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## REVIEW ARTICLE

## Sustainable Synthetic Approaches Involving Thiocyanation and Sulfur-Cyanation: An Update

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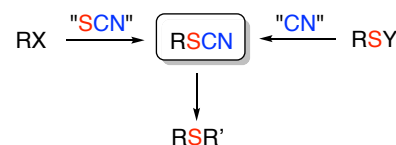
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**Abstract:** This review highlights the achievements in the synthesis of organic thiocyanates (OTCs) over the past five years (late 2015 to mid-2019) and is intended as a follow-up on our tutorial review published in *Chemical Society Reviews* in 2016. The discussion places a special emphasis on sustainable synthetic approaches involving thiocyanation or sulfur-cyanation. The large number of contributions within this short period of time clearly indicates that the chemistry of OTCs provides a growing interest and a rapid evolution.**Keywords:** Organic thiocyanates, thiocyanation, S-cyanation, sustainable synthetic methods, domino reactions, multicomponent reactions, difunctionalization.

## 1. INTRODUCTION

Organic thiocyanates (OTCs) represent a very important class of organosulfur compounds, with a wide application as precursors in synthetic and medicinal chemistry, chemical biology and material sciences. In a recent tutorial review published in *Chemical Society Reviews* in 2016 [1], we highlighted modern methods for the preparation and original synthetic applications of OTCs, covering the literature between 2000 and 2015. Publications, having been discussed in the previous review, are not included here. The present review deals with new achievements in the synthesis of OTCs over the past five years (late 2015 to mid-2019) with emphasis on sustainable synthetic approaches. We particularly pointed out innovative strategies that have emerged recently, which involve thiocyanation (C-SCN bond formation) or sulfur-cyanation (S-CN bond formation) in more complex transformations such as difunctionalization, heterocyclization, domino and multicomponent reactions.

To prepare OTCs, two main strategies are currently used: one involves introducing a thiocyanate function on a substrate by using a thiocyanating agent and the other includes the reaction of a substrate bearing a sulfur-atom with a cyanating agent (Scheme 1).



Scheme 1. Synthesis of OTCs by thiocyanation or S-cyanation; in tandem SCN transformation.

Whatever the method used, in some reported transformations, the resulting thiocyanate was not isolated or was an unstable intermediate, which reacted in intermolecular or intramolecular manner to afford other S-containing compounds.

## 2. REACTIONS INVOLVING THIOCYANATION

The thiocyanate function can be introduced on various substrates such as functionalized aliphatic compounds, aromatics and heteroaromatics, or on unsaturated carbon-carbon bonds. Depending on the thiocyanating agent and the reaction conditions used, nucleophilic, electrophilic, or radical SCN-species can be involved in these transformations. New reagents or activation methods are highlighted, as well as the thiocyanation of particular substrates.

## 2.1. Reactions with Preservation of the SCN Group

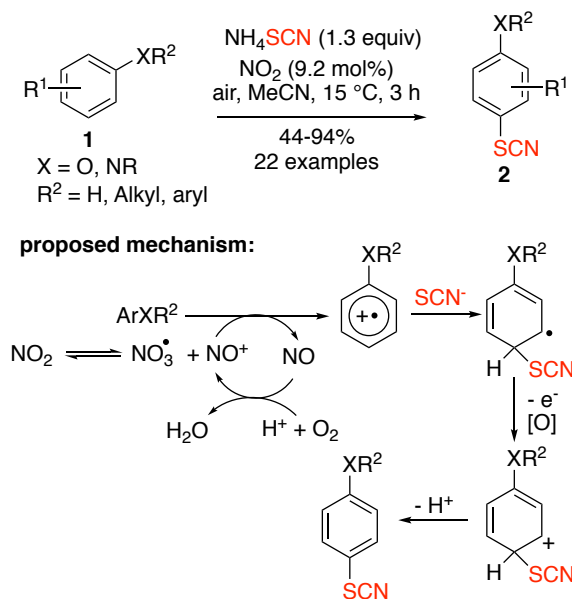
In this section, thiocyanation reactions that led to final products containing a thiocyanate function are described.

## 2.1.1. New Methods or Reagents for Thiocyanation

In the oxidative thiocyanation of various aromatic compounds (1) with ammonium thiocyanate, with air used as the oxidant, NO<sub>2</sub> was added as a new catalyst, inexpensive and

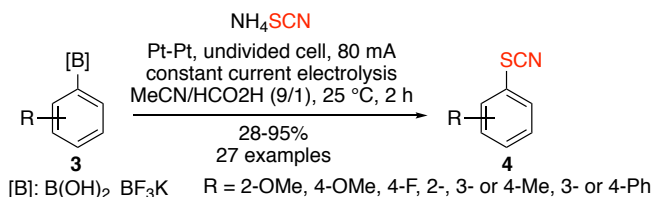
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easy to separate from the final products [2]. The reaction was compatible with various electron-donating or electron-withdrawing substituents present on the aromatic ring, leading to the corresponding thiocyanates (2) in moderate to high yields (Scheme 2). The authors proposed the  $\text{NO}^+$  species as the reaction catalyst, which is generated from  $\text{NO}_2$ . The aromatic ring reacts with  $\text{NO}^+$  to give the aromatic radical cation and  $\text{NO}$ . The aromatic radical cation reacts with  $\text{SCN}^-$  anion to form a radical intermediate, which undergoes electron transfer and deprotonation to afford the aryl thiocyanate product.  $\text{NO}$  is oxidized by  $\text{O}_2$  to regenerate the catalytically active species  $\text{NO}^+$ .



Scheme 2.  $\text{NO}_2$ -catalyzed oxidative thiocyanation of aromatics.

An electrochemical transition-metal-free method to access aryl thiocyanates was described for the first time by Gooßen and coworkers (Scheme 3) [3]. Aryl boronic acids or potassium trifluoroborates (3) were reacted with  $\text{NH}_4\text{SCN}$  in an undivided cell with simple Pt sheet electrodes and led to the thiocyanate products (4), only  $\text{H}_2$  being released as a by-product at the cathode. Thiocyanogen ( $\text{SCN})_2$  electrophile was generated *in situ* by anodic oxidation of thiocyanate anion, avoiding the formation of side products as in the case when chemical oxidants are used.

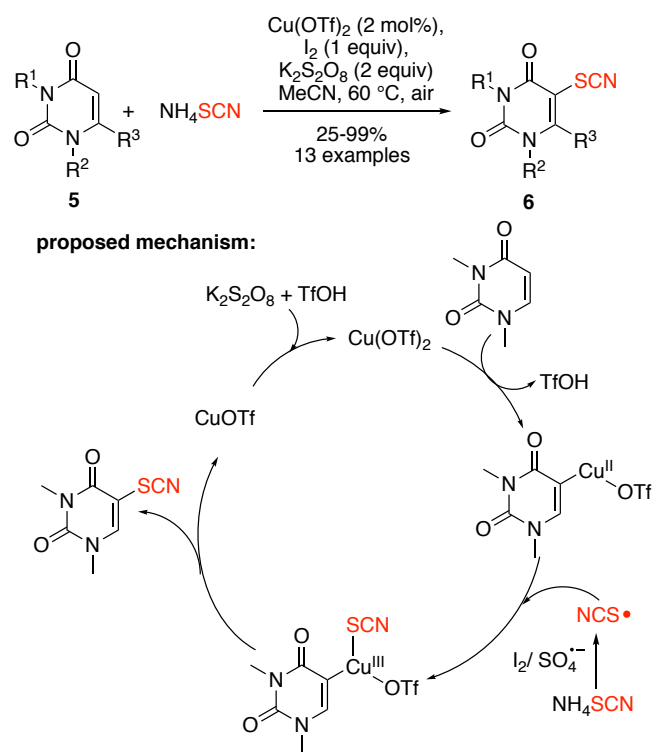


Scheme 3. Electrochemical thiocyanation of aryl boronic derivatives.

The authors supposed that the reaction may be facilitated by coordination of  $\text{SCN}^-$  to the boronic acid, activating the boron-based leaving group. Moreover, the formed anionic species increases the concentration of both the reagents at the anode. The method was applicable to variously substituted

substrates leading to the corresponding aryl thiocyanates in good yields.

Due to their numerous biological and pharmacological activities, uracils represent interesting substrates for diverse functionalizations. A recent publication described the regioselective introduction of thiocyanate function in the 5-position of uracils (Scheme 4) [4]. The method consists of the copper-catalyzed direct C–H thiocyanation of uracils (5) using ammonium thiocyanate and is applicable to a broad range of substrates, leading to 5-substituted uracil thiocyanates (6) in moderate to excellent yields. The proposed reaction mechanism involves a radical pathway. The  $\text{Cu(II)}$  species initially interacts with uracil leading to a  $\text{Cu(II)}$  uracil complex. Then, this intermediate is attacked by a thiocyanate radical ( $\text{SCN}^\bullet$ ), which is generated from the reaction of thiocyanate anion with the  $\text{I}_2/\text{K}_2\text{S}_2\text{O}_8$  oxidant system to form a  $\text{Cu(III)}$  intermediate. The latter undergoes reductive elimination to give the 5-thio-substituted uracil product and release  $\text{Cu(I)}$  species. Oxidation of  $\text{Cu(I)}$  would regenerate the  $\text{Cu(II)}$  species to resume the catalytic cycle.

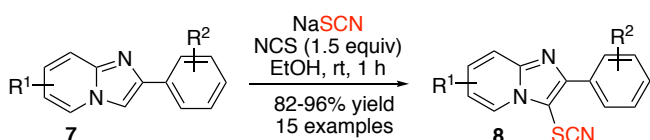


Scheme 4. Copper-catalyzed regioselective thiocyanation of uracils.

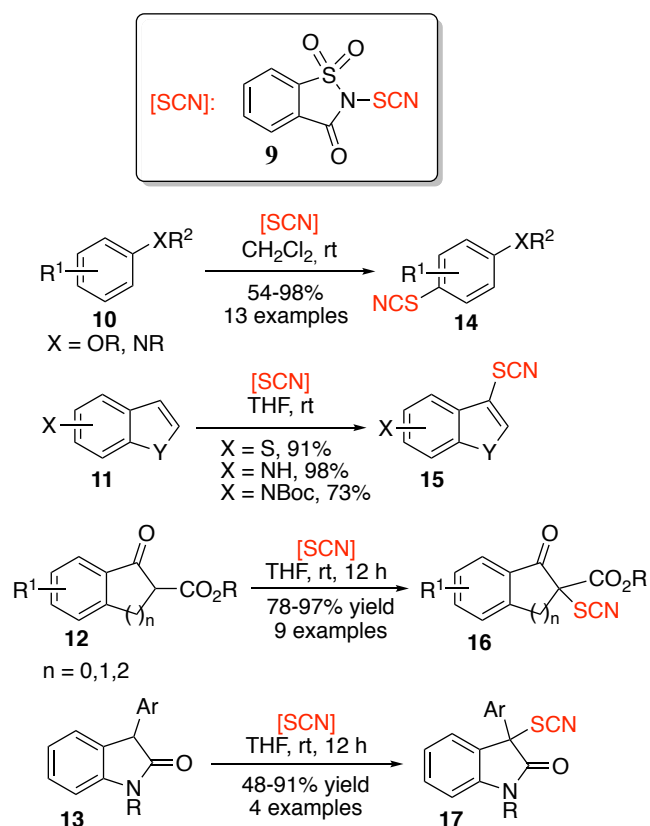
Imidazopyridines (7) are fused heterocycles having therapeutic properties. Among the various modifications of these structures, the introduction of a thiocyanate function has been studied. The direct C–H thiocyanation was achieved by using a combination of sodium thiocyanate as the  $\text{SCN}^-$  source and N-chlorosuccinimide (NCS) as the oxidant, affording 3-thiocyanatoimidazo[1,2-a]pyridines (8) in good to excellent yields (Scheme 5) [5]. Ethanol was used as a green and efficient reaction solvent.

N-Thiocyanatosaccharin (9) was prepared and used as a new electrophilic thiocyanation agent (Scheme 6) [6]. This reagent was prepared on a gram scale (71% overall yield) in

two steps by treatment of Saccharin with tert-butyl hypochlorite and subsequent reaction of the resulting *N*-chlorosaccharin with AgSCN. This new reagent was efficient for the thiocyanation of a wide range of nucleophiles (10-13) such as benzothioophenes, indoles, oxindoles, anilines, phenols,  $\beta$ -keto carbonyl compounds, and aromatic ketones, under mild reaction conditions. When a gram-scale thiocyanation was carried out on 5-bromoindole (11, X = 5-Br, Y = NH), the resulting product (15) was obtained in 91% yield and the starting material Saccharin was recovered with 85% yield after a simple workup, then reused.



Scheme 5. Thiocyanation of imidazopyridines.



Scheme 6. N-Thiocyanatosaccharin as a thiocyanation agent.

The utilization of ultrasound irradiation in organic synthesis has been shown interesting to conserve energy and reduce waste. Therefore, the ultrasound-promoted thiocyanation of phenols, anilines, and indoles (**18**) and (**19**) was studied and reported (Scheme 7) [7]. The reaction was performed with NH<sub>4</sub>SCN in the presence of *N*-chlorosuccinimide (NCS), using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the solvent, at room temperature, and led to the desired thiocyanate derivatives (**20**) and (**21**) in good to excellent yields. The proposed mechanism consists of the reaction of NCS and NH<sub>4</sub>SCN, generating *N*-thiocyanatosuccinimide as the electrophilic SCN species.

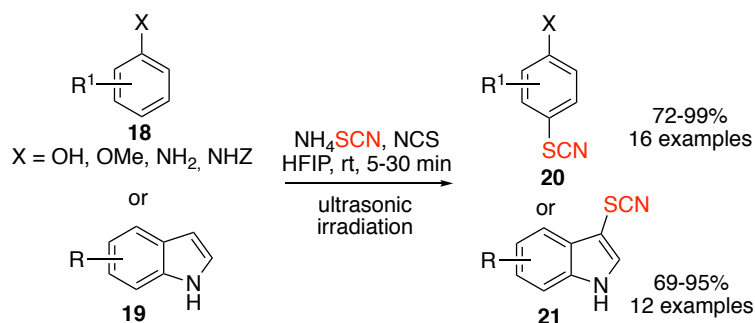
HFIP solvent was supposed to activate NCS through hydrogen bonding to accelerate the formation of *N*-thiocyanatosuccinimide.

Thiourea has also been used in a catalytic amount to accelerate the formation of *N*-thiocyanatosuccinimide from NCS and NH<sub>4</sub>SCN (Scheme 8) [8]. By using this system, the thiocyanation of indoles and aromatic amines led to the corresponding thiocyanates in good yields. The authors proposed that thiourea activates NCS *via* either hydrogen bonding mode or a halogen bond interaction mode.

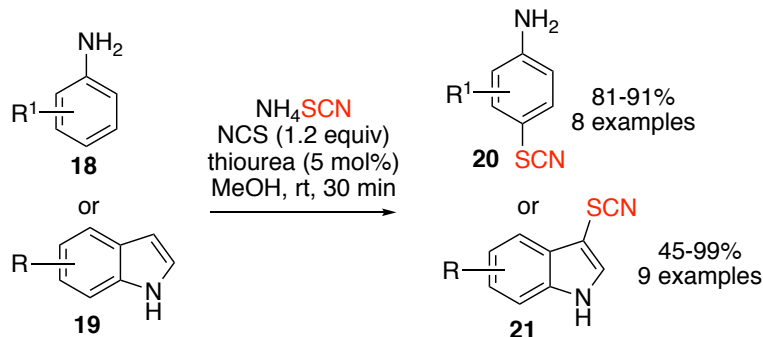
The thiocyanate function was efficiently introduced in the 3-position of indole derivatives (**22**) and in 4-position of aniline derivatives (**23**) by using a copper-catalyzed aerobic oxidative reaction with KSCN as the thiocyanating agent and O<sub>2</sub> as the oxidant (Scheme 9) [9]. The catalytic system consisted of the combination of Cu(OTf)<sub>2</sub>, *N,N,N',N'*-tetramethyl-ethylenediamine (TMEDA), and BF<sub>3</sub>·Et<sub>2</sub>O. The reaction worked well for both strong electron-withdrawing and electron-donating groups on the substrates, leading to the thiocyanation products (**24**) and (**25**) in excellent yields. The mechanism proposed for the indole-case involves a Cu(III) species, the BF<sub>3</sub> Lewis acid activating the C3 position of the substrate. For the aniline case, the authors proposed the generation of SCN radical initiated by copper-mediated single electron transfer (SET).

There have been very few studies devoted to the thiocyanation of alkynes. Recently, a metal-catalyzed thiocyanation of terminal alkynes (**26**) was reported, leading to alkynylthiocyanates (**27**) or  $\alpha$ -thiocyanoketones (**28**) depending on the reaction conditions used (Scheme 10) [10]. *N*-thiocyanosuccinimide (NTS) or *N*-thiocyanophthalimide (NTP) were used as thiocyanating agents. Using silver oxide as the catalyst, the reaction with NTP was applicable to a wide range of substrates, including aryl-, alkenyl-, and alkyl-substituted alkynes, affording the corresponding alkynylthiocyanates in good yields. The reaction potentially proceeded through the silver acetylide intermediate, which underwent addition to the electrophilic SCN species to produce the alkynylthiocyanates and regenerate the catalyst. Alternatively, when the reaction was performed in a two-step procedure under silver/gold relay catalysis, a range of substituted  $\alpha$ -thiocyanoacetophenones were obtained in good to high yield. The transformation includes the first step generation of ketone *via* Ag-catalyzed hydration followed by subsequent thiocyanation assisted by the gold catalyst.

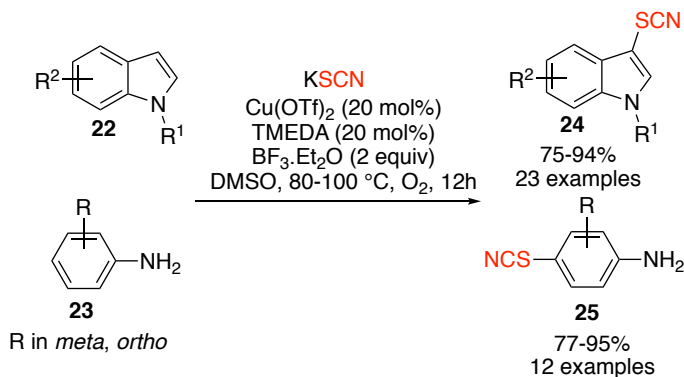
Enaminones represent an interesting class of functionalized alkenes, with rich reactivity. The thiocyanation on the  $\alpha$ -position of tertiary enaminones (**29**) has been achieved with NH<sub>4</sub>SCN, by using visible light photocatalytic conditions, in the presence of Rose Bengal (RB) as the photocatalyst (Scheme 11) [11]. When Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O was employed as a photocatalyst, the reaction provided NH<sub>2</sub>-functionalized thiocyanate enaminones (**31**) *via* a thiocyanation/transamination difunctionalization process. The mechanism may start with the formation of the SCN free radical by the reaction of NH<sub>4</sub>SCN with the excited RB\* species generated from the visible light irradiation of the RB catalyst. The addition of the SCN radical to the C=C bond provides a free radical intermediate, which is oxidized into the carbocation intermediate. The deprotonation of the latter



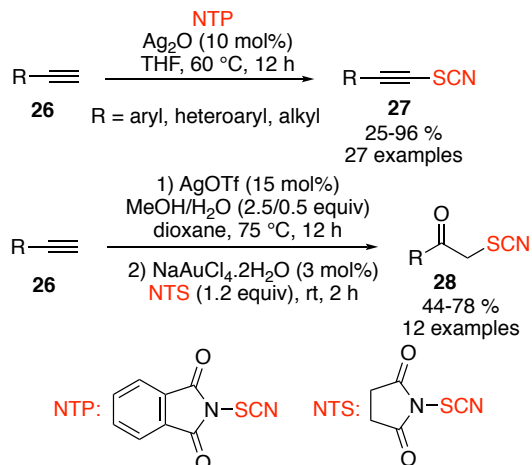
Scheme 7. Ultrasound and HFIP activated thiocyanation.



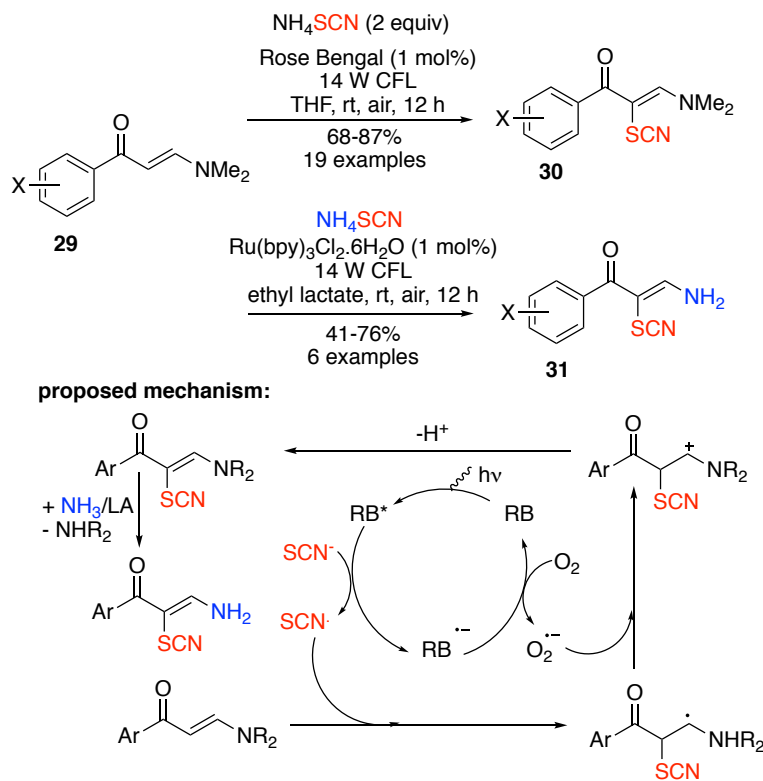
Scheme 8. Thiourea-promoted thiocyanation of indole and aniline derivatives.



Scheme 9. Copper-catalyzed thiocyanation of indole and aniline derivatives.



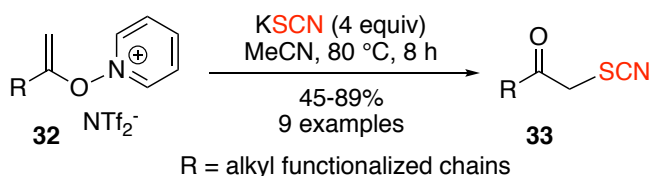
Scheme 10. Metal-catalyzed thiocyanation of terminal alkynes.



Scheme 11. Thiocyanation of enaminones induced by visible light.

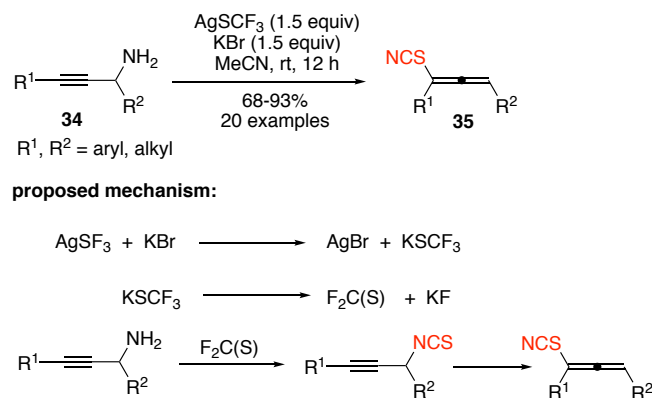
yields a thiocyanate product (30). When the Ru-catalyst is employed, a transamination between the tertiary enaminones and the ammonium is promoted, as the Ru-catalyst may also act as a Lewis acid (LA) catalyst.

The *N*-alkenoxypyridinium salts, easily prepared by gold-catalyzed addition of pyridine *N*-oxide to alkynes, have been used as umpoled enolates to introduce a thiocyanate function in  $\alpha$ -position of a ketone [12]. The *N*-alkenoxypyridinium salt (32) reacted with KSCN in acetonitrile leading to various  $\alpha$ -thiocyanated ketones (33) in good yields and with excellent functional group tolerance (Scheme 12). Pyridine and KNTf<sub>2</sub> were produced at the same time.

Scheme 12.  $\alpha$ -Thiocyanation of ketones using umpoled enolates.

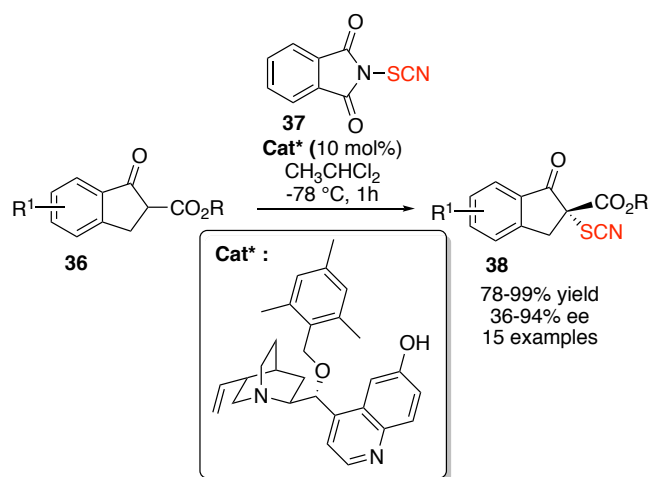
Allenyl thiocyanates (35) were prepared by an efficient cascade reaction starting from propargyl amines (34), by treatment with AgSCF<sub>3</sub> and KBr (Scheme 13) [13]. In this transformation, the isothiocyanate intermediate is formed *in situ*, then a [3,3]-sigmatropic rearrangement occurs to give allene products in high yields. The mechanism proposed by the authors starts with the reaction between AgSCF<sub>3</sub> and KBr to give potassium trifluoromethanethiolate (KSCF<sub>3</sub>) and AgBr, which precipitate. KSCF<sub>3</sub> can generate difluorothio-ketone (F<sub>2</sub>C=S) and potassium fluoride (KF) *via* a chemical equilibrium. The propargyl amine reacts with the thioketone

to form propargyl isothiocyanate, which is subsequently transformed to the corresponding allenyl thiocyanate through [3,3]-sigmatropic rearrangement.



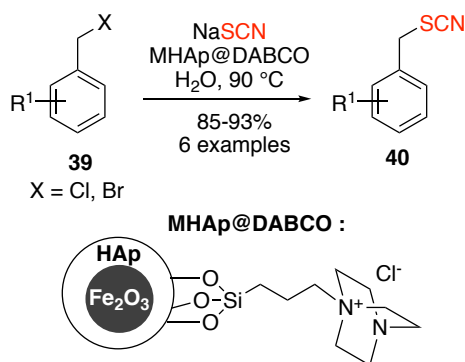
Scheme 13. Synthesis of allenyl thiocyanates.

The catalytic asymmetric  $\alpha$ -thiocyanation of cyclic  $\beta$ -ketoesters (36) was reported for the first time by using bi-functional cinchona alkaloid catalysis and *N*-thiocyanatophthalimide (37) as the electrophilic thiocyanation reagent (Scheme 14) [14]. Various chiral  $\alpha$ -thiocyanato  $\beta$ -ketoesters (38) with a quaternary carbon center have been prepared in excellent yields (up to 99%) and high enantioselectivities (up to 94% ee). By using quinidine and quinine derivatives, both (*R*)- and (*S*)-enantiomers of thiocyanate have been obtained. Different modifications were made on the quinidine structure to improve the enantioselectivity, and the best results were obtained with a free phenolic OH and a protected benzylic OH.



Scheme 14. Asymmetric organocatalyzed thiocyanation of cyclic  $\beta$ -ketoesters.

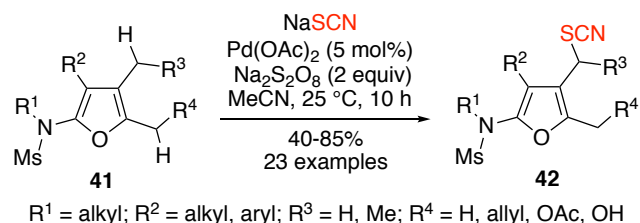
For green chemistry and industrial applications, recycling and reusing catalysts represent an important issue. In this context, a magnetic heterogeneous phase-transfer nanocatalyst was developed and used in the nucleophilic substitution of benzyl halides (39) with thiocyanate anion (Scheme 15) [15]. The MHAp@DABCO nanocatalyst was prepared from 1,4-diazabicyclo[2.2.2]octane (DABCO) that was grafted on mesoporous magnetic hydroxyapatite (MHAp). This catalyst can be used safely and efficiently in water and can be recovered easily by application of a magnetic field, then reused and stored.



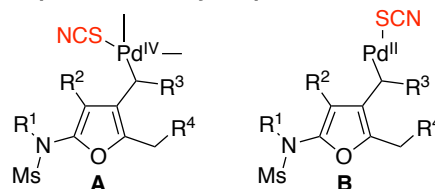
Scheme 15. Magnetic hydroxyapatite-immobilized DABCO in thiocyanation of benzyl halides.

Compared to aryl and heteroaryl thiocyanates, the main general methods to access benzyl and alkyl thiocyanates is to avoid using transition metal-mediated procedures. The first example of transition-metal-catalyzed  $sp^3$ -C-H bond thiocyanation was recently reported [16]. The method was developed on 2-aminofurans substrates (41) by using NaSCN as the thiocyanation reagent, under Pd-catalysis, in the presence of Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as the oxidant, and led selectively to 2-amino-4-thiocyanatomethylfurans (42) in good yields and with a broad substrate scope (Scheme 16). The site selectivity may be attributed to the difference between the C-H acidities in  $\alpha$ -position of R<sup>3</sup> and of R<sup>4</sup>. The authors proposed a Pd(IV) species A produced after reductive elimination of the product with regeneration of the Pd(II) catalyst, or a Pd(II) species B, which led by reductive elimination to the product and Pd(0).

The Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> oxidized Pd(0) to Pd(II) for the next catalytic cycle.



proposed palladium catalytic species:



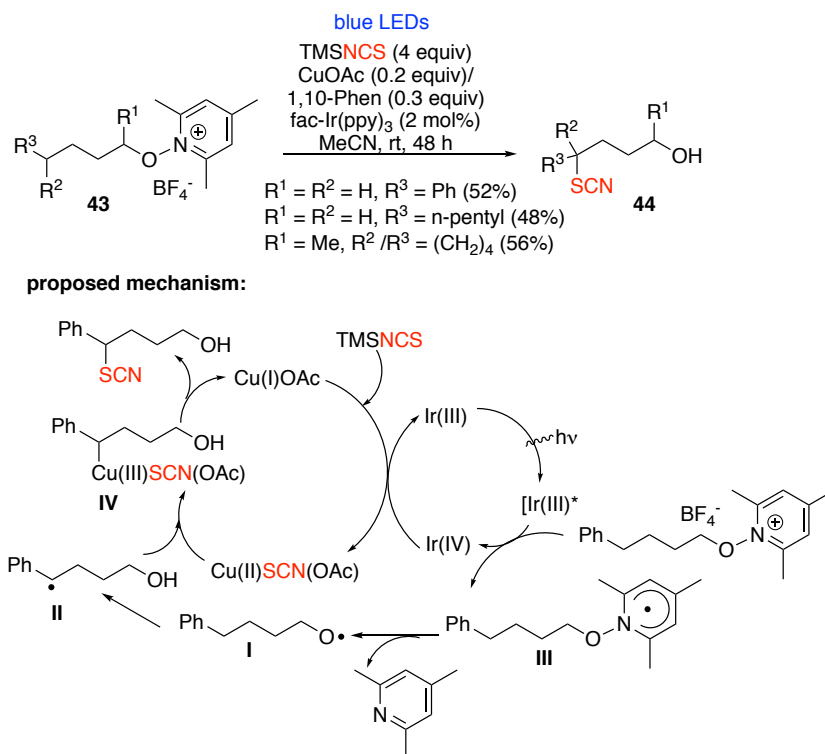
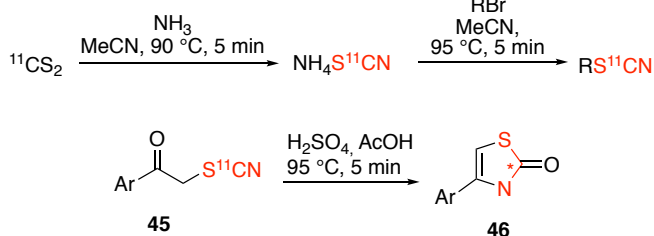
Scheme 16. Pd-catalyzed  $sp^3$ -C-H bond thiocyanation.

Until recently, the thiocyanation of unactivated alkanes was uncommon or unknown. An original method was reported by Zhu and coworkers, describing a dual photoredox/copper catalysis of the reaction between N-alkoxy-pyridinium salts (43) with silyl isothiocyanate (TMSNCS) to afford  $\delta$ -thiocyanato alcohols (44) in good yields (Scheme 17) [17]. Three substrates were selected and described to show the efficiency of thiocyanation of benzylic, aliphatic, and tertiary positions. The reaction takes place *via* a domino process involving alkoxy radical generation, 1,5-hydrogen atom transfer (1,5-HAT) and copper-catalyzed thiocyanation of the resulting C-centered radical. The mechanism proposed by the authors involves the reduction of the substrate by Ir(III)\* excited species to produce the radical III and Ir(IV). The latter oxidizes Cu(I) in the presence of TMSNCS to afford Cu(II)SCN(OAc) salt with the regeneration of the Ir(III) species. The fragmentation of radical III generates the alkoxy radical I, which gives radical II after 1,5-HAT. The latter reacts with Cu(II)SCN(OAc) affording Cu(III) species IV. Reductive elimination affords the thiocyanate product with the release of Cu(I) salt.

Positron emission tomography (PET) is a nuclear medicine imaging technique for the diagnosis of a disease. The two most common PET nuclides are carbon-11 and fluorine-18 and chemists developed a range of small reactive molecules to incorporate these elements into tracers. For this purpose, ammonium [<sup>11</sup>C]thiocyanate was prepared by reacting [<sup>11</sup>C]CS<sub>2</sub> with ammonia, and then used as a nucleophilic reagent in radiolabelling reactions to access <sup>11</sup>C-labelled organic thiocyanates (Scheme 18) [18]. Moreover, <sup>11</sup>C-labelled thiazolones (46) can be easily prepared from  $\alpha$ -thiocyanatophenones (45) *via* acid-mediated cyclisation.

### 2.1.2. Difunctionalization Including Thiocyanation

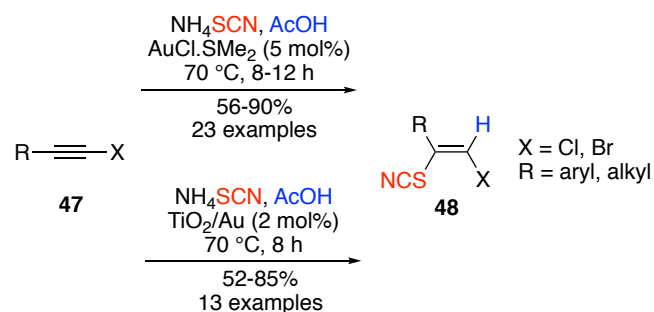
In this section, the reactions will be described in which an electrophilic substrate (alkyne, alkene, epoxide, enamine) is modified by the introduction of one thiocyanate and of another function, leading to difunctionalized products. Hydrothiocyanation of alkynes to access vinyl thiocyanates is also included in this part.

Scheme 17. Photoredox/copper-catalysis to access  $\delta$ -thiocyanato alcohols.Scheme 18. Preparation and utilisation of [<sup>11</sup>C]thiocyanate.

The regio and stereoselective hydrothiocyanation of haloalkynes (47) was developed in both homogeneous and heterogeneous versions, by using gold(I)-catalysis and nanoparticle gold catalysis, respectively [19]. Ammonium thiocyanate was used as the SCN source and the hydrogen came from the acetic acid, which is the protic solvent. Halovinyl thiocyanates (48) were obtained in excellent yields and with exclusive anti-selectivity (Scheme 19). In the heterogeneous version, it was possible to recycle the commercially available TiO<sub>2</sub>/Au catalyst by simple filtration of gold nanoparticle after each run. Five runs have been done without significant loss of catalytic activity.

For the hydrothiocyanation of alkynes activated by an electron-withdrawing group, an eco-friendly procedure using ultrasound-promoted Brønsted acid ionic liquid (BAIL) catalysis has been recently developed [20]. In a minimal of organic solvent, various substrates (49) were reacted with KSCN and water was the hydrogen source to afford Z-vinyl thiocyanates (50) with good to excellent yields (Scheme 20). The use of ultrasonic radiation enhanced the reaction rate and reduced the side reactions. The products and catalyst

were separated by suction filtration. The presence of the acid was essential for this sulfa-Michael reaction. The activated alkyne was reversibly protonated by the BAIL to generate a cationic intermediate, which tautomerized into a zwitterionic complex. The latter is attacked by the thiocyanate anion on the  $\beta$ -carbon to produce a thiocyanate intermediate, which is protonated by water from the less hindered face, *trans* to SCN, leading to Z-vinyl thiocyanates.

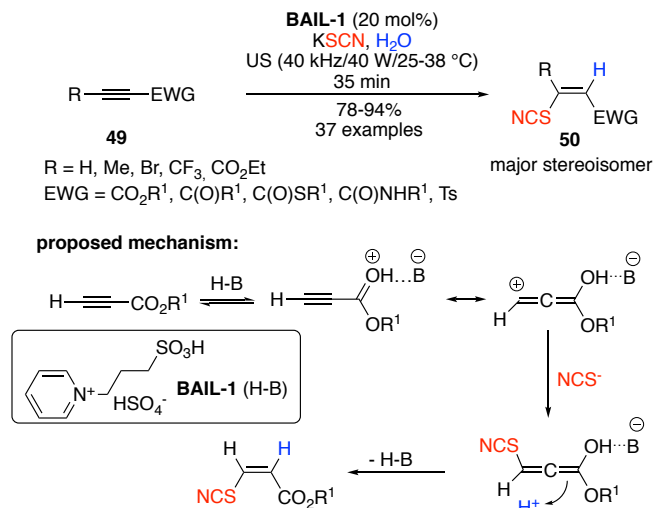


Scheme 19. Gold-catalyzed hydrothiocyanation of haloalkynes.

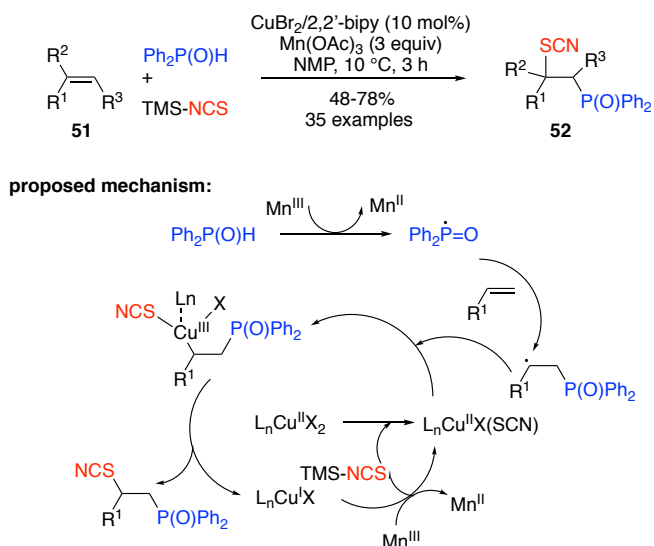
Thiocyanate and phosphinoyl functions were introduced on alkenes (51) by a *one-pot* 1,2-difunctionalization process [21]. The alkene was reacted with diphenylphosphine oxide and trimethylsilyl isothiocyanate in the presence of Mn(OAc)<sub>3</sub> and a catalytic amount of CuBr<sub>2</sub> and 2,2'-dipyridyl (Scheme 21). The method was applicable to acyclic and cyclic alkenes bearing various aromatic or aliphatic substituents, leading to diphenyl(2-thiocyanatoethyl)phosphine oxide derivatives (52) in good yields. The proposed reaction mechanism starts with the generation of the P-radical by



oxidation of the  $\text{Ph}_2\text{P}(\text{O})\text{H}$  with  $\text{Mn}(\text{III})$ . The radical addition to the alkene gives a  $\beta$ -phosphonylated radical, which subsequently reacts with the  $\text{Cu}(\text{II})$  thiocyanate complex formed from  $\text{TMSNCS}$  and  $\text{Cu}(\text{II})$  complex. The resulting  $\text{Cu}(\text{III})$  complex undergoes the elimination of  $\text{Cu}(\text{I})$  species and affords the 1,2-difunctionalized product.  $\text{Cu}(\text{I})$  is re-oxidized into  $\text{Cu}(\text{II})$  by  $\text{Mn}(\text{III})$ .



Scheme 20. Hydrothiocyanation of activated alkynes.



Scheme 21. Thiocyanophosphinylation of alkenes.

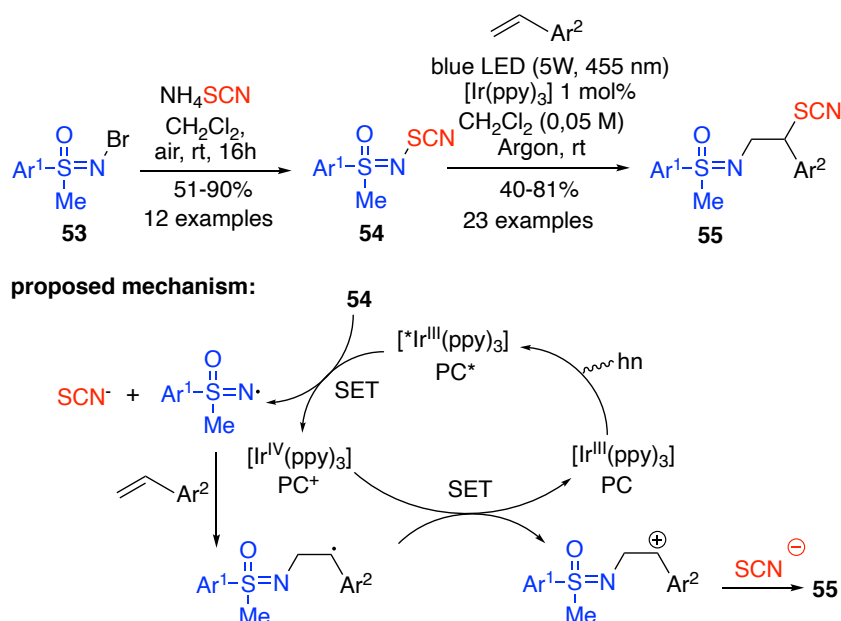
Bolm and coworkers obtained N-thiocyanato sulfoximines (54) by the reaction between N-bromo sulfoximines (53) with ammonium thiocyanate, and used these reagents in the 1,2-difunctionalization of styrene derivatives (Scheme 22) [22]. The reaction proceeded under photocatalysis and involved N-centered sulfoximidoyl radicals, leading to products (55) bearing a thiocyanate function and a sulfoximine function on vicinal positions. The following mechanism was proposed by the authors: the photocatalyst fac-[ $\text{Ir}(\text{ppy})_3$ ] (PC) accepts a photon from weak fluorescent light to generate excited state  $\text{PC}^*$ . Single-electron transfer (SET) from  $\text{PC}^*$  onto N-thiocyanato sulfoximine leads to  $\text{PC}^+$

providing the sulfoximidoyl radical and  $\text{SCN}^-$  anion. After the addition of the sulfoximidoyl radical to the styrene, the resulting radical is oxidized by  $\text{PC}^+$  to give a benzyl cation. Finally, the photocatalyst comes back to its original oxidation state (PC) to start a new catalytic cycle.

By coupling ammonium thiocyanate with activated ketones (56) under photocatalysis conditions, using air as the terminal oxidant, (*E*)-3-amino-2-thiocyanato- $\alpha,\beta$ -unsaturated compounds (57) were obtained in large variety, in good to excellent yields (Scheme 23) [23]. The ammonium thiocyanate was doubly used as an amine and thiocyanate source, and water was the only byproduct. The postulated mechanism begins with the visible light induced SET oxidation of  $\text{NH}_4\text{SCN}$  by the fluorescein photocatalyst in its excited state ( $\text{PC}^*$ ), generating the  $\text{SCN}^-$  radical and the reduced photocatalyst  $\text{PC}^{\cdot-}$ . The latter is oxidized with  $\text{O}_2$  to regenerate the photocatalyst. The  $\text{SCN}^-$  radical abstracts a hydrogen to produce an  $\alpha$ -carbonyl radical together with thiocyanic acid (HSCN). The obtained radical is then trapped by other  $\text{SCN}^-$  radicals or by  $(\text{SCN})_2$  to form an  $\alpha$ -thiocyanated ketone intermediate, of which electron-deficient carbonyl group is easily attacked by nucleophilic  $\text{NH}_3$ . Final elimination of water affords the product.

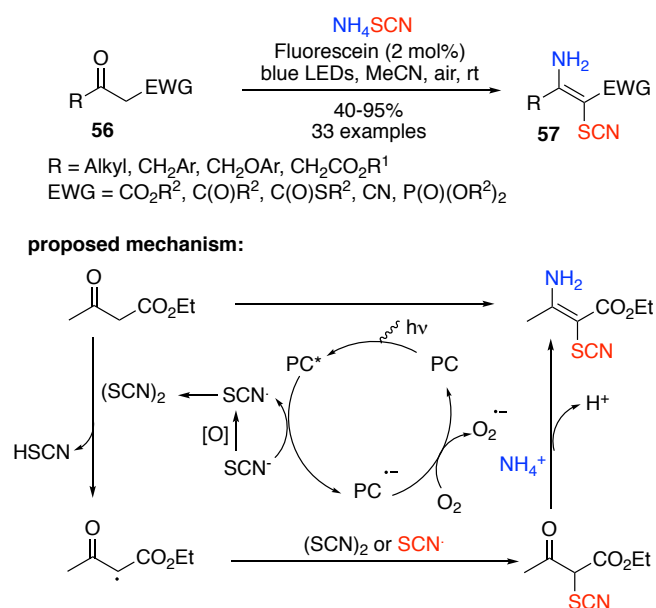
A simple and sustainable procedure enabled the stereoselective *one-pot* synthesis of aryl substituted (*E*)-2-thiocyanatoacrylic acids (59) by using three simple and easily available reagents: chloroacetic acid, ammonium thiocyanate and an aromatic aldehyde (Scheme 24) [24]. The reaction worked at room temperature and gave the desired products in excellent yields. The plausible mechanism involves as the first step the nucleophilic substitution of chlorine by the thiocyanate anion to form a 2-thiocyanatoacetic acid. Then, the latter interacts with ammonium acetate to produce the ammonium 2-thiocyanatoacetate salt of which methylene group is deprotonated to undergo Knoevenagel condensation with the aldehyde to furnish the final product.

Oxirane derivatives (60) were regioselectively released in the reaction with aroyl isothiocyanate reagents (61), in the presence of a catalytic amount of N-methyl imidazole (NMI), leading to *O*-aroyl  $\beta$ -thiocyanate alcohols (Scheme 25) [25]. The thiocyanate group of the reagent acted as the nucleophile, while the aroyl group acted as the electrophilic partner trapping the formed alkoxide. The regioselectivity is controlled by the nature of the epoxide substituent R: in the case of an aryl substituent, the thiocyanate attacked at the benzylic position giving the product regioisomer 62a, while for nonaromatic derivatives, the thiocyanate attacked at the less hindered position, leading to the opposite regioisomer of type 62b. In this atom-economic process organocatalyzed by NMI, solvent-free C-S and C-O bonds simultaneously formed. The following mechanism was proposed: NMI nitrogen attacked at the carbonyl carbon of the aroyl isothiocyanate to form a zwitterionic intermediate, which released  $\text{SCN}^-$  anion giving an NMI aroylate species. Epoxide coordinated with the latter facilitating the nucleophilic attack by the  $\text{SCN}^-$  to give alkoxy intermediate. The alkoxy nucleophile attacked the electrophilic aroyl-NMI intermediate and afforded the difunctionalized product with a concomitant release of NMI-organocatalyst. In another study, the same research group reacted aroyl or acyl isothiocyanate with aziri-



Scheme 22. Photocatalytic thiocyanate/sulfoximine difunctionalisation of alkenes.

dine, without any catalyst, and obtained in this case 1-iminothiazolidines *via* a ring-opening/cyclization domino reaction [26].



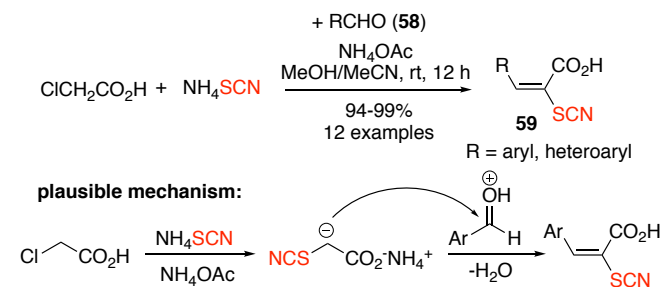
Scheme 23. Aminothiocyanoation of activated ketones promoted by visible-light.

### 2.1.3. Thiocyanation/cyclisation Domino Reactions

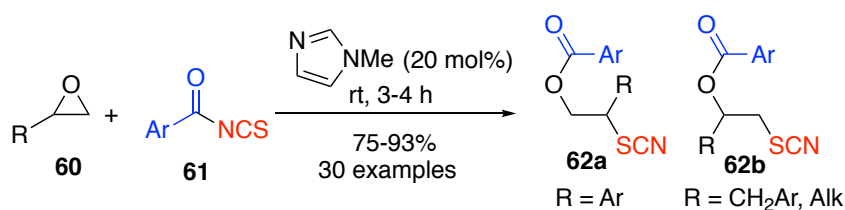
In this section, the domino reactions will be described in which the introduction of the thiocyanate function is accompanied by a subsequent carbo- or hetero-cyclization, leading to thiocyanated heterocyclic compounds.

3-Thiocyanatobenzothiophenes (64) were synthesized by a photocatalyzed cascade reaction from 2-alkynylthioanisoles (63) and ammonium thiocyanate, in the presence of Eosin Y (EY), of visible light as a green energy

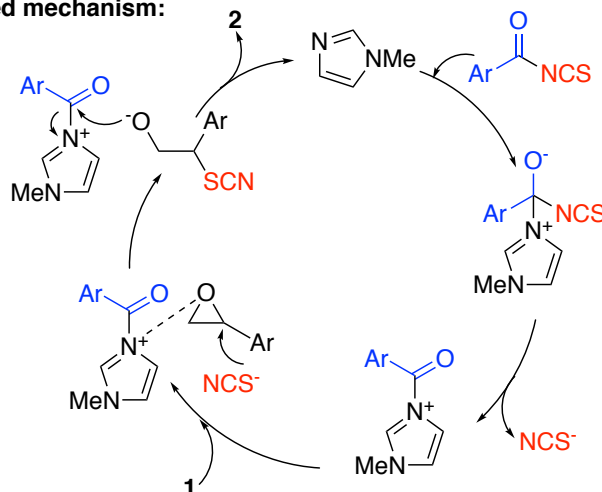
source, and of oxygen as a green terminal oxidant (Scheme 26) [27]. The supposed mechanism involves the formation of the SCN-radical through the SET process mediated by EY. The regioselective addition of SCN-radical to alkyne gives a vinyl radical intermediate, which undergoes an intramolecular radical cyclization to give a S-radical cyclic intermediate. The latter one is oxidized by either the EY\* (excited photocatalyst) or oxygen to deliver a sulfonium intermediate, which is demethylated in the presence of a nucleophile to provide the product.

Scheme 24. A three-component synthesis of aryl substituted (*E*)-2-thiocyanatoacrylic acids.

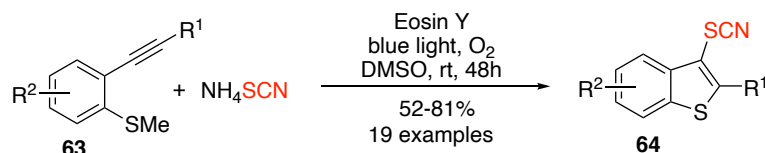
Various enaminones (65) were reacted with KSCN in the presence of  $K_2S_2O_8$ , at room temperature, and led to 3-thiocyanatochromenones (66) *via* a domino underwent thiocyanation/cyclization process in good yields (Scheme 27) [28]. The authors also developed a one-pot version of the method starting from 2-hydroxyl acetophenones. The proposed mechanism starts with the SCN-radical generation *via* the oxidation of KSCN by  $K_2S_2O_8$ , followed by the addition of SCN-radical to the double bond of the enaminone to give a new radical intermediate. The latter is oxidized to the corresponding carbocation, which undergoes cyclization by an attack of the hydroxy nucleophile. Finally, the elimination of *N,N*-dimethylamine affords the thiocyanated chromenones.



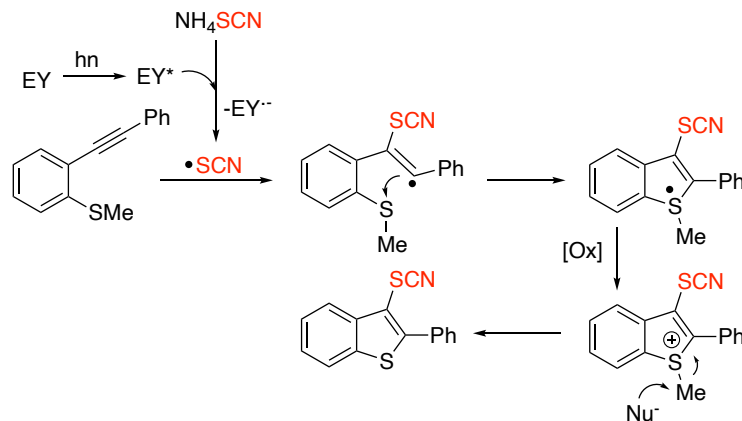
proposed mechanism:



Scheme 25. Organocatalyzed thiocyanation/*O*-arylation of oxiranes using aryl isothiocyanates.



proposed mechanism:

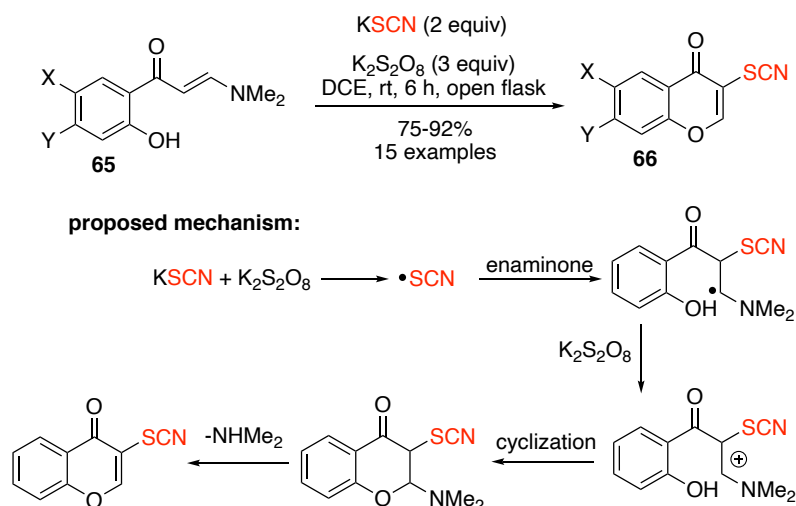
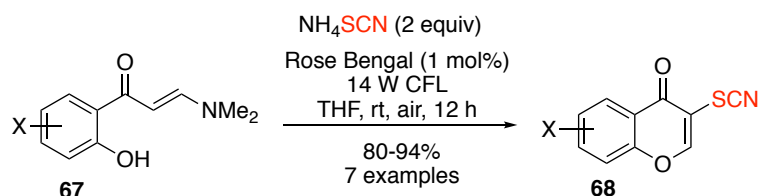
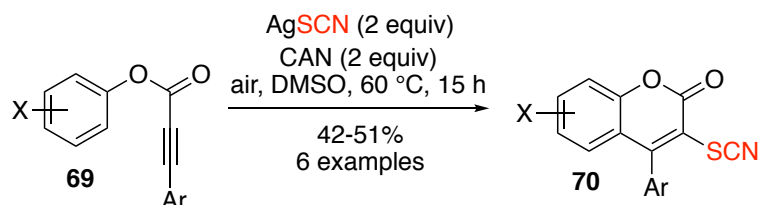


Scheme 26. Synthesis of 3-thiocyanatobenzothiophenes *via* photocatalyzed thiocyanation/heterocyclization.

The method enabling the thiocyanation on the  $\alpha$ -site of tertiary enamines using ammonium thiocyanate under photocatalytic conditions in the presence of Rose Bengal [11], was also applied to *N,N*-dimethylenaminones derivatives (**67**) with an ortho-hydroxyphenyl substructure. In this case, 3-thiocyanated chromones (**68**) were obtained *via* intramolecular annulation (Scheme **28**). Seven products of this type were synthesized, with good to excellent yields.

Due to their wide spectrum of biological activities, coumarins represent interesting scaffolds in medicinal chemis-

try, thus encouraging their diverse functionalization. 3-Thiocyanated coumarins (**70**) were prepared by a thiocyanation/cyclization domino process starting from alkynoates (**69**) and AgSCN, in the presence of Ce(NH<sub>4</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>6</sub> (CAN) as the oxidant (Scheme **29**) [29]. The AgSCN/CAN combination generates SCN-radicals. Several aryl alkynoates with various substituents were compatible with the reaction conditions to give the corresponding products in moderate yields. In the case of one example with an alkyl substituent on the triple bond, acetonitrile was the best solvent, however, a lower yield of 22% was obtained.

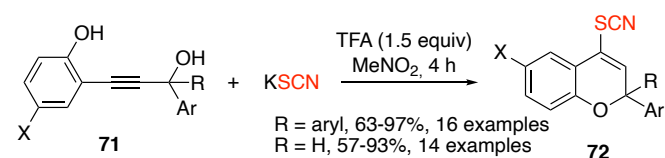
Scheme 27. Synthesis of 3-thiocyanated chromenones using KSCN/K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> system.Scheme 28. Photocatalytic synthesis of 3-thiocyanated chromenones using NH<sub>4</sub>SCN/Rose Bengal system.

Scheme 29. Synthesis of 3-thiocyanated coumarins.

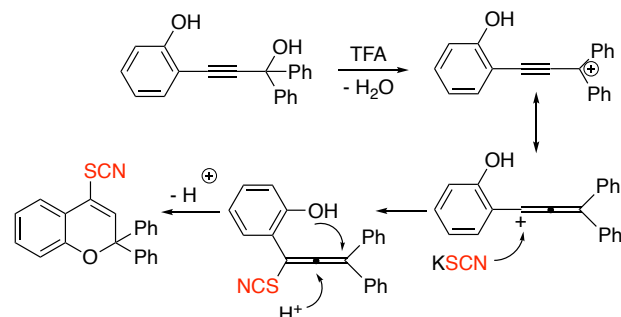
4-Thiocyanated 2*H*-chromenes (**72**) were synthesized from 2-propynol phenols (**71**) and KSCN, in the presence of trifluoroacetic acid (TFA) as a Brønsted acid catalyst (Scheme **30**) [30]. The transformation proceeded in good to excellent yields and tolerated various functional groups on the substrates. The suggested mechanism involves the formation of a propargylic cation by the dehydration of 2-propynolphenol in the presence of TFA. Subsequent tautomerization affords an allenic cation intermediate. The nucleophilic attack of the SCN<sup>-</sup> anion onto this latter intermediate furnished a thiocyanated allene, which underwent intramolecular cyclization to give after release of a proton as the desired product.

The intramolecular aminothiocyation of unactivated alkenes (**73**) with sodium thiocyanate was developed by *in situ* generated iodine thiocyanate under aerobic conditions. The reaction represents an efficient method to access new thiocyanated *N*-heterocycles (**74**) with good isolated yields (Scheme **31**) [31]. Mixing iodine and sodium thiocyanate with oxygen afforded iodine thiocyanate ISCN and dithiocyanatoiodate I(SCN)<sub>2</sub> active species, which were detected by LC-MS analysis. Two mechanistic pathways were proposed,

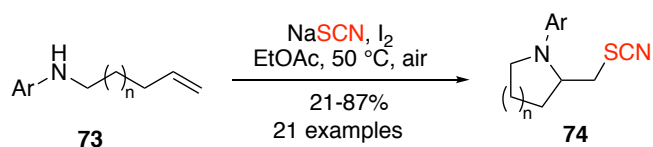
involving either an iodonium ion or a sulfonium ion intermediate.



**proposed mechanism:**

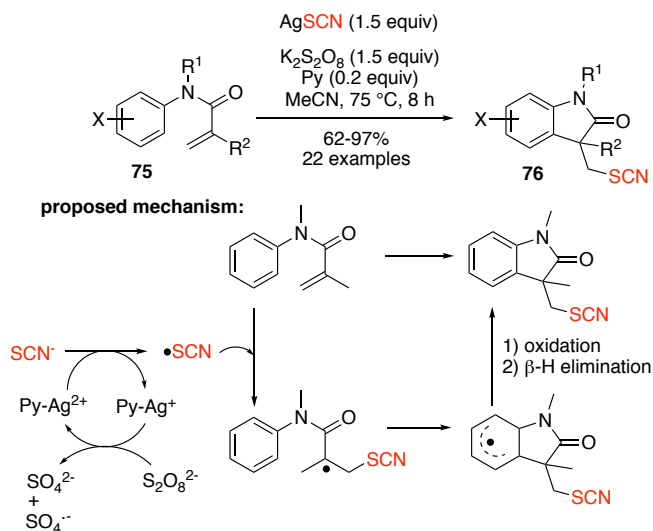


Scheme 30. TFA-mediated synthesis of 4-thiocyanated chromenes.



Scheme 31. Intramolecular aminothiocyation of unactivated alkenes.

The arylthiocyation of activated alkenes (75) was developed by using a silver thiocyanate/pyridine-mediated oxidative SCN-radical addition/cyclization domino process [32]. The reaction led to 3-alkylthiocyanato-2-oxindoles (76) in good to excellent yields (Scheme 32). Mechanistic studies performed by the authors suggested that the Py-mediated oxidation of Ag(I) to Ag(II), accelerated the formation of SCN-radical. The addition of the latter on the double bond afforded the alkyl radical which after cyclisation, gave an aromatic radical, which was oxidized to the cationic species, to give the desired product after  $\beta$ -H elimination.



Scheme 32. Arylthiocyation of activated alkenes.

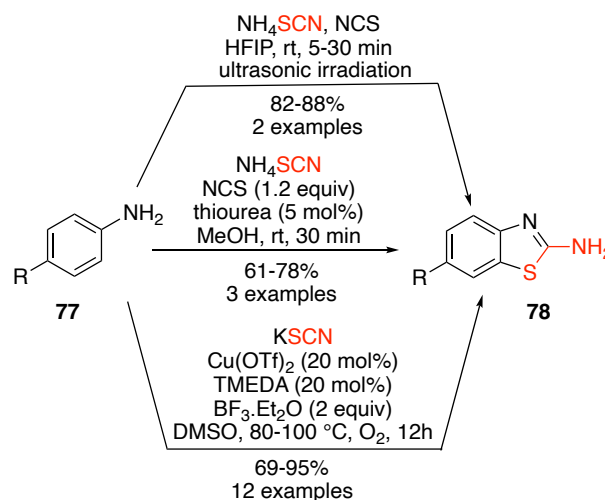
## 2.2. Reactions with the Transformation of the SCN Group

In many reactions, the thiocyanate functionality is installed as a reactive intermediate that is directly transformed in the course of a domino sequence. It is important to remind that thiocyanates have two electrophilic sites centered on the sulfur atom as well as the carbon of the nitrile function. Thus, depending on the location of the nucleophilic attack, the three thiocyanate atoms can be found totally or only partially in the structure of the obtained products. In the case of the latter, the thiocyanate transient-functionality has to be seen as an electrophilic source of sulfur.

### 2.2.1. With Remaining of All SCN Atoms

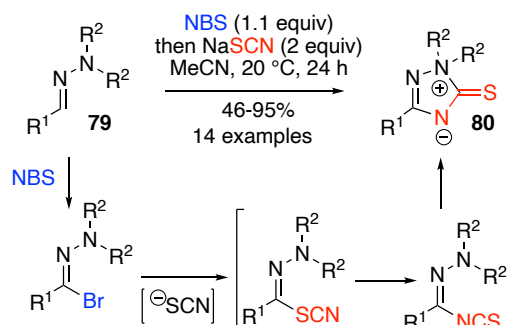
As mentioned previously (§2.1.1), anilines can be thiocyanated through direct functionalization of the aromatic ring using the thiocyanate anion [7-9]. Usually, the cyanation takes place at the *para* position, however, when this position is substituted, the second favored position becomes the *ortho* one and in that case, a subsequent cyclization *via* the nucleophilic attack of the nitrogen of the aniline on the cyano group

of the SCN can occur to form the corresponding amino-benzothiazole (78) (Scheme 33). This approach is very interesting as it allows the rapid access to diversely functionalized heterocycles that can be found in a wide range of bioactive compounds [33].



Scheme 33. Thiocyanation/cyclization sequence to form benzothiazole derivatives.

Following the strategy of post-cyclization, Bouyssi, Monteiro *et al.*, reported the synthesis of sulfur containing 1,2,4-triazoles thanks to a practical one-pot approach involving a thiocyanation step of *N,N*-dialkylhydrazone derivatives (79) (Scheme 34). In that case, after the bromination of the hydrazone starting material, a thiocyanate salt is added to the reaction mixture to form an intermediate that subsequently performs a thiocyanate-to-isothiocyanate isomerization. The newly generated compound is then cyclized to lead to valuable 1,2,4-triazolium species (80) [34].

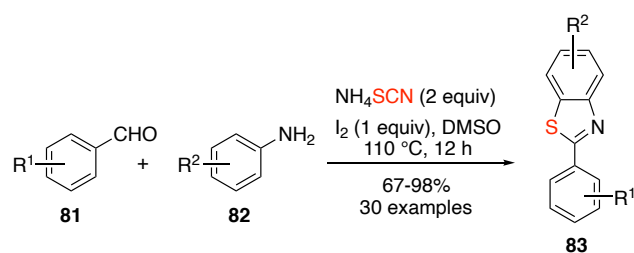


Scheme 34. Synthesis of triazolium derivatives through thiocyanation of hydrazone derivatives.

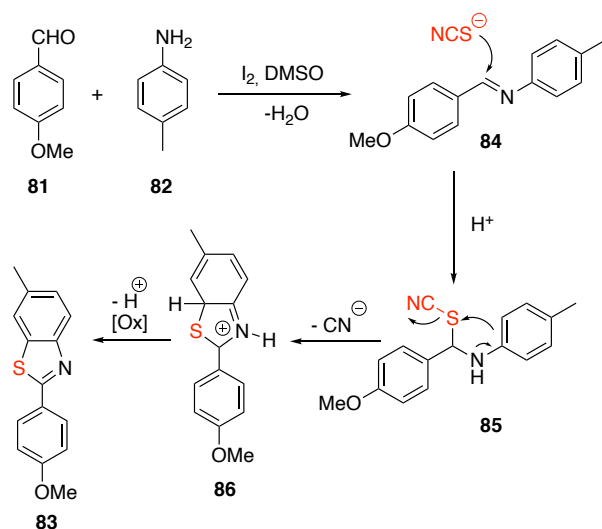
### 2.2.2. With the Loss of the CN Moiety

As mentioned earlier, thiocyanate functionality can be seen as an electrophilic provider of sulfur. In that case, a nitrile moiety is only a leaving group that will not be found in the final product formed. For instance, Hajra *et al.*, reported the three-component synthesis of 2-arylbenzothiazole derivatives starting from benzaldehydes, anilines and an ammonium thiocyanate salt (Scheme 35). Under these conditions, the thiocyanate anion is added onto the imine ((84)

resulting from the condensation of aldehyde (81) and aniline (82) to lead to an intermediate (85) that subsequently cyclizes *via* a Friedel-Craft type reaction to form the targeted heterocycle (83) [35].



proposed mechanism:



Scheme 35. Synthesis of 2-arylbenzothiazoles *via* a 3-component reaction.

If the intramolecular reaction is interesting, in terms of molecular diversity, it is often more interesting to perform intermolecular reactions. Zhou *et al.*, developed the C-H functionalization of flavone (87) at the  $\alpha$ -position. This method makes use of the KSCN salt to form thiocyanate (89) in which a copper catalyst can be inserted to finally promote the cross-coupling with the flavone (87) to form the corresponding thioether (90) (Scheme 36) [36]. The main interest

of this tandem reaction lies in the fact that this approach avoids going through the thiol compound, which, in addition to having a strong odor, could lead to unwanted by-products such as disulfides for instance.

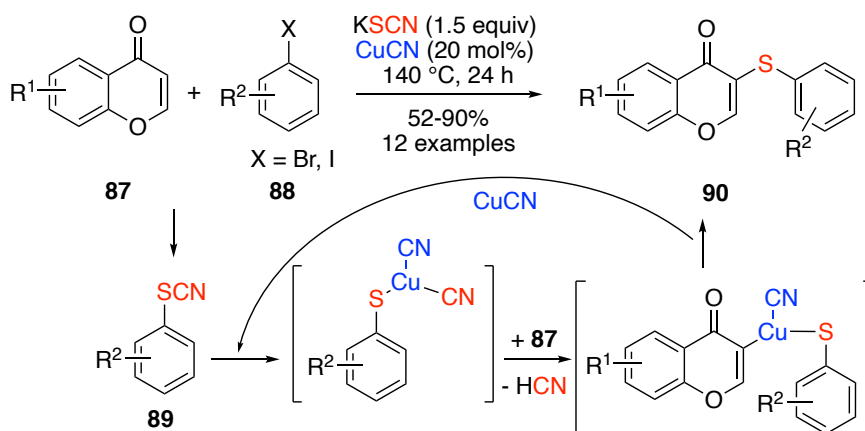
### 3. REACTIONS INVOLVING S-CYANATION

The formation of thiocyanates through *S*-cyanation appears as a straightforward method; however, this approach has been less investigated than the incorporation of the full thiocyanate function [37]. This can be explained by the starting material required. Indeed, thiols can have strong odors and they are easily oxidized into their corresponding disulfides.

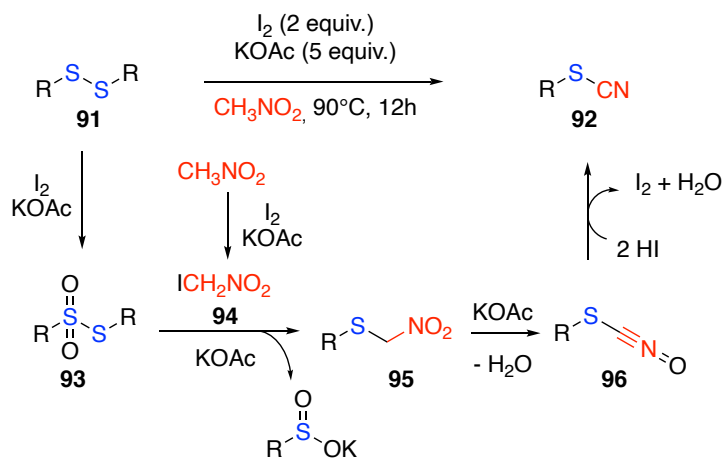
Despite this statement, very interesting developments have been made in this field over the last few years. Among the most significant advances, the development of new "green" cyanating agents is undoubtedly one of the most interesting. In 2015, Hu, Tang *et al.*, reported the use of nitromethane as a reagent to form thiocyanate starting from disulfides (Scheme 37). Presumably, the reaction proceeds *via* the formation of iodonitromethane (94) that can then react with an oxidized form of the disulfide (91) (thiosulfonate (93)) to lead to the intermediate (95) that undergoes two successive dehydration to finally reach the targeted thiocyanate (92). Notably, one molecule of disulfide leads to one molecule of thiocyanate as sacrificial sulfinate is generated during the course of the reaction [38].

In 2018, Guo, Zheng, and Fan *et al.* reported the photocatalytic cyanation of thiols using ammonium thiocyanate salt as a green "CN" source. Interestingly, in this case, the thiocyanate salt does not transfer the SCN moiety but only the nitrile moiety by a cleavage of the S-CN bond due to the combined action of visible-light and Rose bengal as a photocatalyst under air atmosphere (Scheme 38). This reaction presumably leads to the formation of the thiyl radical (99) that is then reacted with the thiocyanate anion to form an intermediate (100), leading to the targeted thiocyanate (98) with the loss of hydrogen sulfide [39].

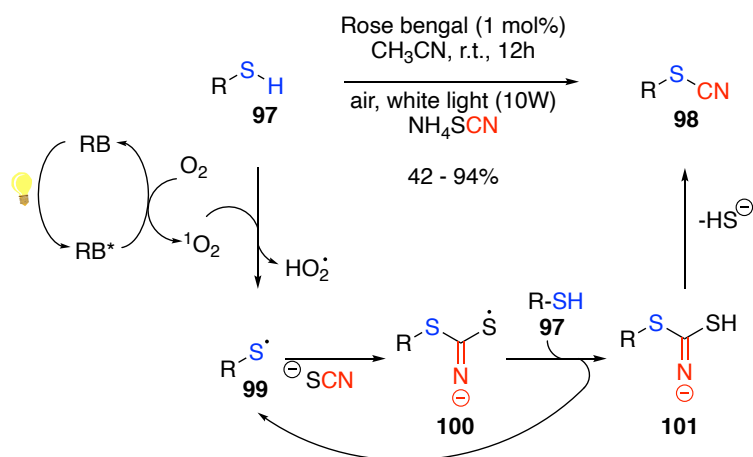
In 2016, Donnard, and Gulea *et al.* reported the synthesis of amino-benzothiazole derivatives using a copper-mediated three-component reaction involving an *S*-cyanation key step (Scheme 39). In that case, starting from *ortho*-aminothiophenols (102) or their corresponding diaryldisulfides



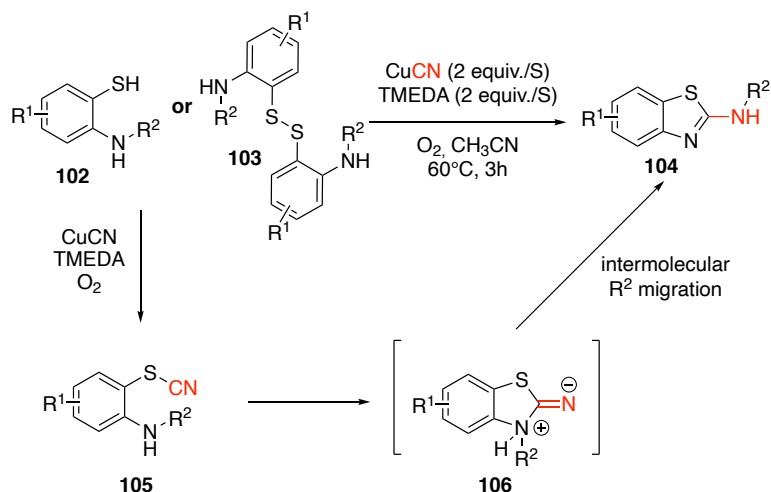
Scheme 36. Synthesis of flavone-based thioether through the formation of a thiocyanate.



Scheme 37. Synthesis of thiocyanate using nitromethane as cyanating agent.



Scheme 38. Photocatalytic synthesis of thiocyanate using ammonium thiocyanate as a cyanating agent.



Scheme 39. 3-component approach to benzothiazole derivatives involving S-cyanation of thiophenols or diaryl disulfides.

(103), they performed the cyanation of the sulfur atom by an oxidative coupling due to the use of CuCN [40] to form a thiocyanate (105) that can be subsequently attacked by the nitrogen atom to lead to a benzothiazole intermediate that can intermolecularly transfer its protecting group to reach the targeted heterocycle (104) [41, 42].

## CONCLUSION

In conclusion, even if the thiocyanate functional group has been known for decades (centuries), the field is still really dynamic and many new synthetic methodologies are emerging almost every week. Among the recent innovations,

the development of greener processes involving less toxic reagents is undoubtedly one of the most important requirements to the field.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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