Check for updates

Electrophilic glycoluril-based reagents for atom-economic thiocyanation and selenocyanation of (hetero)arenes†

Paula Casasús, [ID] Jordi Mestre, [ID] Roksana Radłowska, [ID] Miguel Bernús [ID] and Omar Boutureira [ID] *

Two electrophilic glycoluril-based *N*-XCN reagents (X = S, Se) were developed for introducing SCN/SeCN groups into aromatic substrates, including the late-stage modification of bioactive molecules. Their application produces minimal waste, enables simple purification, and offers potential for reagent regeneration. Additionally, their compatibility with green solvents and flow technology was demonstrated. The sustainability of the process was evaluated using green metrics and Ecoscale values, emphasizing the complementary roles of the reagents and solvent recovery in enhancing atom economy and reducing waste.
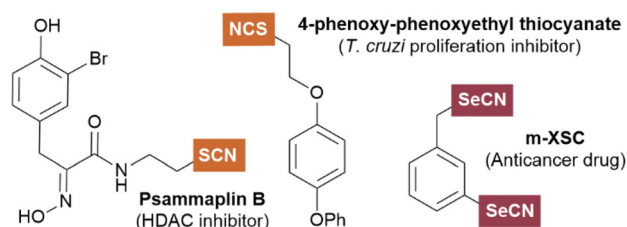
Introduction

Organic thiocyanates and their selenium analogues have attracted significant attention due to their presence in various natural products[1a] and pharmaceuticals,[1b–h] enhancing their antibacterial, antifungal, and anticancer properties (Fig. 1A). The thiocyanate group is a versatile yet underused functional group that can be converted into a range of sulfur-containing derivatives, such as thiols, disulfides, and thioethers.[2] Likewise, selenocyanation serves as an efficient and straightforward method for incorporating selenium moieties into organic molecules that are often challenging to obtain.[3]

Currently, several anionic reagents are employed for thiocyanation, often *via* the *in situ* formation of electrophilic agents,[4] while selenocyanation remains less developed.[5] Nucleophilic thio- and selenocyanate salts are commonly used not only in polar reactions but also in radical reactions (including those light-driven),[6] particularly when combined with oxidants such as cerium ammonium nitrate (CAN),[7] *tert*-butyl hydroperoxide (TBHP),[8] or potassium peroxodisulfate ($K_2S_2O_8$).[9] Additionally, these salts can also be used in cross-coupling reactions involving transition metals.[10] In contrast, electrophilic sources of SCN and SeCN groups offer complementary reactivity.[11] For example, Bacon and Angus first introduced thiocyanogen chloride (Cl-SCN) for the functionalization of alkenes and arenes; however, this reagent is inconvenient due to its poor stability and high toxicity.[12] More

recently, bench-stable thio- and selenocyanation reagents featuring *N*-chalcogen linkages have emerged as versatile alternatives for functionalizing various organic scaffolds (Fig. 1B).[13–19] However, all of the reported reagents can only transfer one unit of SCN/SeCN per molecule, which decreases atom economy and contributes to significant waste generation.
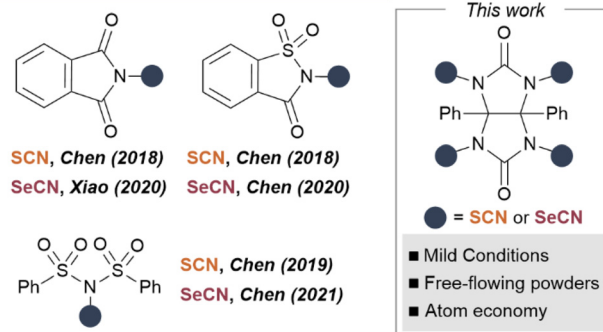

Fig. 1 (A) Examples of bioactive molecules containing SCN/SeCN groups. (B) Selected electrophilic *N*-SCN and *N*-SeCN reagents. HDAC = histone deacetylase.

Departament de Química Analítica i Química Orgànica, Universitat Rovira I Virgili, C/Marcel·lí Domingo 1, 43007 Tarragona, Spain. E-mail: omar.boutureira@urv.cat
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d5ob00536a

This journal is © The Royal Society of Chemistry 2025

Org. Biomol. Chem., 2025, **23**, 4463–4470 | **4463**

Furthermore, its application typically requires an additive/external catalyst, complicating purification and often necessitating flash-column chromatography for isolation. Our aim was to develop an electrophilic reagent capable of rapidly introducing thio- and selenocyanide groups into complex molecules with high selectivity, low waste, and simple purification. Given that N-SCN/SeCN motifs have demonstrated high efficiency in delivering thio- and selenocyanide groups, we turned our attention to glycoluril-based scaffolds, which feature four nitrogen centres per molecule. In fact, this core structure has been used for the electrophilic radioiodination of proteins[20] and has also shown applications as a mild oxidizing agent.[21] Surprisingly, no additional applications have been reported that utilized this glycoluril scaffold for installing other electrophiles. With four N-XCN (X = S, Se) bonds, the reagents can deliver four SCN or SeCN groups per equivalent, thereby maximizing the atom economy of the transformation.

Results and discussion

Synthesis of reagents

Their preparation can be achieved through a proposed 3-step synthesis for both reagents (Scheme 1). First, the condensation of urea **1** with benzyl **2** in the presence of trifluoroacetic acid affords the bicyclic diphenylglycoluril compound **3** in good yield (74%, 36 g).[22] Next, chlorination with trichloroisocyanuric acid (TCCA) produces tetrachlorodiphenylglycoluril **4**, also known as Iodo-Gen® (89%, 26 g),[23] which can subsequently react with ammonium thiocyanate or potassium selenocyanate to yield **5a** (95%, 4 g) or **5b** (80%, 2.5 g). Importantly, all steps were carried out in multigram quantities without the use of column chromatography. Reagents **5a** and **5b** are free-flowing powders that remained stable without decomposition when
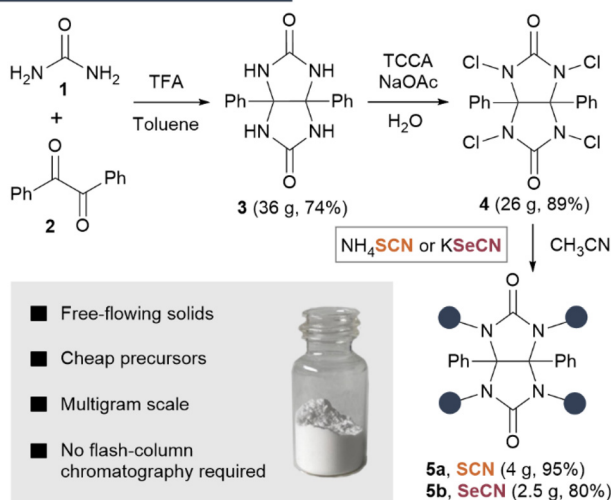
stored at −20 °C under argon for several months. Moreover, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) further demonstrated the stability of both reagents in the solid state at temperatures below 160 °C for **5a** and 147 °C for **5b** (Fig. S1 and S2, ESI†).

Scope and derivatization

With these reagents in hand, we performed a scope assessment using indoles as model substrates (Scheme 2A). Initially, a reaction was performed with 1 equivalent of 1H-indole and 0.33 equivalents of reagents (**5a** for thiocyanation or **5b** for selenocyanation) in CH$_3$CN (0.16 M) at room temperature. Pleasingly, 3-(thiocyano)indole **6a** and its selenium analogue **6b** (with antifungal activity)[1g] were obtained in 99% yield in just 10 min. Remarkably, the modified indoles **6a** and **6b** were obtained in high-purity through simple filtration followed by solvent removal. We then evaluated a series of halogen-substituted indoles, which afforded products **7–9a,b** in good to excellent yields (up to 99%).[1g] Deactivated indoles with electron-withdrawing nitrile and nitro groups at the 5-position reacted smoothly, affording products **10–11a,b** in >98% yield. The presence of a carboxylic acid group slightly reduced the yields, although **12a** and **12b** were still obtained in good to excellent yields (80% and 73%, respectively). Electron-donating 5-methoxy, N-methyl, and 2-methyl indoles were also well tolerated, delivering products **13–15a,b** in excellent yields (91–99%). When the most reactive C3 position of the indole[24] was substituted by a methyl group, functionalization selectively occurred at the C2-position, affording **16a** and **16b** in 64% and 79% yield, respectively. Moving to other heteroaromatics, the reaction of 1H-pyrrole afforded products **17a,b** in good yields (up to 99%). However, using 2,5-dimethylpyrrole resulted in a mixture of products, with the monosubstituted product **18a** obtained in 72% yield, and the di-functionalized product **19a** isolated in 20% yield. For selenocyanation, a more complex mixture was obtained, although mono-functionalized **18b** was isolated in 55% yield. Other electron-rich aromatic substrates, such as phenol, 3,5-dimethylphenol, and aniline, were functionalized in excellent yields, affording the corresponding para-substituted products **20–22a,b** in up to 99% yield. However, the more deactivated N-acetyl aniline remained unreactive, even with trifluoromethanesulfonic acid (TfOH)[15] as a catalyst. For less activated aromatic substrates, such as anisole, reactivity significantly diminished, resulting in conversions of only up to 50%. However, the addition of 1.5 equivalents of TfOH significantly increased reactivity, giving **23a,b** in 75% and 69% yield, respectively. TfOH was also required for mesitylene **24a** (86%) and **24b** (70%) and anthracene **25a,b** (73%).

We then aimed to functionalize more complex substrates by testing a series of natural products, pharmaceuticals, and agrochemicals (Scheme 2A). Preliminary attempts with dopamine and other neurotransmitters, hormones, and metabolites (such as melatonin, serotonin, L-adrenaline, tryptamine, and 5-hydroxytryptamine) using **5a** resulted in a mixture of products. Similarly, a protected catechol dopamine derivative
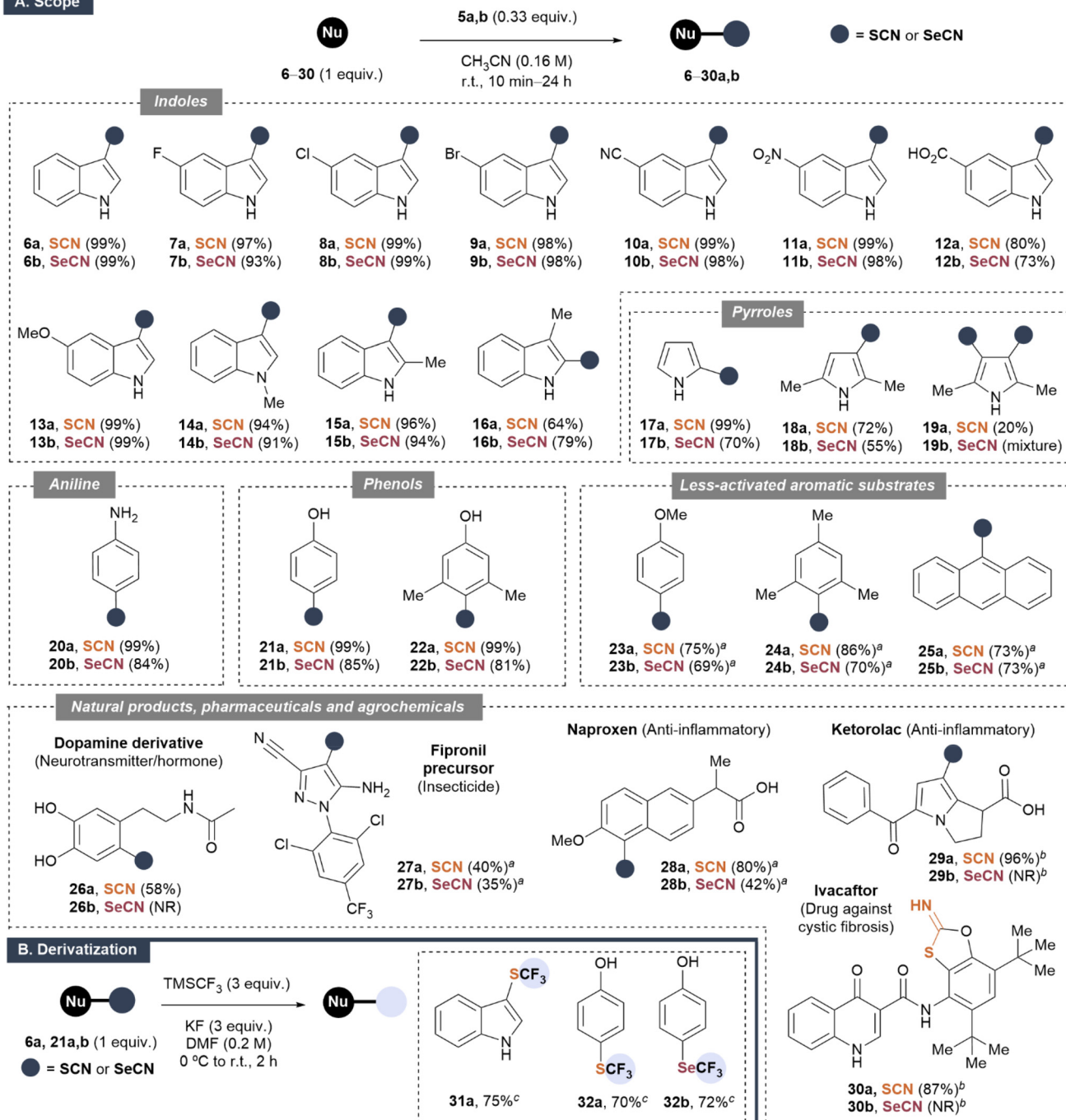

Reagent's preparation

Scheme 1 Synthesis of **5a,b** from commercially available urea **1** and benzyl **2**. See the ESI† for details. TFA = trifluoroacetic acid, TCCA = trichloroisocyanuric acid.

4464 | Org. Biomol. Chem., 2025, **23**, 4463–4470

This journal is © The Royal Society of Chemistry 2025

Scheme 2 (A) Scope and (B) derivatization. *General conditions*: (hetero)arene (0.3–0.5 mmol) and **5a,b** (0.099–0.165 mmol) in CH$_3$CN (0.16 M) unless otherwise indicated. *a* With TfOH (0.45–0.75 mmol) in CH$_2$Cl$_2$ (0.16 M). *b* In CH$_2$Cl$_2$ (0.16 M). *c* **6a**, **21a**, or **21b** (0.1–0.3 mmol), TMSCF$_3$ (0.1–1 mmol), and KF (0.4–1 mmol) in DMF (0.2 M). See the ESI† for details. TMS = trimethylsilyl, DMF = *N,N*-dimethylformamide. NR = No Reaction.

reacted with an electrophilic SCN reagent, revealing that certain aliphatic primary amines, such as dopamine, are initially converted to *N*-thiocyanoamines (RNHSCN). These relatively unstable intermediates subsequently evolve into quaternary salts (RNH$_3^+$SCN$^-$), along with unidentified polymeric by-products.[11b] This suggests that protection of primary amines is necessary to achieve selective thiocyanation of the

aromatic ring. For *N*-acetylated dopamine, reagent **5a** delivered the corresponding product **26a** in 58% yield, while no conversion was observed for **5b**. The reaction of **5a** and **5b** with a precursor of the insecticide Fipronil[25] afforded **27a,b** in 40% and 35% yield, respectively.

Naproxen[26] and ketorolac,[27] anti-inflammatory agents, were functionalized to give **28a,b** (80% and 42%, respectively), and

This journal is © The Royal Society of Chemistry 2025

Org. Biomol. Chem., 2025, **23**, 4463–4470 | **4465**

29a in 96% yield, while no conversion was observed for **29b**. In the evaluation of Ivacaftor **30**,[28] a drug used to treat cystic fibrosis, we encountered an intriguing reaction previously reported with *ortho*-phenols and *ortho*-anilines.[9b] The thiocyanate group installed in the molecule reacted with the *ortho*-phenol moiety to form a stable oxathioimine **30a** in 87% yield. This compound was confirmed by IR spectroscopy, which showed the absence of the characteristic C≡N stretching band (~ 2100 cm^{-1}).[29] The analogous reaction with **5b** resulted in no conversion of the starting material.
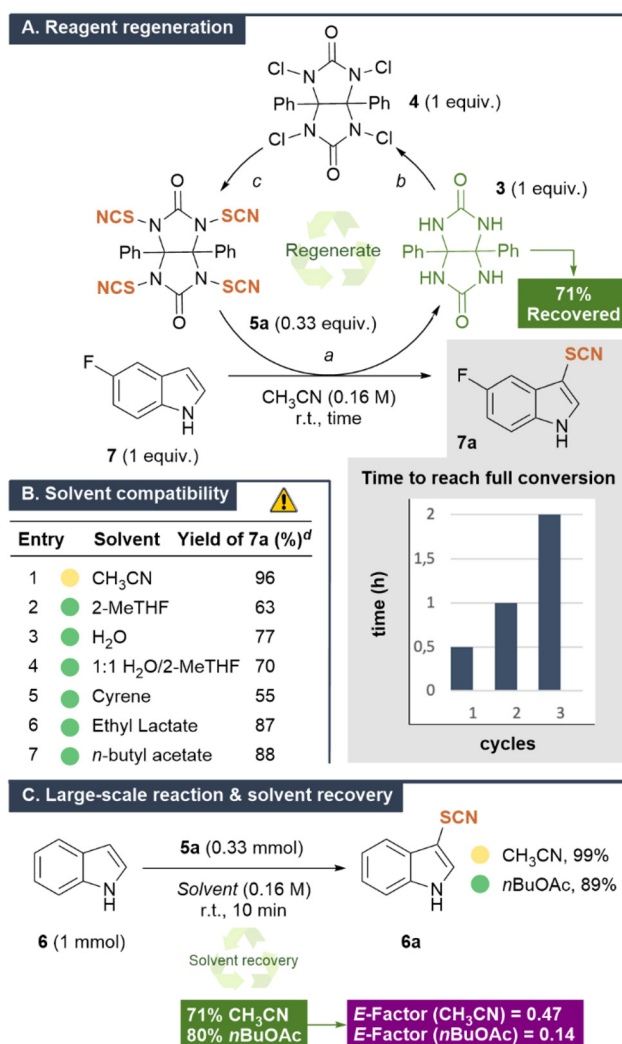
Next, to further complement our recently developed technologies focused on the incorporation and evaluation of polyfluoroalkylthio motifs (SR_F),[30] we carried out the derivatization of SCN and SeCN groups to demonstrate their utility as reactive handles for accessing trifluoromethylthio and selenoether derivatives (Scheme 2B).[31] Indole and phenol derivatives **6a**, **21a**, and **21b** were treated with TMSCF$_3$ and potassium fluoride in DMF, converting the SCN and SeCN groups into the corresponding SCF$_3$ and SeCF$_3$ analogues in yields greater than 70%.

Reagent regeneration, compatibility with green solvents, and green metrics comparison

After assessing the reactivity of our reagents, we explored whether the sustainability of our protocol could be improved by regenerating them.[15a,32] A key consideration was that, after the thio- or selenocyanation reaction, the precursor **3**, generated from **5a** and **5b**, is poorly soluble in most organic solvents, allowing it to be easily separated by filtration and subjected to a two-step regeneration cycle (Scheme 3A). Thus, upon completion of the reaction between 5-fluoroindole **7** and **5a**, the mixture was filtered to recover the solid precursor **3** (71%). Chlorination with TCCA, followed by reaction with ammonium thiocyanate enabled the synthesis of reagent **5a**. The regenerated reagent **5a** remained reactive toward 5-fluoroindole **7**, achieving full conversion to **7a** after 1 h. A further recycling-reactivity test revealed that, although 2 h were required to reach full conversion, the reagent maintained effectiveness. These experiments indicate a slight decrease in the reagent reactivity after each cycle, which can be compensated for by simply extending the reaction time.

We then evaluated the compatibility of environmentally friendly, green solvents, including 2-methyltetrahydrofuran, water, Cyrene™, ethyl lactate, and *n*-butyl acetate, revealing that the reaction outcome was not significantly influenced by the solvent choice, except for the slight erosion observed with Cyrene™ (Scheme 3B).[33]

Additionally, the greenness of our process was assessed by evaluating several key green metrics (section 3, ESI†).[31,34] Initially, the simple *E*-factor (sEF), which excludes solvents when calculating waste generation, was determined for the optimized reaction between 1*H*-indole **6** and reagent **5a**, yielding a value of 0.67 – comparable to those in bulk chemical industries.[35] However, when the comprehensive *E*-factor, which includes solvent contribution, was calculated, the value increased significantly to 28.1 for CH$_3$CN and 31.4 for

Scheme 3 (A) Reagent regeneration, (B) solvent compatibility, (C) large-scale reaction and solvent recovery. *General conditions*: [a] **7** (0.5 mmol) and **5a** (0.19 mmol) in CH$_3$CN (0.16 M). [b] **3** (0.06 mmol), TCCA (0.1 mmol), and NaOAc (0.4 mmol) in H$_2$O (0.08 M). [c] **4** (0.05 mmol) and NH$_4$SCN (0.23 mmol) in CH$_3$CN (0.04 M). [d] Determined by ^{19}F NMR analysis of the crude reaction mixture, using 1,3-bis(trifluoromethyl)benzene as the internal standard. See the ESI† for details. Color code; volatile organic compound-VOC (yellow) and environmentally friendly solvent (green).

*n*BuOAc, highlighting the substantial impact of solvents on waste generation. To address this, two large-scale reactions were conducted using a waste-minimized protocol that enabled efficient solvent recovery by simple distillation (Scheme 3C).[31] When CH$_3$CN was used, 71% of the solvent was successfully recovered, reducing the *E*-factor to 0.47. Similarly, with *n*BuOAc as the solvent, an 80% recovery rate further minimized the *E*-factor to an impressive 0.14 – close to the limit observed in oil refining (*E*-factor < 0.1).[35] These results underscore the critical role of solvent recovery in reducing waste generation and improving the sustainability of the process.

4466 | *Org. Biomol. Chem.*, 2025, **23**, 4463–4470

This journal is © The Royal Society of Chemistry 2025

Further analysis focused on comparing the sustainability of our protocol with similar methods employing alternative thiocyanating reagents.[15a,16a] This was done by calculating Atom Economy (AE), Reaction Mass Efficiency (RME), and Ecoscale scores (sections 3 and 4, ESI†). Our protocol achieved an AE of 70% and an RME of 60%, outperforming alternative methods using reagents R1 and R2, which exhibited significantly lower AE values of 49% and 37%, respectively, as well as RME values of 40% and 30%, respectively (Table 1). Moreover, in these comparative protocols, solvent contribution was notably high, leading to E-factors of 35.6 and 25.5 for R1 and R2, respectively. Finally, an additional evaluation was conducted using Ecoscale analysis, highlighting the advantage of our protocol in eliminating the need for chromatographic purification. This aspect significantly improved the Ecoscale score, resulting in a value of 82 when using CH_3CN. In contrast, the selected procedures were penalized for requiring purification, obtaining scores of 77 for R1 and 72 for R2, respectively. Notably, when nBuOAc was used as the solvent in our protocol, the highest Ecoscale value of 87 was achieved, as it avoided safety-related penalties while price and availability factors remaining consistent across all protocols. This highlights the superior sustainability of our method, which outperformed the alternatives in AE, RME, and Ecoscale value, despite a slight yield decrease with nBuOAc.

Flow chemistry

Given the low solubility of reagents 5a,b (Table S1, ESI†), we considered immobilizing them in a packed bed reactor for compatibility with flow technology.[36] This setup employs a syringe pump to push a solution of a nucleophile through a cartridge filled with thiocyanating reagent 5a via polytetrafluoroethylene (PTFE) tubing (section 5, ESI†). Because significant leaching of 5a was observed during initial attempts using CH_3CN, the flow rate of the nucleophile was optimized using a 0.2 M chloroform solution of 5-fluoroindole 7 as a model substrate, as its reduced solubility suppressed the leaching. Flow rates greater than 0.67 mL min^{-1} resulted in a mixture of unreacted 5-fluoroindole 7 and product 7a

(Table S2, entries 1–5, ESI†), while reducing the flow rate to 0.5 mL min^{-1} yielded the desired product with full conversion and 91% yield, with a residence time of approximately 8 min (Table S2, entry 6, ESI†). Once the optimal flow rate was established, a new cartridge containing 5a was prepared to evaluate consecutive reactions. A sequence of nucleophiles, interspersed with chloroform washes, was flowed through the same packed bed reactor without the need to load a new cartridge for each substrate, and the resulting crude products were collected.

The thiocyanated products of 5-fluoroindole (7a, 91%), aniline (20a, 90%), and phenol (21a, >99%) were obtained in pure form after solvent evaporation (Fig. 2). At this point, we considered replacing chloroform with the greener alternative nBuOAc,[33,37] which was used in our previous solvent screening assessment (Scheme 3B) and possesses a similar solubility profile compatible with our flow setup (Table S1, ESI†). Thus, the same procedure was repeated and, although a slight yield erosion was observed, the corresponding products, – 5-fluoroindole (7a, 82%), aniline (20a, 79%), and phenol (21a, 88%) – were still obtained in pure form. This demonstrates the compat-
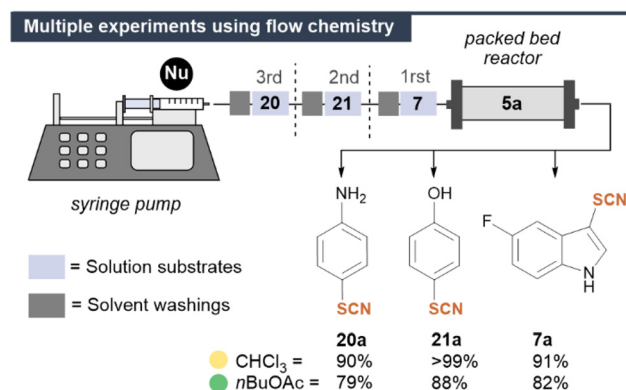

Fig. 2 Multiple consecutive experiments using flow chemistry. See the ESI† for details. Color code; volatile organic compound-VOC (yellow) and environmentally friendly solvent (green).

Table 1 Comparison of green metrics, Ecoscale values, and yields

Entry	Reagent	Solvent	AE[a] (%)	RME[a] (%)	sEF[b]	E-Factor[b]	Solvent contribution (%)	Ecoscale[a] (%)	Yield[a] (%) 6a
1	5a	CH_3CN	70	60	0.67	0.47[c]	97	82	99
2	5a	nBuOAc	70	60	0.67	0.14[c]	97	87	89
3	R1	THF	49	40	1.52	35.6	95	77	98
4	R2	CH_3CN	37	30	2.38	25.5	90	72	98

AE = Atom Economy, RME = Reaction Mass Efficiency, sEF = simple E-factor. [a] 100 is the ideal value. [b] 0 is the ideal value. [c] Values considering solvent recovery.

This journal is © The Royal Society of Chemistry 2025

Org. Biomol. Chem., 2025, 23, 4463–4470 | 4467

ibility of the thiocyanating reagent **5a** with flow chemistry, highlighting that multiple consecutive reactions can be performed without manipulating the reagent. This results in clean product formation and facilitates easy purification, as the insoluble reagent's precursor **3** is effectively retained in the cartridge.

Conclusions

In summary, two electrophilic reagents were developed for the direct introduction of SCN and SeCN groups *via* a three-step synthetic route. These readily available reagents enable late-stage thio- and selenocyanation across a broad substrate scope, including indoles, pyrroles, aniline, phenols, less-activated aromatics, natural products, pharmaceuticals, and agrochemicals. The reactions proceed under mild, metal-free conditions (catalyst-free for most substrates) with good to excellent yields. Their versatility was further demonstrated through trifluoromethylation of indole-SCN and phenol-SCN/SeCN derivatives. Additionally, reagent regeneration was achieved by leveraging the low-solubility of diphenylglycoluril precursor **3**, formed during reactions with nucleophiles. Importantly, these reagents also proved compatible with environmentally friendly solvents. Sustainability assessments using green metrics and Ecoscale values highlighted significant improvements in atom economy (AE), reaction mass efficiency (RME), and waste reduction (*E*-factor) *via* efficient solvent recovery, outperforming similar protocols. Finally, the applicability of these reagents in flow chemistry was confirmed, enabling consecutive reactions without reagent manipulation. Overall, this study showcases the broad utility and potential of these reagents for efficient synthetic transformations, offering high atom economy and reduced waste generation.

Author contributions

P. C., J. M, R. R., and M. B. performed all the experiments. O. B. supervised the project and was responsible for funding acquisition. All the authors contributed to the preparation of the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

References

1 (*a*) C. Jiménez and P. Crews, *Tetrahedron*, 1991, **47**, 2097–2102; (*b*) E. Elhalem, B. N. Bailey, R. Docampo, I. Ujváry, S. H. Szajnman and J. B. Rodriguez, *J. Med. Chem.*, 2022, **45**, 3984–3999; (*c*) D. Plano, D. N. Karelia, M. K. Pandey, J. E. Spallholz, S. Amin and A. K. Sharma, *J. Med. Chem.*, 2016, **59**, 1946–1959; (*d*) W. Ali, M. A. Pérez, M. A. Marć, N. S. Jiménez, J. Handzlik and E. D. Álvarez, *Curr. Pharmacol. Rep.*, 2018, **4**, 468–481; (*e*) Y. Huang, Y. Cheng, M. Wei, Z. Peng, W. Tian, Z. Liu, J. Li and J. Cui, *Bioorg. Chem.*, 2024, **144**, 107149; (*f*) W. Hou and H. Xu, *J. Med. Chem.*, 2022, **65**, 4436–4456; (*g*) P. M. Quatrin, D. F. Dalla Lana, L. C. G. Bazana, L. F. S. de Oliveira, M. L. Teixeira, E. E. Silva, W. Lopes, R. F. S. Canto, G. P. Silveira and A. M. Fuentefria, *New J. Chem.*, 2019, **43**, 926–933; (*h*) C. Morán-Serradilla, D. Plano, C. Sanmartín and A. K. Sharma, *J. Med. Chem.*, 2024, **67**, 7759–7787.

2 (*a*) T. Castanheiro, J. Suffert, M. Donnard and M. Gulea, *Chem. Soc. Rev.*, 2016, **45**, 494–505; (*b*) A. W. Erian and S. M. Sherif, *Tetrahedron*, 1999, **55**, 7957–8024; (*c*) M. Gulea, F. Hammerschmidt, P. Marchand, S. Masson, V. Pisljagic and F. Wuggenig, *Tetrahedron: Asymmetry*, 2003, **14**, 1829–1836; (*d*) X. Lu, H. Wang, R. Gao, D. Sun and X. Bi, *RSC Adv.*, 2014, **4**, 28794–28797; (*e*) M. Pawliczek, L. K. B. Garve and D. B. Werz, *Org. Lett.*, 2015, **17**, 1716–1719; (*f*) C. Matheis, M. Wang, T. Krause and L. J. Goossen, *Synlett*, 2015, 1628–1632.

3 (*a*) J. M. Sonego, S. I. de Diego, S. H. Szajnman, C. G. Rodriguez and J. B. Rodriguez, *Chem. – Eur. J.*, 2023, **29**, e202300030; (*b*) Y. A. Lin, O. Boutureira, L. Lercher, B. Bhushan, R. S. Paton and B. G. Davis, *J. Am. Chem. Soc.*, 2013, **135**, 12156–12159; (*c*) J. C. Guillemin, G. Bajor, E. H. Riague, B. Khater and T. Veszprémi, *Organometallics*, 2007, **26**, 2507–2518; (*d*) A. Ghasseminn, X. V. Farrés, P. F. Alewood and T. Durek, *Bioorg. Med. Chem.*, 2013, **21**, 3473–3478.

4 (*a*) H. Chen, X. Shi, X. Liu and L. Zhao, *Org. Biomol. Chem.*, 2022, **20**, 6508–6527; (*b*) D. He, J. Yao, B. Ma, J. Wei, G. Hao, X. Tuo, S. Guo, Z. Fu and H. Cai, *Green Chem.*, 2020, **22**, 1559–1564; (*c*) A. S. Kirillov, E. A. Semenov, O. V. Bityukov, M. A. Kuznetsova, V. N. Demidova, A. N. Rogozhin, A. P. Glinushkin, V. A. Vil' and

4468 | *Org. Biomol. Chem.*, 2025, **23**, 4463–4470

This journal is © The Royal Society of Chemistry 2025

A. O. Terent'ev, *Org. Biomol. Chem.*, 2023, **21**, 3615–3622; (*d*) S. Saha, A. B. Pinheiro, A. Chatterjee, Z. T. Bhutia and M. Banerjee, *Green Chem.*, 2024, **26**, 5879–5889; (*e*) C. Wang, Z. Wang, L. Wang, Q. Chen and M. He, *Chin. J. Chem.*, 2016, **34**, 1081–1085; (*f*) H. Zhang, Q. Wei, S. Wei, J. Qu and B. Wang, *Eur. J. Org. Chem.*, 2016, 3373–3379; (*g*) Q. Chen, Y. Lei, Y. Wang, C. Wang, Y. Wang, Z. Xu, H. Wang and R. Wang, *Org. Chem. Front.*, 2017, **4**, 369–372.

5 (*a*) P. G. Karmaker and F. Huo, *Asian J. Org. Chem.*, 2022, **11**, e202200226; (*b*) V. Nair, A. Augustine and T. G. George, *Eur. J. Org. Chem.*, 2002, 2363–2366; (*c*) A. Hassanpour, E. Ghavidelaghdam, A. G. Ebadi, M. R. Poor Heravi and E. Vessally, *RSC Adv.*, 2021, **11**, 22305–22316.

6 (*a*) Q. Yan, S. Chen, J. Fan and Z. Li, *Org. Biomol. Chem.*, 2023, **21**, 9112–9122; (*b*) J. Vigier, M. Gao, P. Jubault, H. Lebel and T. Besset, *Chem. Commun.*, 2024, **60**, 196–199; (*c*) S. Chen, Q. Yan, J. Fan, Y. Gao, X. Yang, L. Li, Z. Liu and Z. Li, *Green Chem.*, 2022, **24**, 4742–4747; (*d*) Q. Xie, Y. Yang, W. Zhang, Z. Gao, X. Li, J. Tang, C. Pan and G. Yu, *Chem. Sci.*, 2021, **12**, 5631–5637; (*e*) F. Buttard, J. Vigier, H. Lebel and T. Besset, *Eur. J. Org. Chem.*, 2024, e202301205; (*f*) P. G. Karmaker, Md. A. Alam and F. Huo, *RSC Adv.*, 2022, **12**, 6214–6233.

7 V. Nair, T. G. George, L. G. Nair and S. B. Panicker, *Tetrahedron Lett.*, 1999, **40**, 1195–1196.

8 N. Muniraj, J. Dhineshkumar and K. R. Prabhu, *ChemistrySelect*, 2016, **5**, 1033–1038.

9 (*a*) D. Yang, K. Yan, W. Wei, G. Li, S. Lu, C. Zhao, L. Tian and H. Wang, *J. Org. Chem.*, 2015, **80**, 11073–11079; (*b*) T. B. Mete, T. M. Khopade and R. G. Bhat, *Tetrahedron Lett.*, 2017, **58**, 415–418.

10 (*a*) I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov and P. V. Ptrovskii, *Mendeleev Commun.*, 2006, **16**, 250–251; (*b*) I. Yavari, T. Damghani and M. Nematpour, *Helv. Chim. Acta*, 2013, **96**, 2214–2217; (*c*) H. Jiang, W. Yu, X. Tang, J. Li and W. Wu, *J. Org. Chem.*, 2017, **82**, 9312–9320; (*d*) S. Thanna, C. M. Goins, S. E. Knudson, R. A. Slayden, D. R. Ronning and S. J. Sucheck, *J. Org. Chem.*, 2017, **82**, 3844–3854.

11 (*a*) M. Gao, M. Vuagnat, M. Y. Chen, X. Pannecoucke, P. Jubault and T. Besset, *Chem. – Eur. J.*, 2021, **27**, 6145–6160; (*b*) A. Klásek and V. Mrkvička, *J. Heterocycl. Chem.*, 2003, **40**, 747–752; (*c*) F. Buttard and T. Besset, *SynOpen*, 2023, **7**, 117–120; (*d*) J.-A. Xiao, Y.-C. Li, X.-L. Cheng, W.-Q. Chen, J.-G. Cui, Y.-M. Huang, J. Huang, Q. Xiao, W. Su and H. Yang, *Org. Chem. Front.*, 2019, **6**, 1967–1971.

12 A. B. Angus and R. G. R. Bacon, *J. Chem. Soc.*, 1958, 774–778.

13 (*a*) F. D. Toste, V. De Stefano and I. W. J. Still, *Synth. Commun.*, 1995, **25**, 1277–1286; (*b*) J. Y. See and Y. Zhao, *Org. Lett.*, 2018, **20**, 7433–7436; (*c*) M. Gao, M. Vuagnat, P. Jubault and T. Besset, *Eur. J. Org. Chem.*, 2021, e202101255.

14 (*a*) J. Qiu, D. Wu, P. G. Karmaker, H. Yin and F. X. Chen, *Org. Lett.*, 2018, **20**, 1600–1603; (*b*) J. Qiu, D. Wu, L. Yuan,

P. Long, H. Yin and F.-X. Chen, *J. Org. Chem.*, 2019, **84**, 7917–7926; (*c*) M. Gao, M. Chen, X. Pannecoucke, P. Jubault and T. Besset, *Chem. – Eur. J.*, 2020, **26**, 15497–15500.

15 (*a*) D. Wu, J. Qiu, P. G. Karmaker, H. Yi and F. X. Chen, *J. Org. Chem.*, 2018, **83**, 1576–1583; (*b*) W. Wei, L. Liao, T. Qin and X. Zhao, *Org. Lett.*, 2019, **21**, 7846–7850; (*c*) L. J. N. Waddell, M. R. Senkans and A. Sutherland, *J. Org. Chem.*, 2023, **88**, 7208–7218.

16 (*a*) C. Li, P. Long, H. Wu, H. Yi and F. X. Chen, *Org. Biomol. Chem.*, 2019, **17**, 7131–7134; (*b*) X.-F. Song, A.-H. Ye, Y.-Y. Xie, J.-W. Dong, C. Chen, Y. Zhang and Z.-M. Chen, *Org. Lett.*, 2019, **21**, 9550–9554; (*c*) A.-H. Ye, Y. Zhang, Y.-Y. Xie, H.-Y. Luo, J.-W. Dong, X.-D. Liu, X.-F. Song, T. Ding and Z.-M. Chen, *Org. Lett.*, 2019, **21**, 5106–5110; (*d*) H. Wu, C. Shao, D. Wu, L. Jiang, H. Yin and F.-X. Chen, *J. Org. Chem.*, 2021, **86**, 5327–5335.

17 J. A. Xiao, X. L. Cheng, R. F. Meng, X. S. Qin, H. Peng, J. W. Ren, Z. Z. Xie, J. G. Cui and Y. M. Huang, *Synthesis*, 2020, 954–960.

18 D. Wu, J. Qiu, C. Li, L. Yuan, H. Yin and F.-X. Chen, *J. Org. Chem.*, 2020, **85**, 934–941.

19 D. Zhu, A. H. Ye and Z. M. Chen, *Synthesis*, 2021, 3744–3750.

20 P. J. Fraker and J. C. Speck, *Biochem. Biophys. Res. Commun.*, 1978, **80**, 849–857.

21 (*a*) T. Unak, Z. Akgun, Y. Yildirim, Y. Dumanb and G. Erenel, *Appl. Radiat. Isot.*, 2001, **54**, 749–752; (*b*) H. Yuan, J. Luo, S. Field, R. Weissleder, L. Cantley and L. Josephson, *Bioconjugate Chem.*, 2005, **16**, 669–675; (*c*) A. K. Zad, A. Shiri, M. A. Zolfigol and S. Mallakpour, *Synthesis*, 2009, 2729–2732.

22 P. J. Gilissen, A. Swartjes, B. Spierenburg, J. P. J. Bruekers, P. Tinnemans, P. B. White, F. P. J. T. Rutjes, R. J. M. Nolte and J. A. A. W. Elemans, *Tetrahedron*, 2019, **75**, 4640–4647.

23 A. Shiri and A. K. Zad, *Synthesis*, 2009, 2797–2801.

24 (*a*) M. Bandini and A. Eicholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608–9644; (*b*) G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.*, 2010, **39**, 4449–4465.

25 A. S. Moffat, *Science*, 1993, **261**, 550–551.

26 N. M. Davies, A. G. Roseth, C. B. Appleyard, W. Mcknight, P. Del Soldato, A. Calignano, G. Cirino and J. L. Wallace, *Aliment. Pharmacol. Ther.*, 1997, **11**, 69–79.

27 B. H. Resman-Thrgoff, *Ann. Pharmacother.*, 1990, **24**, 1098–1104.

28 P. B. Davis, U. Yasothan and P. Kirkpatrick, *Nat. Rev. Drug Discovery*, 2012, **5**, 349–350.

29 (*a*) P. O. Kinell and B. Strandberg, *Acta Chem. Scand.*, 1959, **13**, 1607–1622; (*b*) A. Lex, P. Pacher, O. Werzer, A. Track, Q. Shen, R. Schennach, G. Koller, G. Hlawacek, E. Zojer, R. Resel, M. Ramsey, C. Teichert, W. Kern and G. Trimmel, *Chem. Mater.*, 2008, **20**, 2009–2015.

30 (*a*) M. Bernús, G. D. Núñez, W. C. Hartley, M. Guasch, J. Mestre, M. Besora, J. J. Carbó and O. Boutureira, *J. Med. Chem.*, 2025, **68**, 4787–4800; (*b*) M. Spennacchio, M. Bernús, J. Stanić, D. Mazzarella, M. Colella,

This journal is © The Royal Society of Chemistry 2025

Org. Biomol. Chem., 2025, **23**, 4463–4470 | **4469**

J. J. Douglas, O. Boutureira and T. Noël, *Science*, 2024, **385**, 991–996; (*c*) P. Casasús, J. Mestre, M. Bernús, S. Castillón and O. Boutureira, *Adv. Synth. Catal.*, 2023, **365**, 3438–3443; (*d*) J. Mestre, M. Bernús, S. Castillón and O. Boutureira, *J. Org. Chem.*, 2022, **87**, 10791–10806.

31 C. Pooput, M. Medebielle and W. R. Dolbier, *Org. Lett.*, 2004, **6**, 301–303.

32 Y.-X. Cheng, X.-G. Yang, F.-H. Du and C. Zhang, *Green Chem.*, 2024, **26**, 5914–5920.

33 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.

34 (*a*) H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, A. W. Lounsbury, K. E. Mellor, N. Z. Janković, Q. Tu, L. N. Pincus, M. M. Falinski, W. Shi, P. Coish, D. L. Plata and P. T. Anastas, *Green Chem.*, 2018, **20**, 1929–1961;

(*b*) D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521–527.

35 (*a*) R. A. Sheldon, *Chem. Ind.*, 1992, 903–906; (*b*) R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273–1283; (*c*) R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43; (*d*) R. A. Sheldon, *Green Chem.*, 2023, **25**, 1704–1728.

36 (*a*) V. Hessel, S. Mukherjee, S. Mitra, A. Goswami, N. N. Tran, F. Ferlin, L. Vaccaro, F. M. Galogahi, N.-T. Nguyen and M. Escribà-Gelonch, *Green Chem.*, 2024, **26**, 9503–9528; (*b*) L. Capaldo, Z. Wen and T. Noël, *Chem. Sci.*, 2023, **14**, 4230–4247; (*c*) A. A. Heredia, S. M. Soria-Castro, W. D. Castro-Godoy, I. D. Lemir, M. López-Vidal, F. R. Bisogno, J. E. Argüello and G. Oksdath-Mansilla, *Org. Process Res. Dev.*, 2020, **24**, 540–545.

37 F. Gao, F. Ferlin, R. Bai, M. Li, L. Vaccaro and Y. Gu, *Green Chem.*, 2021, **23**, 3588–3594.

4470 | *Org. Biomol. Chem.*, 2025, **23**, 4463–4470

This journal is © The Royal Society of Chemistry 2025