction was initiated by a homolytic Se-Se bond cleavage, generating the Se-centered radical species I (Scheme 5). The process could follow a radical annihilation in the absence of molecular oxygen (Scheme 4, Eq. B). However, O2 can improve the reaction rate, oxidizing the radical I to deliver the Se-based electrophilic species II and 1 equiv. of the superoxide ion. In the presence of the species II, substrate 1 is converted to seleniranium III, which undergoes an intramolecular annihilation to produce sulfonium IV. Then, the intermediate IV undergoes a nucleophilic substitution, in the presence of the superoxide ion (O2•−), to release the desired product 3 and the peroxyl radical V (67). Finally a visible light-promoted decomposition of V affords the respective aldehyde VI and a hydroxyl radical, which is converted to H2O2 (Scheme 5).

**Conclusion**

Here, we described the use of visible light (blue LED) as an efficient energy source to promote the selenocyclization of properly substituted alkynylpyridyl sulfides in the presence of diorganyl diselenides. By this new approach, twenty-one Se-containing thieno[2,3-b]pyridines were prepared in most cases in excellent yields and under mild conditions. A radical mechanism involving the Se-Se bond cleavage could be involved in the key step of the photo-promoted reaction.

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**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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