Photochemical C_{sp}²–H bond thiocyanation and selenocyanation of activated arenes, batch and continuous-flow approaches

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Abstract

Herein, we report an eco-friendly photochemical oxidative C_{sp}²–H thiocyanation and selenocyanation of activated arenes. The reaction proceeds under Violet LED irradiation in the presence of K₂S₂O₈, which quickly oxidizes KSCN and KSeCN, finally producing arylthio/selenocyanates. Using this benign, atom-economic protocol, the desired chalcogenide products were obtained regioselectively, with isolated yields that range from very good to excellent. Although, mechanistic study indicates that it is difficult to distinguish between a radical to a S_EAr reaction mechanism between the photo-induced formed •SCN, for the former, or NCSSCN, for the latter, to the aromatic heterocycles. The inhibition experiment together with the observed reactivity and regioselectivity, would be in agreement with the latter. The synthetic methodology designed could be successfully adapted to continuous-flow systems in a segmented-flow regime, employing the organic phase as the product reservoir. Using this setup, the advantage of the latter can be demonstrated by reducing the reaction time and improving the product yields. Similarly, the scaling up of the reaction to gram scale resulted in favorable outcomes by the flow setup, which installs the photo-flow chemistry as a powerful tool to be included into routine reaction procedures, which have great relevance for the pharmaceutical industry.

Graphical abstract

Keywords Photo-oxidation · Chalcogenides · Thio/selenocyanation · Continuous-flow

Dedications: Dedicated to Prof. Angelo Albino on occasion of his 75th anniversary.

Extended author information available on the last page of the article

Fig. 1 Example of widely used organosulfur compounds

1 Introduction

Organosulfur compounds are usually associated with stinking substances, being this stinkiness their most recognized sensory characteristic. However, these compounds can be found in nature as structures which are currently considered essential for life like penicillin and amino acids (cysteine and methionine). Also, they can be found in drugs for the treatment of inflammatory diseases [1], Alzheimer [2], cancer [3], and human immunodeficiency virus (HIV) [4], as well as in materials of technological interest such as PEDOT [5] (Fig. 1). The continuous demand and interest in this type of compounds is under ongoing growth. This is why organic chemists are constantly developing novel methodologies to obtain them. One of the main difficulties in the production of organosulfur compounds lies in the use of thiols and sulfides, which, besides their particular unpleasant smell, are usually sensitive precursors (oxidation or decomposition).

Therefore, their manipulation is difficult and is the focus of researchers interested in looking for alternative procedures that combine efficiency and practicality to obtain these compounds. To address this problem, thiocyanates emerge as important precursors in organic chemistry to install a sulfur atom into a molecule. For many years, these compounds have been an important area of study and development in organic chemistry due to the great versatility of this functional group. Depending on the desired structure, the thiocyanate group, as well as the nitrile one, can react to give different functionalities, by either keeping or not the sulfur atom in the molecule, (Scheme 1). Therefore, the versatility of thiocyanate group has motivated the exploration of diverse thiocyanation protocols.

Of the most frequent methods applied to functionalize organic compounds with thiocyanate (^-SCN , 1), anion

oxidation is the most used. For this purpose, 1 can be oxidized with a wide range of reagents, namely: bromine [6], diiodo pentoxide (I_2O_5) [7], iodic acid (HIO_4) [8], and thermally activated potassium persulphate ($\text{K}_2\text{S}_2\text{O}_8$) [9, 10], which are used in halogenated solvents, such as dichloromethane or chloroform. For years, organic chemists developed methodologies for the thiocyanation and selenocyanation of various substrates using transition metals [11] which, despite their productive benefits, have disadvantages associated to notable toxicity, waste generation, and financial cost. In addition, new methodologies have evolved from toxic or dangerous oxidizing agents to chemical photoreactions using

Scheme 1 Chemical transformations of the thiocyanate group

Scheme 2 General chemical reactions of (hetero)aryl thiocyanation

environmentally harmless organic dyes [12, 13], heterogeneous photo-catalysts [14, 15], or electrochemical procedures (Scheme 2) [16–18].

Nowadays, the implementation of the continuous-flow technology appears as chemoselective, safer and greener procedure for the synthesis of organosulfur compounds, which can be easily scaled up to a gram scale [19]. In addition, photochemical transformations can similarly benefit in improved yields, decreased reaction time-scales, and reduced catalyst loadings due to the highly efficient irradiation that result from having a short path length [20, 21]. In this sense, the use of continuous-flow chemistry has emerged as a powerful technique for photochemical processes applied to the production of fine chemicals and active pharmaceutical ingredients (APIs) [22–25].

Here we report the photochemical C_{sp}^2 -H substitution by the SCN group in the presence of persulphate anion using environ benign solvents (water/acetonitrile, Scheme 2). In addition, the methodology is extended to selenocyanate anions, we propose a possible reaction mechanism and, to add value to our synthetic methodology, we also asses a continuous-flow approach.

2 Results and discussion

2.1 Synthesis of 3-thiocyanate indole, reaction condition optimization

The reaction between thiocyanate anion 1 in the presence of persulphate anion and indole was explored as a first example. Although the oxidizing agent potassium persulphate was reported for similar reactions, its use is mainly associated to thermal initiation in pure organic solvents for preparative purposes. Our hypothesis is based on the irradiation of persulphate anion (2) to break the peroxide bond (O–O, also called peroxide bridge) affording sulfate radicals, responsible for thiocyanate oxidation (see mechanistic discussion, Scheme 10). On the other hand, previous studies reported the incompatibility of this reaction to an aqueous medium, for which, the development of a methodology using water as predominantly solvent represents a positive improvement.

Optimization of the reaction condition involves different thiocyanate anion sources (KSCN or NH_4SCN), different persulphates ($K_2S_2O_8$ or $(NH_4)_2S_2O_8$) and indole (3a), to obtain 3-thiocyanate indole (4a) under different irradiation sources. Table 1, summarizes the most representative optimization results.

Table 1 Optimization of indole reaction with thiocyanate and persulphate anions

Entry	MSCN (equiv.)	$M_2S_2O_8$	Time (h)	Conversion (%)
1 ^b	NH_4SCN (3)	$K_2S_2O_8$	0.75	97
2 ^b	NH_4SCN (3)	$(NH_4)_2S_2O_8$	0.75	94
3 ^c	NH_4SCN (3)	$K_2S_2O_8$	1	traces
4 ^d	NH_4SCN (3)	$K_2S_2O_8$	1.5	47
5 ^e	NH_4SCN (3)	$K_2S_2O_8$	1	100(99 ^f)
6 ^e	NH_4SCN (1)	$K_2S_2O_8$	6	30
7 ^e	NH_4SCN (2)	$K_2S_2O_8$	6	100(99 ^f)
8 ^e	NH_4SCN (2)	$K_2S_2O_8$	1	89
9 ^e	KSCN (3)	$K_2S_2O_8$	0.75	100(99 ^f)

(a) Reaction conditions: 1 (MSCN), 2 ($M_2S_2O_8$, 1.5 equiv.), 3a (0.2 mmol, 1 equiv.) under air atmosphere, room temperature, 2 mL binary solvent system water:acetonitrile (4:1). Conversion determined by gas chromatography (b) Irradiation source Rayonet[®] equipped with 6 lamps (300 nm). (c) Dark reaction. (d) Sun light as irradiation source (e) Violet LED (400 nm) as irradiation source. (f) Isolated yield

Table 1 shows the results of the optimization reaction conditions exploration to obtain the product 4a. The first remarkable result was the solvent choice that, in this case, consists of a binary system of water: acetonitrile (4:1). This solvent mixture is widely reported in the literature because it is a mainly aqueous medium that, where the addition of a co-solvent (acetonitrile), facilitates the organic reagent solubilization. Then, different amounts of the oxidizing agent (2), thiocyanate (1), different irradiation sources, and reaction times were tested, in most of the cases, very good conversions are obtained. When 1.5 equivalents of potassium persulphate against indole, under 0.75 h of UVB light 97% of conversion was observed, this result remains almost unchanged when ammonium persulphate is used instead (Table 1, entry 1 and 2). Considering that the exchange of potassium persulphate for the corresponding ammonium salt does not generate any advantage, the study was continued with the potassium salt. It is also possible to observe that the light is needed, since no product is obtained in the absence of irradiation and/or heat (Table 1, entry 3). An interesting experiment was the possibility of carrying out the thiocyanation of indole under sunlight irradiation; in this case an encouraging result of 47% of product was obtained (Table 1 entry 4). The main problem that affects these reactions is the low reproducibility that this system would present because it depends on the particular climatic conditions (winter time 1:30 p.m., average temperature 23 °C). To this point, our best condition was achieved under 1 h of UVB light irradiation, isolating near quantitative yield of 4a (Table 1, entry 5).

Since the reaction can be induced by heat or light, to eliminate any thermal contribution, the use of the Rayonet® reactor was replaced by a LEDs photo-reactor equipped with violet LEDs. So, the next step is to verify the effect of the counter ion of thiocyanate anion and change the irradiation source to violet LED. As mentioned above, the ammonium cation tends to increase the solubility of the ions in organic solvents, which could be translated into higher yields at shorter reaction times. Thus, the amount of ammonium thiocyanate salt helps to obtain good results at shorter reaction times. A clear example can be observed using of a lesser amount of ammonium thiocyanate (Table 1, entries 6 and 7), where the conversion rate increases from 30 to 100%, and product 4a is quantitatively isolated at 6 h irradiation time. Furthermore, it is possible to reduce the reaction time from 6 to 1 h without significantly affecting the results previously obtained (Table 1, entry 8). Finally, potassium thiocyanate salt was evaluated as it is more inexpensive, under the same reaction condition; it was possible to obtain 4a with excellent isolated yields, reducing the reaction time to 0.75 h (Table 1, entry 9).

Scheme 3 Scope of the thiocyanation of aromatic compounds. Reaction conditions: KSCN (0.6 mmol), K₂S₂O₈ (0.3 mmol) and 3 (0.2 mmol) in 2 mL of water:acetonitrile (4:1), room temperature, under Violet LED, 45 min irradiation time

3 C–H Thiocyanation of (hetero)aromatic compounds

Once the reaction conditions are optimized, a number of substrates were evaluated, starting from indole derivatives to other aromatic systems, such as anilines and pyrroles (Scheme 3).

In the case of substrates where the aromatic system corresponds to an indole ring (2-methylindole (3b), *N*-methylindole (3c), and 7-azaindole (3d)), the thiocyanation was successfully carried out. In all the cases, substitution at the carbon 3 can be obtained with excellent isolated yields (higher than 76%) even for the poorer electron 7-azaindole (Schemes 3, 4a–d). When the C3 position is blocked, the system is no reactive at all, which can be observed in the

Scheme 4 Intramolecular cyclization reaction for benzothiazole formation

absence of product for 3-methylindole (3n). Particularly, when indole heterocycles are N- or C-substituted by strong electron-withdrawing groups (Scheme 3o–q), no thiocyanation product was detected. These observations suggest that a possible electrophilic aromatic substitution mechanism is involved.

This methodology was extended to the pyrrole heterocycles (3e–g), obtaining isolated yields between 60 and 99% (Schemes 3, 4e–g). In these cases, the substitution by the thiocyanate occurs regioselectively at C2, similarly to the regioselectivity expected for a S_EAr reaction.

In agreement with the results obtained so far, a series of anilines were also evaluated providing excellent results (Schemes 3, 4h–m). Mostly the observed product corresponds to the substitution at the *para* position to the amino group, which, can also be expected by a S_EAr like reaction. It is also necessary to mention that the substrates used have electron donor groups, such as methyl or methoxy groups. A lack of reaction is also observed in the case of anilines having strong electron-withdrawing groups like CN in 3r.

An interesting benzothiazole product 4 m was obtained, by the thiocyanation of *para*-toluidine. This heterocycle has a great value due to their multiple uses including agrochemical, pharmacological and technological applications [26]. Thus, product 4 m is explained from the substitution by SCN group at the C2 position, since the C4 position is blocked. Then, the carbon of SCN group has a certain electrophilic character and it could be attacked by the NH_2 nucleophilic substituent. Due to the geometry of the substrate 3 m (*para*-toluidine), intramolecular cyclization is possible followed by the formation of a five-membered ring 4 m. Shortly, this methodology also allows the synthesis of heterocycles, simply and efficiently (Scheme 4).

4 C–H Selenocyanation of (hetero)aromatic compounds

To demonstrate the potential and scope of the photo-induced thiocyanation reaction system, the use of a selenium analog was explored. For such purposes, due to its similar structure and reactivity, potassium salt of selenocyanate (KSeCN) as a selenium source was used and under the same previously optimized conditions. In doing so, the selenocyanate showed excellent results in the oxidative reaction of indole

Scheme 5 Selenocyanation of aromatic systems. Reaction conditions: $K_2S_2O_8$ (0.3 mmol), KSeCN (0.6 mmol), 3 (0.2 mmol), in 2 mL of water:acetonitrile (4:1), room temperature under violet LED, 45 min irradiation time

derivatives, pyrroles and anilines, with isolated yields above 70% in every case (Scheme 5a, e, i, j, m). Also, when *para*-toluidine was evaluated as a substrate, the benzoselenazole product 5 m was obtained. The formation of this last compound is equivalent to the one proposed in Scheme 4 with the difference that 4-methyl-2-selenocyanate aniline was obtained as the intermediate.

5 Thiocyanation protocol in flow

Considering the importance of the development of novel and more sustainable protocols applied to the synthesis of valuable organosulfur/selenocompounds, the thiocyanation methodology was transferred to continuous-flow systems. To our knowledge, up till now, this widely used reaction has not yet been studied using continuous-flow photochemistry. Focusing on process intensification, in our first approach in flow, a 5.4 mL PFA photo-reactor coil (750 mm I.D.) equipped with a violet LED (16×3 W at 400 nm) was constructed. A solution of the reagents (KSCN, $K_2S_2O_8$ and indole) in water: acetonitrile, was introduced in one feed streams. Also, the concentration, residence time and flow rate were optimized. These results are shown in Table S1 (see supplementary information).

After the initial optimization, an 88% of conversion was obtained within 10 min of residence time (entry 1,

Table S1). However, under this condition, the product 3-thiocyanate indole (4a) was not completely soluble in the reaction mixture. Reactor fouling with the product resulted in a random flow profile over time. With this observation in mind, we decided evaluated a segmented-flow setup, adding an organic solvent in which 4a can be dissolved.

In many cases, the use of biphasic reaction systems offers advantages over the use of monophasic reactions, where often an organic solvent miscible with water is needed to increase the solubility of organic species involved. Compared to the conventional batch systems, segmented-flow capillary micro-reactors are especially suited for biphasic systems due to the enhanced surface area/volume ratio between the phases and the improved mixing within the segments. In this sense, performing liquid–liquid reactions in flow has many unique advantages, such as reactions between components with different solubility behaviors and separation between reactants, products and catalysts, since they are compartmented in different phases [27].

With this in mind, we evaluated a segmented-flow system for the thiocyanation in flow, with water:acetonitrile/ CH_2Cl_2 phases. A solution of KSCN , $\text{K}_2\text{S}_2\text{O}_8$ and indole in $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (4:1) was charged into the syringe 1 and, at the same time, CH_2Cl_2 was charged into the syringe 2. Both syringes were connected through a FEP-tubing and mixed in a T connector, and the reagents were continuously introduced to the photo-flow system (see supplementary information, Images I and II). Under optimized conditions, the reaction was efficiently performed after 2.5 min of the residence time with a 94% isolated yield of 4a (entry 7, Table S1).

To evaluate the potential of this segmented-flow setup, we explored the scope of the photochemical $\text{C}_{\text{sp}}^2\text{-H}$ substitution by ^-SCN and $^-\text{SeCN}$. Thus, *N*-methyl pyrrole (3e) and *para*-toluidine were used as examples; the results are stated in Scheme 6. This continuous-flow thio- or selenocyanation protocol resulted efficient for activated electron-rich arenes, achieving an excellent yield of the products in only 2.5 min of irradiation.

Additionally, the process was easily scaled up to a gram scale, where the segmented photo-flow system involves a $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (4:1) solution of a 3a (1.01 g) with potassium thiocyanate (2.46 g) and $\text{K}_2\text{S}_2\text{O}_8$ (3.45 g) charged into the syringe 1, and a CH_2Cl_2 charged into the syringe 2. At flow rate of 1.08 mL/min for 150 min under violet LED irradiation, as a result, 1.08 g of 4a formation was obtained (72% yield, Scheme 6).

At this point, our proposed methodology involves advantages like simple operation under environmentally friendly conditions. Though light activation of persulphate anion was necessary since conversion was extremely low in the absence of light. The photo-initiated reaction has the additional benefit of the use of harmless violet LED irradiation

Scheme 6 Application of continuous photo-flow synthesis of chalcogen-containing heterocycles. Reaction conditions: Syringe 1: $\text{K}_2\text{S}_2\text{O}_8$ (1.5 mmol), KS/SeCN (3 mmol), 3 (1 mmol), in 10 mL of water:acetonitrile (4:1). Syringe 2: 10 mL CH_2Cl_2 room temperature under violet LED irradiation. Flow: 1.08 mL/min, 2.5 min residence time (irradiation time)

which accelerates the reaction at both, batch and continuous-flow, essayed procedures.

6 Mechanistic studies

Up till now, several mechanistic studies of thiocyanation reaction have carried out. However, the results have not been conclusive due to the dichotomy presented by this system, where it is difficult to differentiate the product formation from an electrophilic aromatic substitution ($\text{S}_{\text{E}}\text{Ar}$) to the $^{\bullet}\text{SCN}$ addition at the aromatic ring. Our experimental findings point to a reaction mechanism through the dimer (NCSSCN), which is formed by coupling between two radicals (coming from the oxidation of the thiocyanate anion). In contrast, there is a possibility that the radical $^{\bullet}\text{SCN}$ does not form this intermediate and that it adds to the aromatic system. To distinguish the addition of the radical ($^{\bullet}\text{SCN}$) from the electrophilic substitution by NCSSCN , would be disguised by a substrate which is able to give a ring closure reaction as a radical clock probe. For this purpose, two substrates bearing terminal alkenes were tested. Thus, Scheme 7 displays two possible situations: in mechanism A (Scheme 7A) the addition of the radical occurs on the

Scheme 7 Possible cyclization of the indole system as radical probe

alkene, and as a consequence the new radical could add to the indole ring causing a ring closure, while in mechanism B (Scheme 7B) the addition of the radical occurs at the C3 position of the indole. This radical centered on carbon 2 would add to the double bond of the alkene.

For mechanistic evidence, two functionalized indoles were tested (Scheme 8, 3s, t) both capable of intramolecular cyclization (the main difference between them lies in the length of the chain used as a substituent). The results indicate that the double bond remains intact, the thiocyanation reaction does not change the regioselectivity giving thiocyanate indoles 4 s and 4t in 62% and 20% yields (Scheme 8a, b, respectively).

Additionally, the effect of a known radical scavenger such as TEMPO was studied as a stable iminoxyl radical, which could act as an inhibitor in a radical-mediated reaction. As a result, the presence of TEMPO in the reaction mixture did not lead to a significant inhibition of the formation of the 3-thiocyanate indole, 4a (Scheme 9).

From all these observations, we can propose three reaction pathways starting from the photolysis of the persulfate anion (2), which generates two sulfate radicals (2a). These species are strong oxidizing agents ($\text{SO}_4^{\bullet-}$ / SO_4^{2-}) whose oxidation potential is 2.6 V [28]. This strong oxidant

Scheme 8 Mechanistic studies for the cyclization of *N*-allyl indoles (45 min irradiation time)

Scheme 9 Mechanistic study, effect of TEMPO (45 min irradiation time)

intermediate opens three possible reaction routes, as indicated in Scheme 10, where the aromatic heterocycle is symbolized as substituted benzene. Starting from path A, radical 2a reacts by electron transfer with substrate 3, whose oxidation potentials vary between 0.3 V and 1.4 V [29] from easily oxidizable substrates, such as *ortho*-anisidine (3j) to *N*-acetylindole (3o). In this way, all the heterocycles studied can react with 2a to form their respective radical cations which, after reaction with 1 (^-SCN) followed by hydrogen abstraction, or oxidation and deprotonation, give the observed product 4 (Scheme 10, path A). According to the oxidation potentials of the studied heterocycles, this process would be thermodynamically favorable; however, experimental trend showed that heterocycles bearing electron-withdrawing groups are non-reactive. Based on this evidence, we can safely discard this reaction path. On the other hand, thiocyanate anion 1 is always in higher concentrations than 3, which is easily oxidized under the oxidative reaction conditions; therefore, routes B and C are proposed in Scheme 10. Here, a dichotomy showed up, where the reaction pathway can be a radical (Scheme 10, path B) or a $\text{S}_{\text{E}}\text{Ar}$ reaction (Scheme 10, path C). Although in most of the previous publications, a radical pathway is proposed, where the radical 1a ($^*\text{SCN}$) adds to the aromatic ring to give aryl thiocyanate 4 (Scheme 10, path B) [10]. Even if the mechanistic pathways are difficult to distinguish, the lack of inhibition by TEMPO, together with the absence of cyclized products for the indoles 3 s-t as radical probes (Scheme 8, 4s-t) and the observed regioselectivity of the reaction, would rule out a radical addition mechanism (Scheme 10, path B).

Finally, the proposed path C is in agreement with experimental results, where the observed reactivity is in agreement with the expected one by a $\text{S}_{\text{E}}\text{Ar}$ reaction, where only the electron-rich heterocycles are reactive. In this pathway, once 1a is formed given the higher concentration of the thiocyanate anion, the radical anion $(\text{NCSSCN})^{\bullet-}$ is formed, a species which is well described in the literature, mainly in pulse radiolysis experiments [30]. In an oxidizing environment, $(\text{NCSSCN})^{\bullet-}$ generates the intermediate 1aa, which is the electrophilic species responsible for the $\text{S}_{\text{E}}\text{Ar}$ reaction, giving the observed product 4.

In addition, thiocyanate (^-SCN) and selenocyanate ($^-\text{SeCN}$) anions are productive in the photooxidative thio/

Scheme 10 Mechanistic proposal for the thiocyanation of aromatic systems

seleocyanation of the electron-rich arenes. However, this is not the case for cyanate anion (^-OCN) which is not reactive. For the sulfur and selenium anion, the potential oxidation values are quite similar, being 0.78 V and 0.53 V (vs SCE), respectively, according to literature [31]. For practical purposes, we assume that these reagents respond in a similar way to the presence of persulphate as an oxidizing agent (2.6 V). For cyanate (^-OCN), the redox potential is close to 1.24 V so, according to this value, the reaction could be feasible; however, the oxidation of this anion generates cyanide [32, 33], a very stable species, which would be explained by the fact that cyanate does not react with indole due to its early decomposition under photo-oxidative conditions.

Additionally, an interesting experiment for the understanding of the reaction mechanism involves a competition reaction between thiocyanate (^-SCN) and selenocyanate ($^-\text{SeCN}$) anions, even though both anions can be oxidized and form an electrophilic species (CNZZCN , where $Z = \text{S}$ or Se), the selenium atom has a greater electrophilic character compared to sulfur. The competition reaction between these two anions results in 3-selenocyanatoindole as the only product (5a) evidencing the strong electrophilic nature of the reaction (Scheme 11).

Summarizing, according to our experimental findings, the observed reactivity trend, together with the lack of inhibition by TEMPO, are pieces of evidence against a radical-mediated mechanism. In addition, for the intramolecular radical

probes, namely indoles 3 s and 3t, in both cases, only substitution at C3 on the indole ring is observed. Altogether, it is consistent with a polar S_EAr rather than a $^*\text{SCN}$ -mediated mechanism (Scheme 10, path C).

7 Conclusion

The proposed synthetic methodology had soft and eco-friendly reaction conditions, highlighting the use of light as an energy source. The result of the present study results in a robust reaction system where more than 21 functionalized molecules can be obtained. In addition, the procedure resulted very useful at obtaining C–H functionalized products either with thiocyanate or selenocyanate from good to excellent reaction yields.

The information obtained through the mechanistic study indicates that: even it is difficult to distinguish between a radical mechanism, by addition of $^*\text{SCN}$ to electron-rich arenes (Scheme 10, path B), from a S_EAr reaction between NCSSCN and the aromatic heterocycles (Scheme 10, path C). The lack of TEMPO inhibition together with the observed regioselectivity, would be in agreement with a further oxidation of ^-SCN to give NCSSCN , the latter add to the aromatic heterocycle to give the observed products after deprotonation (S_EAr). Thus, the soft character of the electrophilic dimers (NCS–SCN or NCSe–SeCN) would

Scheme 11 Competition reaction between thio- and selenocyanate anions

be responsible for the lack of reactivity of indoles and anilines bearing electron-withdrawing substituents.

Most importantly, the synthetic methodology designed in this work could be successfully adapted to continuous-flow systems. Taking into account the low solubility of the product in the solvent of the reaction, slug flow conditions were needed, with the organic phases acting as a reservoir of the product. The advantage of using the continuous-flow technology for the thiocyanation/selenocyanation protocol was demonstrated by the improvement reaction time, yields and easy scale-up. To the best of our knowledge, this contribution represents one of the first examples where photochemical thio- and selenocyanation are applied to a continuous-flow process.

8 Experimental section

General methods

Irradiation was conducted in a Rayonet photoreactor RPR-100 (16 × 3000 Å lamps, $\lambda_{em} = 300 \pm 10$ nm). ^1H , ^{13}C and ^{77}Se 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 × 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 × 0.25 mm × 0.25 μm with a 5% phenylpolysiloxane phase column. Ionization was achieved by electronic impact (70 eV) and positive detection set-up mode. HRMS spectra were recorded on a GCT Premier orthogonal acceleration time-of-flight (oa-TOF) GC mass spectrometer.

Chemicals: The following reagents were commercially purchased from Sigma-Aldrich Chemicals Co, and used without prior purification: potassium thiocyanate (KSCN), ammonium thiocyanate (NH_4SCN), potassium selenocyanate (KSeCN), potassium cyanate (KOCN), potassium persulphate ($\text{K}_2\text{S}_2\text{O}_8$), ammonium persulphate ($(\text{NH}_4)_2\text{S}_2\text{O}_8$), indole, 7-azaindole, 2-methylindole, 3-methylindole, *N*-methylindole, *N*-acetylindole, 2-carboxyacidindole, *N*-methylpyrrole, 2-acetylpyrrole, pyrrole-2-carboxylic acid, 2-phenylaniline, *N*, *N*-dimethylaniline, *ortho*-anisidine, *ortho*-toluidine, *meta*-anisidine, *para*-toluidine, 4-aminobenzonitrile, allyl bromide, 4-bromo-1-butene and *para*-toluenesulfonyl chloride. Acetonitrile, acetone, dimethylformamide (Merck HPLC grade) were used without any further purification and stored over molecular sieves (4 Å).

General procedure for the synthesis of compounds 3p, 3s, and 3t. The substrate *N*-Tosyl indole (3p) was the

only one that required a previous synthesis. The product is obtained quantitatively as a white solid [34].

The syntheses of *N*-allyl-indole and *N*-butylindole were carried out following the procedures of a bimolecular nucleophilic substitution reaction ($\text{S}_{\text{N}}2$). Wherein, the indole (1equiv) is reacted with a slight excess of the corresponding halide (1.5equiv) in the presence of K_2CO_3 base (3 equiv). Finally, the reaction is extracted using an excess of water, and organic solvents, such as EtOAc or CH_2Cl_2 , are used. The organic phase is treated with anhydrous Na_2SO_4 to eliminate traces of humidity, and concentrated by means of a rotary evaporator under reduced pressure. Pure product is isolated by a chromatographic column monitored by GC analysis.

Experimental procedure for the synthesis of thiocyanate or selenocyanate compounds (batch version): the reaction takes place in a glass vial (penicillin flask) fitted with a magnetic stirrer. The aromatic compound of interest (3, 0.2 mmol, 1equiv), potassium thiocyanate (KSCN) (0.6 mmol, 3equiv) and potassium persulphate (0.3 mmol, 1.5equiv) are added into the vial. The optimized solvent for this reactive system corresponds to a mixture of water: acetonitrile (4: 1), the volume used is 2 mL, corresponding to (1.6: 0.4) mL. The reaction is irradiated for a term of 45 min using a 3 W violet LED ($\lambda = 400$ nm) at room temperature and air atmosphere. Finally, the reaction is extracted using an excess of water, and organic solvents, such as EtOAc or CH_2Cl_2 , are used. The organic phase is treated with anhydrous Na_2SO_4 to eliminate traces of humidity, and concentrated by means of a rotary evaporator under reduced pressure. Pure product is isolated by a chromatographic column monitored by GC analysis.

The same procedure can be validated for the reaction with the reagent potassium cyanate (KOCN) and potassium selenocyanate (KSeCN).

Experimental procedure for the synthesis of thiocyanate or selenocyanate compounds (flow version): The methodology designed for the thiocyanation of aromatic compounds can be extended in the same way for selenocyanate.

The reaction takes place in a photo-reactor with a total volume of 5.4 mL. For this system, two syringes are used: syringe 1 adds the aromatic compound of interest (1 mmol, 1equiv), potassium thio- or selenocyanate (KS/SeCN) (3 mmol, 3equiv) and potassium persulphate (3 mmol, 1.5equiv). The optimized solvent for this reactive system corresponds to a mixture of water: acetonitrile (4: 1), the volume used is 10 mL. Syringe 2 is charged with 10 mL of CH_2Cl_2 . The reaction is irradiated for a term of 2.5 min using 16 violet LEDs ($\lambda = 400$ nm) of 3 W at a room temperature of 25° under air atmosphere. Both syringes are connected through a FEP cannula and their content mixed using

a T-type connector. Finally, the reaction is extracted using an excess of water and organic solvents, such as EtOAc or CH_2Cl_2 , are used. The organic phase is treated with anhydrous Na_2SO_4 to eliminate traces of humidity, and concentrated by means of a rotary evaporator under reduced pressure. Pure product is isolated by a chromatographic column monitored by GC analysis.

Experimental procedure for the synthesis of 3-thiocyanato indole—gram scale (flow version): The reaction takes place in a photo-reactor with a total volume of 5.4 mL. For this system, two syringes are used: syringe 1 adds the aromatic compound of interest (3a, 8.6 mmol, 1equiv), potassium thiocyanate (KSCN) (25.9 mmol, 3equiv) and potassium persulphate (12.9 mol, 1.5equiv). The optimized solvent for this reactive system corresponds to a mixture of water: acetonitrile (4:1), the volume used is 10 mL. Syringe 2, adds 10 mL of CH_2Cl_2 . The reaction is irradiated for a term of 5 min using 16 violet LEDs ($\lambda = 400$ nm) of 3 W at room temperature of 25° under air atmosphere. Both syringes are connected through a FEP cannula and their content mixed using a T-type connector. The reaction was carried out in 6 cycles to achieve 1 g conversion; finally, the reaction is extracted using an excess of water and organic solvents, such as EtOAc or CH_2Cl_2 , are used. The organic phase is treated with anhydrous Na_2SO_4 to eliminate traces of humidity, and concentrated by means of a rotary evaporator under reduced pressure. Pure product is isolated by a chromatographic column monitored by GC analysis. **Spectroscopy data for the obtained products**

3-thiocyanato-1H-indole (4a): (yield 99%) ^1H NMR (400 MHz, CDCl_3) δ 8.59 (s, 1H), 7.86–7.78 (m, 1H), 7.55 (d, $J = 2.8$ Hz, 1H), 7.45 (ddd, $J = 8.0, 3.1, 1.7$ Hz, 1H), 7.38–7.28 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 136.14, 130.98, 127.86, 124.12, 122.12, 119.02, 112.14, 111.80.

2-methyl-3-thiocyanato-1H-indole (4b): (88% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.42 (s, 1H), 7.69 (d, $J = 6.5$ Hz, 1H), 7.36–7.31 (m, 1H), 7.25–7.21 (m, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 141.94, 135.24, 128.94, 123.23, 121.82, 118.39, 111.80, 111.25, 12.32.

1-methyl-3-thiocyanato-1H-indole (4c): (97% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.68 (d, $J = 7.2$ Hz, 1H), 7.31–7.11 (m, 4H), 3.67 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 149.48, 143.16, 136.41, 117.44, 113.90, 112.07, 109.45, 77.16, 21.05.

3-thiocyanato-1H-7-azaindole (4d): (76% yield) ^1H NMR (400 MHz, CDCl_3) δ 10.34 (s, 1H), 8.46 (d, $J = 3.5$ Hz, 1H), 8.25–8.11 (m, 1H), 7.73 (s, 1H), 7.32 (dd, $J = 7.9, 4.8$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 145.11, 131.78, 128.00, 118.11.

1-methyl-2-thiocyanato-1H-pyrrole (4e): (99% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.39 (dd, $J = 12.2, 4.6$ Hz, 2H), 7.11 (dd, $J = 8.3, 1.9$ Hz, 1H), 2.39 (s, 3H). ^{13}C NMR

(101 MHz, CDCl_3) δ 133.19, 128.97, 119.93, 111.30, 101.97, 25.37.

1-(4-thiocyanato-1H-pyrrol-2-yl) ethan-1-one (4f): (60% yield) ^1H NMR (400 MHz, CDCl_3) δ 10.44 (s, 1H), 7.33 (dd, $J = 3.1, 1.4$ Hz, 1H), 7.09 (dd, $J = 2.4, 1.5$ Hz, 1H), 2.47 (d, $J = 2.3$ Hz, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 188.01, 133.51, 129.29, 120.25, 111.61, 102.28, 25.69. ESI-HRMS: m/z calculated for $\text{C}_7\text{H}_6\text{N}_2\text{NaOS}$ [$\text{M} + \text{Na}$] $^+$ 189.0093, found 189.0075.

5-thiocyanato-[1,1'-biphenyl]-2-amine (4h): (80% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.57–7.30 (m, 7H), 6.76 (d, $J = 8.3$ Hz, 1H), 4.05 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 146.17, 137.74, 135.22, 133.43, 129.30, 129.13, 128.99, 128.17, 116.73, 112.35, 109.97. ESI-HRMS: m/z calculated for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{NaS}$ [$\text{M} + \text{Na}$] $^+$ 249.0457, found 249.0443.

N, N-dimethyl-4-thiocyanatoaniline (4i): (77% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.46–7.38 (m, 2H), 6.67 (d, $J = 9.0$ Hz, 2H), 2.99 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 151.85, 134.56, 113.31, 112.66, 106.78, 40.25.

2-methoxy-4-thiocyanatoaniline (4j): (76% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.02 (dd, $J = 8.1, 1.9$ Hz, 2H), 6.96 (d, $J = 1.7$ Hz, 1H), 6.68 (d, $J = 8.1$ Hz, 1H), 4.08 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.81, 139.15, 126.89, 115.07, 114.69, 112.43, 109.30, 55.93.

2-methyl-4-thiocyanatoaniline (4k): (77% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.24–7.15 (m, 2H), 6.65 (d, $J = 8.3$ Hz, 1H), 3.90 (s, 1H), 2.16 (d, $J = 7.3$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.22, 135.10, 132.13, 124.00, 115.90, 112.56, 109.52.

3-methyl-4-thiocyanatoaniline (4l): (88% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.37 (d, $J = 8.4$ Hz, 1H), 7.26 (s, 1H), 6.59 (d, $J = 2.1$ Hz, 1H), 6.51 (dd, $J = 8.3, 2.4$ Hz, 1H), 3.90 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 149.48, 143.16, 136.41, 117.44, 113.90, 112.07, 109.45, 21.05.

6-methylbenzo[d]thiazol-2-amine (4m): (90% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.44–7.37 (m, 2H), 7.11 (d, $J = 7.7$ Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.57, 149.58, 132.38, 131.54, 127.38, 121.12, 118.85, 31.01.

1-allyl-3-thiocyanato-1H-indole (4s): (62% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.82 (dd, $J = 5.9, 2.8$ Hz, 1H), 7.46 (s, 1H), 7.43–7.30 (m, 3H), 6.00 (ddd, $J = 22.5, 10.7, 5.6$ Hz, 1H), 5.34–5.27 (m, 1H), 5.22–5.15 (m, 1H), 4.76 (d, $J = 5.5$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 136.76, 134.13, 132.18, 128.76, 123.62, 121.86, 119.21, 118.90, 111.84, 110.71, 90.82, 49.51. ESI-HRMS: m/z calculated for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{NaS}$ [$\text{M} + \text{Na}$] $^+$ 237.0457, found 237.0434.

1-(but-3-en-1-yl)-3-thiocyanato-1H-indole (4t): (20% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.88–7.73 (m, 1H), 7.50–7.23 (m, 4H), 5.76 (ddt, $J = 17.1, 10.3, 6.9$ Hz, 1H), 5.25–4.94 (m, 2H), 4.21 (t, $J = 7.1$ Hz, 2H), 2.61 (q,

$J = 6.9$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 136.61, 134.17, 133.78, 128.80, 123.56, 121.79, 119.31, 118.47, 111.87, 110.47, 46.78, 34.33, 29.85.

3-selenocyanato-1H-indole (5a): (95% yield) ^1H NMR (400 MHz, CDCl_3) δ 8.71 (s, 1H), 7.75 (dd, $J = 6.0, 3.1$ Hz, 2H), 7.46 (d, $J = 2.8$ Hz, 2H), 7.44–7.40 (m, 1H), 7.34–7.27 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 136.15, 131.93, 128.84, 123.88, 121.96, 119.67, 112.03, 102.03, 89.61, 77.48, 76.84. ^{77}Se NMR (76 MHz, CDCl_3) δ 151.56.

2-methyl-3-selenocyanato-1H-indole (5b): (84% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, $J = 7.63$ Hz, 1H), 7.39 (s, 1H), 7.27–7.38 (m, 3H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 136.37, 130.99, 129.11, 125.18, 125.15, 122.95, 120.82, 120.12, 111.45, 31.36. ^{77}Se NMR (76 MHz, CDCl_3) δ 197.1.

1-methyl-3-selenocyanato-1H-indole (5c): (97% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.78–7.72 (m, 3H), 7.44–7.28 (m, 3H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 137.40, 136.06, 129.72, 123.49, 121.70, 119.99, 110.15, 33.51. ^{77}Se NMR (76 MHz, CDCl_3) δ 197.2. ESI-HRMS: m/z calculated for $\text{C}_{10}\text{H}_8\text{N}_2\text{NaSe}$ $[\text{M} + \text{Na}]^+$ 258.9745, found 258.9727.

3-selenocyanato-7-azaindole (5d): (99% yield) ^1H NMR (400 MHz, CDCl_3) δ 10.49 (s, 1H), 8.46 (d, $J = 4.8$ Hz, 1H), 8.18 (d, $J = 9.0$ Hz, 1H), 7.73 (s, 1H), 7.32 (dd, $J = 7.9, 4.8$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 141.62, 134.92, 128.62, 122.92, 121.50, 118.07, 111.49, 110.93. ^{77}Se NMR (76 MHz, CDCl_3) δ 206.44. ESI-HRMS: m/z calculated for $\text{C}_8\text{H}_5\text{N}_3\text{NaSe}$ $[\text{M} + \text{Na}]^+$ 245.9541, found 245.9524.

1-methyl-2-selenocyanato-pyrrole (5e): (81% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.51–7.36 (m, 2H), 7.11 (dd, $J = 8.3, 1.4$ Hz, 1H), 2.39 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 133.68, 130.29, 121.62, 101.60, 97.61, 77.16, 25.69. ^{77}Se NMR (76 MHz, CDCl_3) δ 165.3.

N, N-dimethyl-4-selenocyanatoaniline (5i): (99% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.54–7.49 (m, 2H), 6.65 (d, $J = 9.0$ Hz, 2H), 3.00 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 151.84, 136.50, 113.49, 108.04, 104.72, 40.26. ^{77}Se NMR (76 MHz, CDCl_3) δ 302.52.

2-methoxy-4-selenocyanatoaniline (5j): (94% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.12 (d, $J = 1.8$ Hz, 1H), 7.10 (d, $J = 1.8$ Hz, 1H), 7.05 (s, 1H), 4.07 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.75, 139.09, 128.76, 116.79, 115.20, 106.65, 102.68, 55.90. ^{77}Se NMR (76 MHz, CDCl_3) δ 318.38.

6-methylbenzo[d][1,3]selenazol-2-amine (5m): (73% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.46–7.39 (m, 2H), 7.11 (d, $J = 7.7$ Hz, 1H), 5.35 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.04, 151.51, 134.99, 132.55, 127.53, 124.56, 120.27, 21.25. ^{77}Se NMR (76 MHz, CDCl_3) δ 524.66.

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Declarations

Conflict of interest The authors have no conflicts to disclose.

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