

Immobilized Rose Bengal as Photocatalyst for Metal-Free Thiocyanation of Azaheterocycles under Continuous Flow Conditions

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Dedicated to Prof. *Scott Denmark*, on the occasion of his 70th birthday

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The immobilization of Rose Bengal onto Merrifield resin and its application in the light-driven metal-free thiocyanation of azaheterocycles *in continuo* were investigated. The supported photocatalyst was used in batch reactions under heterogeneous conditions, with different azaheterocycles, and proved to efficiently promote the reaction. Its recovery and recycle were also demonstrated for up to four times. The resin-supported Rose Bengal was then employed under continuous flow conditions, affording thiocyanate functionalized azaheterocycles with higher space-time-yields than the in-batch transformations, and in a shorter reaction time. The easily modification of the SCN groups was also demonstrated by synthesizing trifluoromethyl thioethers and sulfenyl tetrazoles derivatives in high yields.

Keywords: green chemistry, photocatalysis, photochemistry, Rose Bengal, supported catalysts, thiocyanation reaction.

Introduction

Organosulfur compounds are important synthetic intermediates for target molecules which exhibit biological activity; penicillins and cephalosporins represent the two most important classes of sulfur-based drugs discovered in the early 1900s and still employed as broad-spectrum antibiotics.^[1] Despite their great applicability, the direct introduction of a sulfur atom into an organic molecule is still a challenging task, and the use of sulfides and thiols as direct precursors usually suffers from many drawbacks; these compounds are very sensitive to oxidation and decomposition processes, making their manipulation quite difficult (not to mention that typically they also show an unpleasant smell). Therefore, alternative procedures for the introduction of more versatile sulfur-containing group are highly desirable. A viable alternative to

overcome these issues consists in the introduction of the thiocyanate group (SCN) which can be easily manipulated and converted into many different functional groups^[2,3] giving access to a wide range of derivatives such as sulfides and disulfides,^[4,5] thiocyanates,^[6] thiocarbamates,^[7] trifluoromethyl thiolates,^[8] 1,2-thiobenzonitriles^[9] and many other sulfur containing heterocycles.^[10] Thus, it should not be surprising that many original methodologies for generating C–SCN bonds involving nucleophilic substitution, electrophilic substitution or free-radical thiocyanation have recently been developed,^[11] involving catalytic,^[12] organocatalytic,^[13–15] electrochemical^[16] and photochemical^[17,18] processes; some of them have been successfully investigated under continuous flow conditions.^[19] Among them, photochemical induced thiocyanation reactions involving the use of air as oxidant (instead of stoichiometric oxidants) have recently attracted attentions, since these approaches show a reduced waste production and involve the use of photons to perform synthetic transformations. The first photoredox-catalyzed thiocyanation reaction was

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reported by Li and coworkers in 2014, in which indoles react with SCN radical generated by ammonium thiocyanate in the presence of Rose Bengal as organic dye upon irradiation with visible light and using air oxygen as oxidant.^[20] One year later, Hajra demonstrated that also Eosin Y can be employed as photo-redox catalyst for the radical thiocyanation of imidazo-heterocycles under aerobic conditions^[21] and the same photocatalyst was successfully employed for the thiocyanate functionalization of tetrahydroisoquinolines; although in the latter case, the formation of a radical iminium ion is involved.^[22]

More recently, also nanocomposite photocatalyst materials,^[23] polymeric graphitic carbon nitride materials,^[24] covalent organic frameworks^[25] and metallo-based complexes^[26,27] have been employed in visible-light-induced thiocyanation of indoles.

Unfortunately, the low recyclability and, in some cases, the high cost of these photocatalysts, impose remarkable limitations on scale-up for their industrial applications. One possibility to solve this issue consists in anchoring the photocatalyst onto an inert support;^[28] in this way, the catalytic species could be easily removed upon a completed reaction, facilitating the work-up and, possibly, the reuse in further transformations.^[29,30] Few examples of Eosin Y^[31–34] and Rose Bengal^[34–42] supported materials have been already reported in literature, and their use in photochemical applications confirm that the treatment and purification of the target compound have been greatly facilitated. In this context, we wish to report here our findings on the use of Rose Bengal supported onto Merrifield resin in the direct photochemical metal-free C-3 thiocyanation of indoles under continuous flow conditions, originally reported by Li and coworkers.^[20]

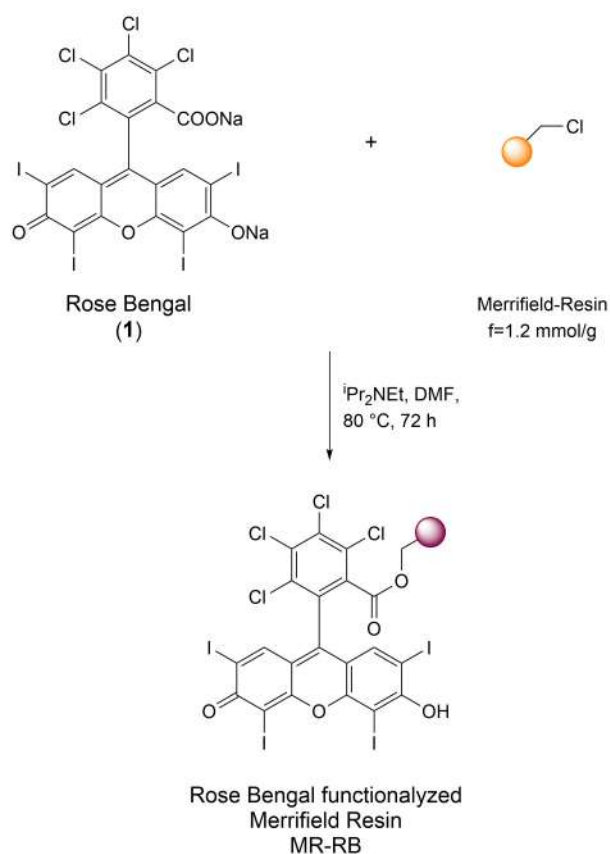
Results and Discussion

Since Rose Bengal is a versatile photocatalyst which has been extensively employed in a variety of photocatalytic organic transformations,^[43] we decided to investigate the use of its immobilized version on the Merrifield-resin as heterogeneous photocatalyst for metal-free C-3 thiocyanation of indoles. Rose Bengal bound to polystyrene is commercially available with the trade name Sensitox® from many suppliers, however it could be easily synthesized according to literature procedures.^[44–47] Following the procedure originally reported by Neckers and Schaap,^[48–51] immobilization of Rose Bengal disodium salt onto Merrifield resin was performed by reacting 1.2 equiv.

of Rose Bengal disodium salt and 2.4 equiv. of $i\text{Pr}_2\text{NEt}$ in the presence of Merrifield-Resin (High-Load 100–200 mesh) at 80 °C for 72 h (Scheme 1). After this time, the mixture was poured into a glass sintered funnel and extensively washed until the running liquids show no sign of purple color anymore. Following this procedure, 9.91 g of supported catalyst were synthesized.

The loading of the resin supported catalyst was 1.02 mmol/g, as determined by weight difference (see Supporting Information). The EDS spectrum of MR-RB material shows the peaks of iodine and oxygen atoms, confirming that the anchoring of Rose Bengal onto the polymer was successful. The presence of chlorine atoms can be ascribed both to the presence of the catalyst anchored on the resin and to the presence of non-functionalized groups of the material itself, whereas the absence of sodium and nitrogen signals shows that the catalyst is linked in its neutral form (Figure 1).

Preliminary studies of the visible-light promoted C-3 thiocyanation reaction were performed using 1*H*-indole **2** as model substrate, ammonium thiocyanate



Scheme 1. Synthesis of solid supported Merrifield-resin Rose Bengal (MR-RB).

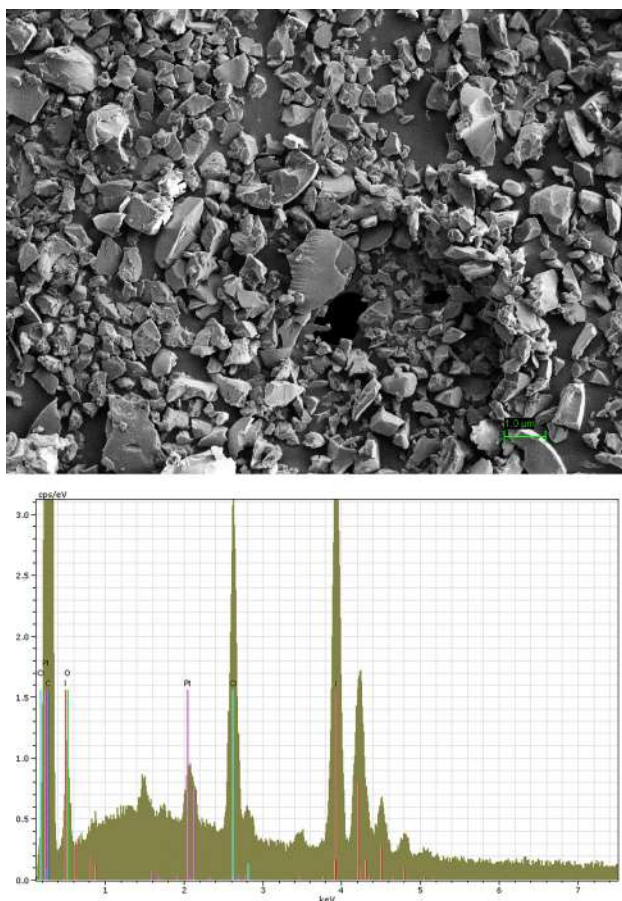


Figure 1. SEM analysis at 500 \times magnification and energy dispersive spectrometer (EDS) analysis of MR-RB catalyst.

as source of SCN radical and air oxygen as abundant and low-cost oxidant.

Homogeneous Rose Bengal disodium salt **1** was initially employed, according to a slightly modified protocol reported by Li^[20] which consists in the reaction of a 0.1 M solution of 1*H*-indole in THF with 1.5 equiv. of NH₄SCN in the presence of 1 mol% of photocatalyst. Original 14 W compact fluorescent lamp with broad light emission profile was replaced by more efficient green light-emitting diodes (LEDs), which are characterized by an almost monochromatic emission light source with a maximum of intensity located at ca. 530 nm. The reaction was carried out in open air; different solvents were screened and the formation of 3-thiocyanato-1*H*-indole (**3**) was monitored by GC using biphenyl as internal standard. Three different home-made, custom designed photoreactors were investigated (see *Figure 2*).

Type A photoreactor^[52] was realized by 3D-printing FDM technology and equipped with LEDs showing

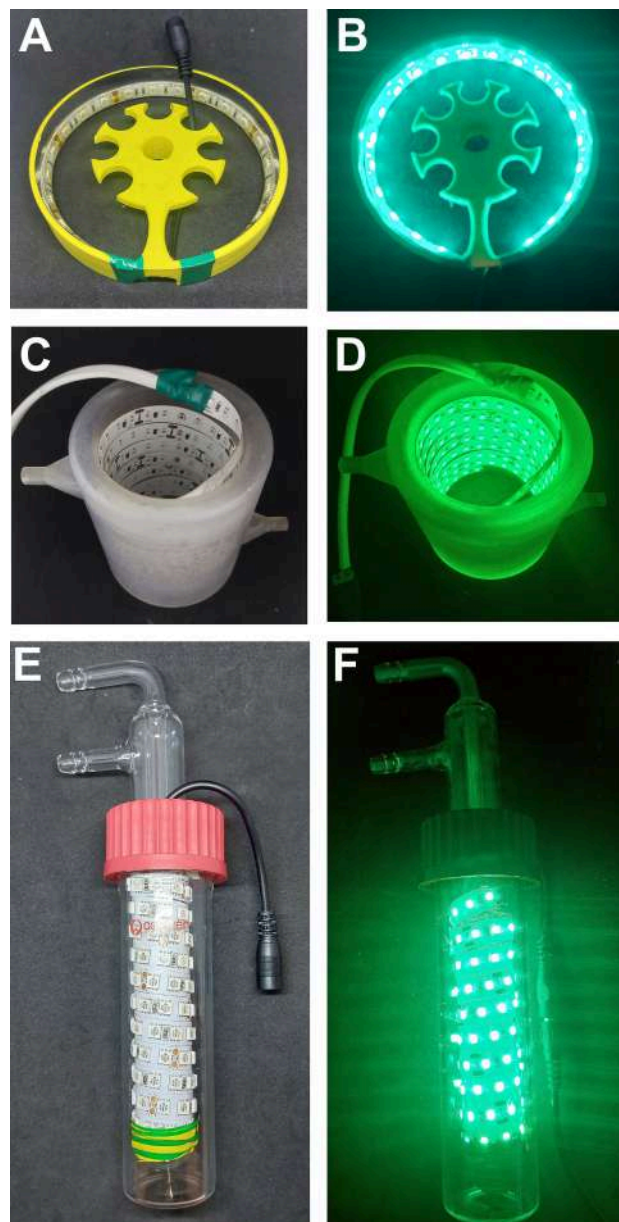


Figure 2. Home-made custom designed photoreactors employed in the metal-free thiocyanation of indole. A,B) Type A photoreactor; C,D) Type B photoreactor, E,F) Type C photoreactor.

6 mW/cm² light intensity. Type B photoreactor consists in a double jacketed cylindrical reaction vessel realized by 3D-printing SLA technology in which a 424 mW/cm² green LEDs strip was wrapped and fixed on the inner wall, whereas type C photoreactor was realized starting from a sublimator apparatus as described in literature,^[32,53–55] using a 424 mW/cm² green LEDs strip.

As previously reported by Li, THF confirmed to be the best solvent for the metal-free thiocyanation of indoles, regardless the type of photoreactor used. Compound **3** was obtained in almost quantitative yield after 16 hours when type B photoreactor was employed (Table 1).

Based on these results, type B photoreactor was selected as the device of choice for further investigation, and the newly synthesized MR-RB material was then investigated in the thiocyanation reaction.

A comparison between the performance between Rose Bengal and MR-RB photocatalyst is reported in Figure 3. The reaction was performed using 1.5 equiv. of NH_4SCN and 1 mol% of catalyst in THF (0.1 M solution), and the formation of product **3** was monitored over the time by GC analysis. It was found that MR-RB allowed to obtain the desired product in shorter reaction times than homogeneous Rose Ben-

gal, since 93% yield is reached after only nine hours (Figure 3, red line vs. blue line). No changes in the reaction profile were observed when the amount of NH_4SCN was increased (green line) and, in both cases, nine hours are sufficient to guarantee a quantitative yield.

The optimized reaction conditions (1 equiv. of substrate, 1 mol% of Rose Bengal anchored on MR resin and 3 equiv. of ammonium thiocyanate) were then employed for the synthesis of a small library of substituted indoles and imidazoheterocycles (Figure 4). To maximize the yield, the reactions were performed for 16 h; in this case, compound **3** was isolated in 96% yield. *N*-Substituted indoles are suitable substrates for this type of transformation since indole **4** has been obtained in 98% yield of isolated product. Electron donating and moderately electron withdrawing groups on the indole ring are very well tolerated: products **5** and **7**, bearing a methoxy group and a bromine, were synthesized in very high yields, while product **6**, with a phenyl group as a substituent, was isolated in 74%. However, the presence of a strong electron-withdrawing group such as the NO_2 group causes a strong decrement in terms of yield; product **8** was obtained in 19% yield only. Unfunctionalized *N*-methyl pyrrole can be subjected to thiolation reaction, leading to the formation of product **9** in 80% yield,

Table 1. Screening of the reaction conditions using different home-made photoreactors.

Photoreactor design	Compound 3 , GC yield [%]				
	CH_3OH	CH_3CN	DMF	THF	Toluene
Type A	30	42	30	85	0
Type B	62	80	60	100 ^[a]	29
Type C	47	55	46	83	34

^[a] Confirmed by yield of isolated product (98%).

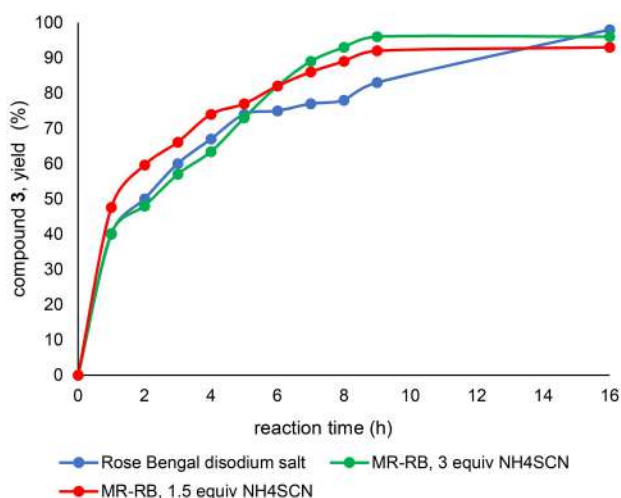


Figure 3. Conversion of compound **3** over the time.

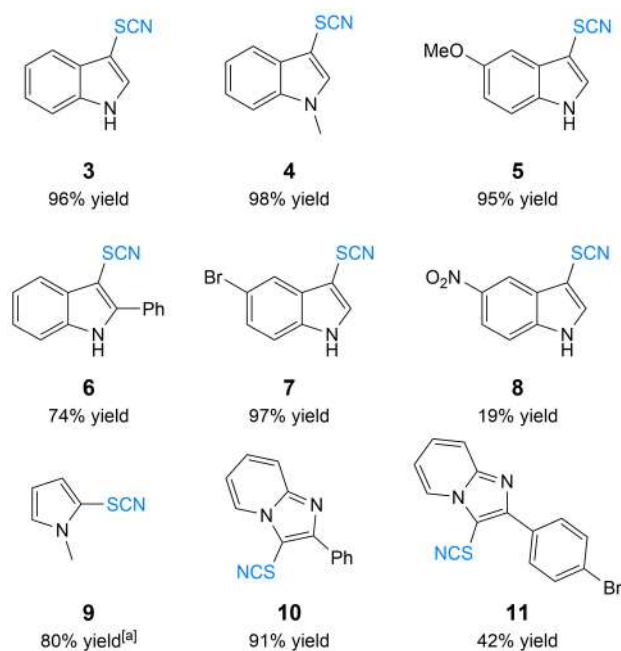


Figure 4. Scope of thiocyanation reaction performed with MR-RB resin.^[a] 3 equiv. of pyrrole were used.

even if in this case, an excess of starting material was employed.

To further extend the scope of the methodology, functionalization of imidazo[1,2-*a*]pyridines was considered.^[21] Compounds **10** and **11** were then synthesized in 91% and 42%, yield respectively, demonstrating the great applicability of this methodology. We would like to point out that, thanks to the presence of the supported dye (MR-RB catalyst), no workup is necessary at the end of the reaction: once the LEDs are switched off, the crude reaction mixture is separated from the catalyst by simple filtration and directly subjected to chromatographic purification.

Once the performances of the supported catalyst were proved, we next investigated the stability of material performing a recycling test. MR-RB was filtered onto a sintered glass funnel, copiously washed with THF and dichloromethane, dried under vacuum until constant weight and reused in the SCN functionalization of compound **2** under the same conditions reported before. The results of these findings are summarized in *Table 2*.

After the first run, compound **3** was isolated in 96% yield, as expected (see *Figure 4*). MR-RB catalyst performed well also in the second and third run, affording the desired product **3** in 96% yield, and in the fourth run (90% yield). The chemical efficiency of the MR-RB catalyst was confirmed until the fifth run, although with a slight decrease in the yield (89%, *entry 5*).

Having demonstrated the feasibility of using the MR-RB catalyst in the thiocyanation reaction of various aza-heteroaromatic compounds, we envisioned the possibility of using this catalyst to develop the transformation under continuous conditions. The continuous process requires the use of type B photoreactor and a glass transparent open vessel, having a porous glass frit at the bottom wall: the open system is

required to ensure the presence of air oxygen, whereas the porous frit allows the continuous collection of the product thus avoiding catalyst leaching phenomena as illustrated in *Table 3* (see *Supporting Information* for pictures of the set-up).

Reagents were fed into the device from the top through the use of a syringe pump, while the product was collected continuously from the bottom vessel using a peristaltic suction pump. The syringe pump and the peristaltic pump were set at identical flow rates in order to ensure the desired constant reaction volume inside the reactor, and the mixing of the heterogeneous mixture was ensured by the presence of a magnetic stirrer (see *Supporting Information* for further details). In a preliminary experiment, 1 equiv. of indole was treated with 3 equiv. of NH₄SCN in the presence of a catalytic amount of MR-RB catalyst upon green light irradiation. Different reaction volumes and residence times for a continuous process were screened: results are reported in *Table 3*. As shown, 3-thiocyanato-1*H*-indole (**3**) was obtained in 59% yield after 100 min as residence time when the reaction was performed at 1 mL scale (*Table 3, entry 1*). Attempts to increase the reaction volume failed, no product formation was observed, because it was not possible to achieve steady-state conditions of the fluidic setup (*entry 2*). Increasing the loading of MR-RB catalyst to 5 mol% allowed to obtain the desired product in 64% yield (*entry 3*), whereas decreasing the residence time to 50 minutes resulted in a slight decrement of the yield (*entry 4*). Doubling the residence time to 200 minutes allows to obtain compound **3** in up to 74% yield.

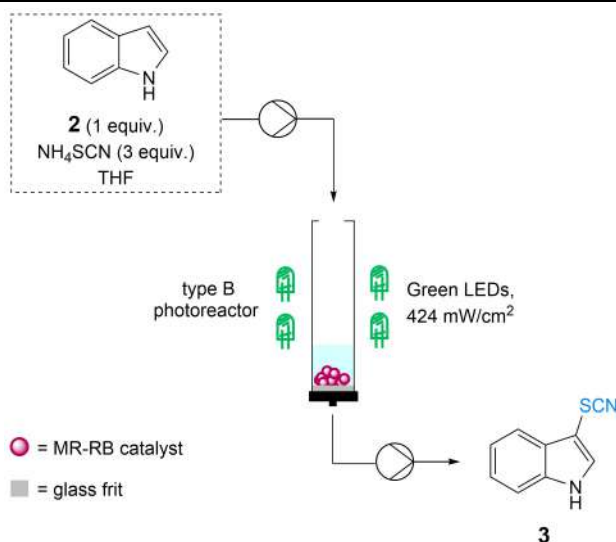
The comparison and judgement of productivities of batch thiocyanation vs. the continuous approach was performed according to a method already established in the literature,^[53,56] and it is summarized in *Table 4*.

All the reactions were performed on the same scale by collecting reactor outputs for the given time, it would take to have the same amount of moles as under batch conditions (0.3 mmol). For a reliable comparison, reactions were referred to the same amount of catalyst employed (0.03 mmol). Thanks to the shorter residence time, the continuous process provided a space-time-yield (STY), a useful metric to compare reactors of different volumes, that was almost six times higher than that of the batch reactor.

Since the aim of this work is to reach high productivities with acceptable levels of conversion, conditions of *Table 4, entry 3* were selected as optimum compromise to perform the visible light MR-RB catalyzed metal-free thiocyanation of different azahe-

Table 2. Recycling tests of MR-RB catalyst.

Entry	Run	Yield [%]
1	1	96
2	2	96
3	3	96
4	4	90
5	5	89

Table 3. Screening of thiocyanate reaction conditions under continuous conditions.


Entry	MR-RB loading [mol%]	Reactor volume [mL]	Residence time [min]	Flow Rate [mL/min]	GC Yield [%]
1	1	1	100	0.01	59 ^[a]
2	1	1.5	100	0.01	traces
3	5	1	100	0.01	64
4	5	1	50	0.02	47
5	5	1	200	0.005	74

^[a] Confirmed by yield of isolated product (58%).

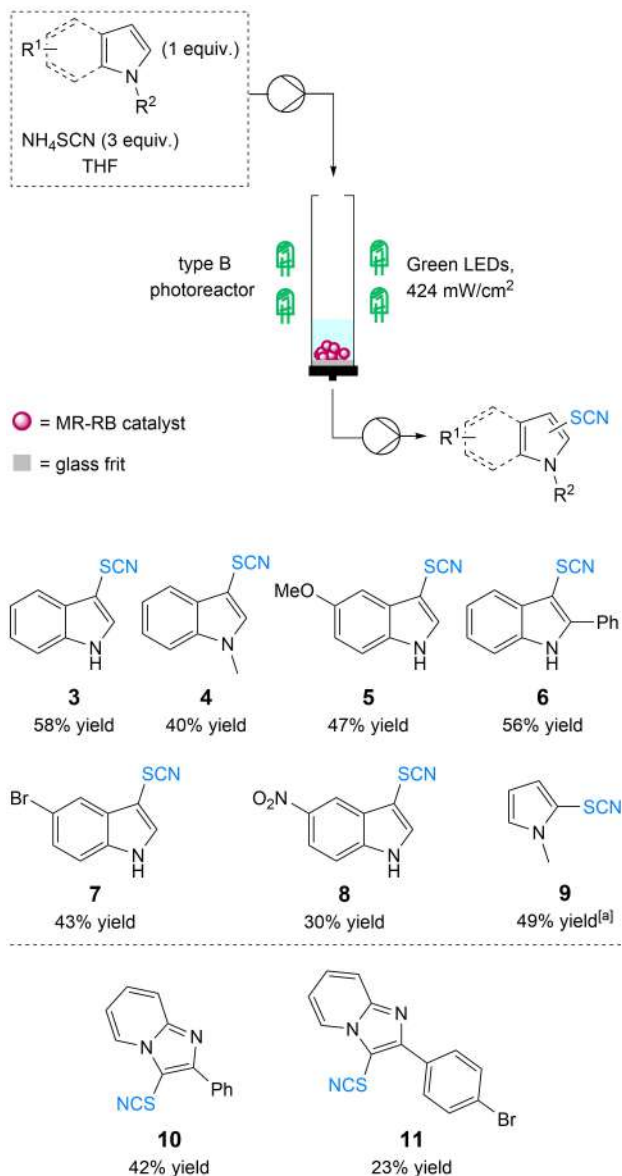
Table 4. Comparison of productivity and space time yield and of normalized relative factors.

Entry	Method	Productivity ^[a] [mmol/h]	Space time yield ^[b] [mmol/mL·h]	Rel. factor ^[c]
1	Batch: 1 mol% Rose Bengal, 16 hours, 98% yield of isolated product	0.0184	0.0061	1
2	Batch: 1 mol% MR-RB, 16 hours, 96% yield of isolated product (compound 3, Figure 4)	0.0176	0.0060	0.98
3	Continuous: 1 mol% MR-RB catalyst, 100 min residence time, 58% yield of isolated product (compound 3, Scheme 2)	0.0071	0.0362	5.92

^[a] Productivity: moles of product (calculated from yield of isolated product) divided by the collection time required to collect the product obtained by the reaction of 0.3 mmol of indole. ^[b] Space-time-yield: moles of product in reactor, divided by residence time and reactor volume (for details on calculations please see the *Supporting Information*). ^[c] Related to space-time-yield.

terocycles under continuous conditions. The outcome of those experiments is depicted in *Scheme 2*. The yields are generally lower compared to those obtained under batch procedure, although satisfactory in all cases. The reaction yield is weakly affected by the electronic characteristics of the substituents where reactants bearing electron-withdrawing groups lead to

the corresponding products in lower yield. The same trend was observed also for the synthesis of imidazo[1,2-*a*]pyridines **10** and **11** which were obtained respectively in 42% and 23% yield. Although these yields may seem lower compared to the traditional approach, it should be noted that the reaction



Scheme 2. Scope of thiocyanation reaction performed with MR-RB resin under continuous conditions.^[a] 10 equiv. of pyrrole were used.

time has been reduced by a factor of 10, resulting in an advantage in terms of productivity.

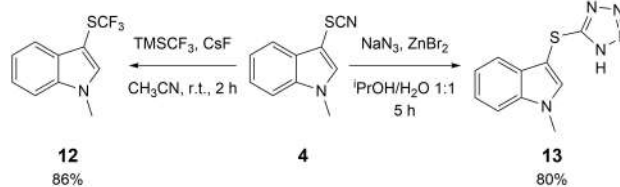
Moreover, since the MR-RB catalyst remains retained in the reaction vessel thanks to the presentation of the glass frit, the reaction work-up is greatly simplified, and the desired product can be easily separated by unreacted materials by a short filtration on silica pad. In addition, no drop in terms of yield were observed after 54 h of continuous running of the system, where compound **3** was isolated in 58% yield.

To further demonstrate that the SCN group is a highly versatile group, compound **4** has been transformed into trifluoromethyl thioether **12**, and 5-sulfenyl tetrazole **13** according to literature protocols (Scheme 3). The direct trifluoromethylthiolation of thiocyanate derivative **4** was performed in the presence of the Ruppert–Prakash reagent (TMSCF₃), affording the 3-[(trifluoromethyl)sulfanyl]-1*H*-indole (**12**) in 86% yield.^[57]

In another synthetic transformation, derivative **4** has been involved in a [3 + 2]-cycloaddition with sodium azide under zinc bromide promotion^[58] allowing the formation of sulfenyl tetrazole **13** in 80% yield.

Conclusions

In conclusion, we have developed a simple and mild thiocyanation of indoles and imidazo[1,2-*a*]pyridines under continuous conditions using Rose Bengal photo-catalyst immobilized on Merrifield resin. The reactivity of different azaheterocycles in the metal-free MR-RB catalyzed thiocyanation reaction performed under green LEDs irradiation has been studied and optimized in batch and under continuous flow conditions. The reaction tolerates various functional groups although electron-poor azaheterocycles reacts in lower yields compared to their electron-rich counterpart. Although modest yields were obtained, the continuous process afforded the products in higher productivities compared to the in-batch reactions, with an easy work up procedure for the catalyst removal. The synthetic elaboration of the SCN group has been demonstrated, making this approach particularly attractive for various applications from drug discovery to industrial-scale syntheses.



Scheme 3. Derivatization of 1-methyl-1*H*-indol-3-yl thiocyanate (**4**).

Experimental Section

General Information

Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel glass plates (0.25 mm thickness), visualized using UV light and eventually stained with vanillin. Flash chromatography was carried out on silica gel (230–400 mesh). Routine NMRs and ^{19}F -NMRs were recorded with a benchtop NMR, Spinsolve 80 ULTRA purchased from Magriteck. Characterizations were recorded with Bruker Avance 300 spectrometer, operating at 300 MHz for ^1H -NMR and 75 MHz for ^{13}C -NMR, with complete proton decoupling. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl_3 , $\delta = 7.26$ ppm). The following abbreviations are used to indicate the multiplicity in NMR spectra: s - singlet; d - doublet; t - triplet; q - quartet; pd - pseudo doublet; dd - double doublet; sext - sextuplet; sept - septuplet; bs - broad signal; m - multiplet. Gas chromatography/mass spectrometry (GC/MS) was performed on GC Agilent 6890 N, inlet: EPC split-splitless; column: Agilent 19091S-433 HP-5MS 5% phenyl methyl siloxane; MS: quadrupole G2589 A EI; Autosampler: Agilent 7683; gas carrier: helium. IR spectra were recorded on a FT/IR-4X FTIR Spectrometer, from JASCO. 3D-printed photoreactors were 3D-printed with Formlabs 'FORM 3' 3D-printer, using Clear V4 or Draft V2 resins. SEM and EDS analysis have been performed with the emission scanning electron microscope 'FE-SEM SIGMA', from ZEISS.

Microwave 'Discover SP', from CEM was used for the synthesis of imidazo[1,2-*a*]pyridines (see *Supporting Information*). LEDs intensity was measured with the optical power meter (Thorlabs PM200), equipped with a S130VC power head with a Si detector. Reported values have been measured setting 80 scans (10 seconds analysis).

Synthesis of MR-RB

A 250 mL three-necked-flask was equipped with a reflux condenser and a mechanically stirring device. 5.0016 g (4.2 mmol, 1.00 equiv., $f_0 = 1.20$ mmol/g) of Merrifield Resin High-Loading 100–200 mesh have been exactly weighted and quantitatively introduced in the flask, followed by 4.8766 g (4.8 mmol, 1.14 equiv.) of Rose Bengal disodium salt. Solids were dispersed in 66.5 mL of DMF, mechanical stirring was turned on and last, 1.75 mL (10.0 mmol, 2.40 equiv.) of distilled

diisopropylethylamine have been added dropwise. After setting the temperature to 80 °C, the suspension was stirred for exactly 72 h. After the reaction was completed, the mixture was poured into an oven-dried glass sintered funnel (pore size 4, pre-weighed) and special care was taken to remove almost all the material out of the flask with generous amounts of methanol. The residue was infused with a mixture of water and methanol and stirred with a glass rod on the septum. After infusing for 5 min, vacuum was attached, and the washing liquid was filtered off; these washings were alternated also using dichloromethane as solvent. The whole process was repeated until the washing liquids became colorless. The supported material was dried under vacuum and its loading was determined by weight difference (*loading* = 1.02 mmol/g).

General Procedure A for the Photocatalytic Thiocyanation, in Batch Conditions

The procedure for the batch experiment is the same with both free and supported catalyst. The reaction was carried out in presence of the internal standard biphenyl, to calculate the GC yield. The reaction was carried out in a 10 mL vial, left open to enable the reaction with atmospheric oxygen. The vial was filled with the desired azaheterocycle (0.3 mmol, 1 equiv.), 3.1 mg of Rose Bengal disodium salt (1 mol%) or 3.26 mg of supported Rose Bengal (1 mol%, *loading* 1.02 mmol/g), 34.2 mg of NH_4SCN (0.45 mmol, 1.5 equiv.) and 7.4 mg of internal standard, biphenyl (0.05 mmol, 0.16 equiv.). All the solid reagents have been dissolved in 3 mL of THF (0.1 M) and the reaction was magnetically stirred. The vial was placed in photoreactor *type B*, and the reaction was irradiated with green light for 16 h, at room temperature. The photoreactor was cooled down with flowing water, while the reaction vial was further cooled with compressed air, to keep it at rt. After 16 h, light was turned off and the reaction mixture was concentrated under reduced pressure. The yield of the reaction was evaluated either by GC/MS or isolating the desired product by column chromatography.

General Procedure B: In continuo Photocatalytic Thiocyanation

The reaction was carried out in a home-made CSTR, built inside an Omnifit column, left open to ensure the contact with atmospheric oxygen and placed in photoreactor *type B* for the desired irradiation. A solution of

substrate (0.1 mmol, 1 equiv.), ammonium thiocyanate (0.3 mmol, 3 equiv.) and eventually internal standard biphenyl (0.016 mmol, 0.16 equiv.) in THF (0.1 M), was continuously fed in the reactor with a syringe pump that ensured the desired flow rate. At the same time, a withdrawing pump connected to the bottom of the Omnifit column allowed the continuous withdrawal of the reaction mixture, out of the reactor. Dead volumes were evaluated to be respectively 30 μL , between the syringe pump and the column, and 610 μL between the output of the column and the collection flask. In order to mimic a CSTR, it's important to set the flowrate of the incoming stream equal to the one of the effluents, so that the volume inside the column is always constant. The volume that ensured an efficient mixing of the reaction was equal to 1 mL. Before starting with the experiment, the column was filled with 1 mL of reaction mixture, the supported photocatalyst (0.005 mmol, 5 mol%) and the magnetic stirrer. Thanks to the glass frit which enabled the selective passage of the solution, the supported catalyst was always kept inside the reactor, without the need to continuously add it to the reaction mixture. The effluent stream was collected in a flask, to proceed with the analysis of the crude and eventually, the isolation of the product. The experiment was considered finished when the system reached stationary conditions, *i.e.*, when the GC yield was always the same after four tests, within 30 min one from the others.

Characterization

1H-Indol-3-yl Thiocyanate (3). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.61 (s, 1H), 7.86–7.76 (m, 1H), 7.54 (d, $J=2.8$, 1H), 7.49–7.41 (m, 1H), 7.36–7.29 (m, 2H).

1-Methyl-1H-indol-3-yl Thiocyanate (4). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.80 (dd, $J=6.5$, 1.9, 1H), 7.42–7.28 (m, 4H), 3.83 (s, 3H).

5-Methoxy-1H-indol-3-yl Thiocyanate (5). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.47 (s, 1H), 7.52 (d, $J=2.9$, 1H), 7.33 (d, $J=8.9$, 1H), 7.20 (d, $J=2.5$, 1H), 6.97 (dd, $J=8.9$, 2.5, 1H), 3.93 (s, 3H).

2-Phenyl-1H-indol-3-yl Thiocyanate (6). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.63 (s, 1H), 7.90–7.81 (m, 1H), 7.79–7.71 (m, 2H), 7.62–7.42 (m, 4H), 7.35 (dd, $J=6.0$, 3.1, 2H).

5-Bromo-1H-indol-3-yl Thiocyanate (7). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.69 (s, 1H), 7.95 (d, $J=1.8$, 1H), 7.57 (d, $J=2.9$, 1H), 7.42 (dd, $J=8.7$, 1.9, 1H), 7.33 (d, $J=8.7$, 1H).

5-Nitro-1H-indol-3-yl Thiocyanate (8). $^1\text{H-NMR}$ (300 MHz, Acetone-d_6): 8.68 (d, $J=2.3$, 1H), 8.26–8.16 (m, 3H), 7.81 (d, $J=9.0$, 1H).

1-Methyl-1H-pyrrol-2-yl Thiocyanate (9). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 6.91 (dd, 1H, CH, $J=2.8$, 1.8), 6.63 (dd, 1H, CH, $J=3.7$, 1.8), 6.20 (dd, 1H, CH, $J=3.7$, 2.8), 3.81 (s, 3H, CH_3). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 128.53, 121.07, 110.35, 109.76, 105.51, 34.70.

2-Phenylimidazo[1,2-*a*]pyridin-3-yl Thiocyanate (10). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.47 (dt, $J=6.8$, 1.2, 1H), 8.11–8.01 (m, 2H), 7.83–7.74 (m, 1H), 7.61–7.42 (m, 4H), 7.16 (td, $J=6.9$, 1.2, 1H).

2-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl Thiocyanate (11). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.47 (d, $J=6.8$, 1H), 8.02–7.91 (m, 2H), 7.78 (d, $J=9.1$, 1H), 7.73–7.62 (m, 2H), 7.51 (ddd, $J=8.8$, 6.8, 1.3, 1H), 7.22–7.12 (dt, 1H).

1-Methyl-3-[(trifluoromethyl)sulfanyl]-1H-indole (12). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.79 (d, $J=7.7$, 1H), 7.40–7.25 (m, 4H), 3.85 (s, 3H). $^{19}\text{F-NMR}$ (80 MHz, CDCl_3): –43.01.

1-Methyl-3-[(1H-tetrazol-5-yl)sulfanyl]-1H-indole (13). $^1\text{H-NMR}$ (300 MHz, DMSO): 7.90 (s, 1H), 7.52 (dd, $J=26.7$, 8.0, 2H), 7.28 (t, $J=7.6$, 1H), 7.16 (t, $J=7.5$, 1H), 3.86 (s, 3H).

Supporting Information

The authors have cited additional references within the *Supporting Information*.^[59–61]

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Nolimits microscopy facility of the University of Milan for SEM analysis.

Data Availability Statement

The data that support the findings of this study are available in the *Supporting Information* for this article.

Author Contribution Statement

Investigation, E. Colombo, M. F. Boselli, S. Rossi. Conceptualization, S. Rossi. Writing – original draft preparation, S. Rossi, Writing – review and editing, L. Raimondi, A. Puglisi, S. Rossi. All authors have read and agreed to the published version of the manuscript.

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