ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Synthesis of Selenocyanates and Selenoethers of Amino Pyrazoles and Amino Uracils by In Situ Triselenium Dicyanide from Malononitrile and Selenium Dioxide

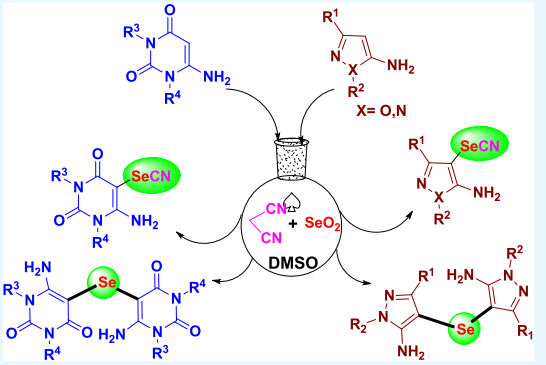
Danish Ali, Nurabul Mondal, Anoop Kumar Panday, and Lokman H. Choudhury*

Cite This: *ACS Omega* 2023, 8, 25349−25357

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Herein, we report an efficient method for synthesis of novel selenocyanates of amino pyrazole, amino uracil, and amino isoxazole derivatives using in situ triselenium dicyanide from the combination of malononitrile and selenium dioxide in DMSO medium. Using the same combination but changing the stoichiometry of reagents and sequence of addition and temperature, symmetrical selenoethers of amino pyrazoles and amino uracils were prepared in good yields. Furthermore, selenocyanates of amino pyrazoles were utilized for the synthesis of corresponding alkynyl selenides in the presence of CuI and Cs_2CO_3. The salient features of this methodology are inexpensive starting materials, short reaction time, and good to very good yields. This method is also applicable for the gram-scale synthesis of selenocyanates of amino pyrazoles and amino uracils.



INTRODUCTION

Selenium-containing organic molecules exhibit a wide spectrum of medicinal properties, such as antiviral, antihypertensive, antioxidant, antimicrobial, and antitumor properties.[1] In addition to these, organoselenium compounds are used as enzyme inhibitors, cytokine inducers, immune modulators, and stimulators for catalytic functions of several enzymes.[1,2] Organic selenocyanates have been studied for anticancer properties.[3] Apart from their pharmaceutical importance, organoselenium compounds are also very useful as intermediates as well as in catalysis.[4] Among organoselenium compounds, selenocyanate derivatives have many applications, as this group can be easily transformed into other functional groups such as selenoethers, diselenides, trifluoromethyl selenides, and selenic acids.[5]

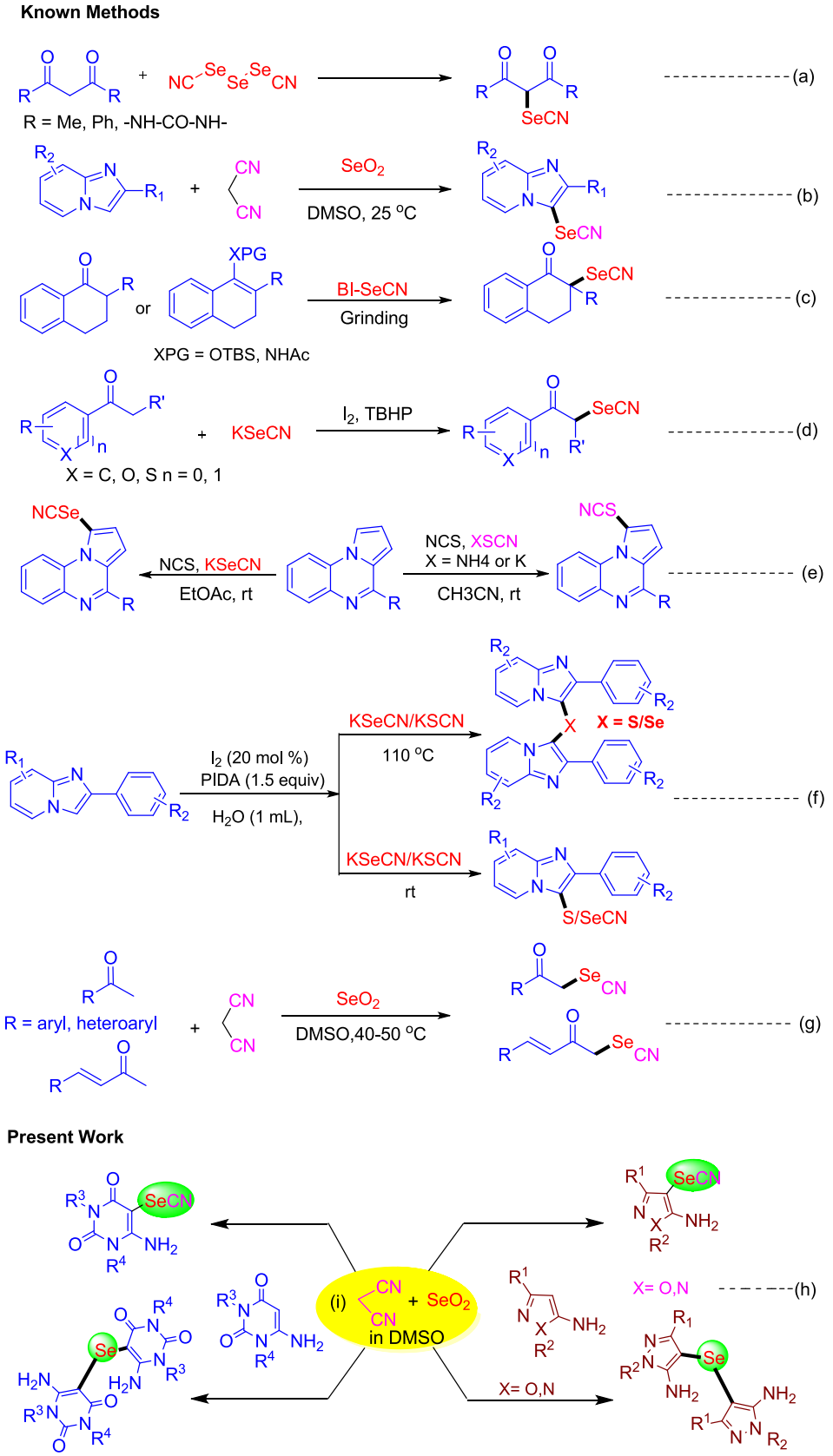
Functionalized pyrazoles are widely found in many natural products and in a variety of synthetic bioactive molecules.[6] Amino pyrazole derivatives are considered as one of the privileged molecules because of their enormous medicinal properties.[7] Pyrazole-linked selenoethers were used as ligands for palladium catalysis and for the preparation of coordination polymers.[8] Apart from these, pyrazole-linked selenoethers also exhibit glutathione peroxidase-like catalytic activities.[9] Similar to amino pyrazoles, amino uracils are also useful starting materials for synthesis of diverse bioactive molecules.[10] Considering the widespread applications and bioactive properties of pyrazole, uracil, and selenoethers, we turned our attention toward developing an efficient method for the synthesis of compounds having pyrazole or uracil-linked selenocyanates and selenoethers. To date, many methods are reported in the literature for selenocyanation of alkenes, alkynes, aryl, and heteroaryl systems by using salt of -SeCN and oxidizing agents.[11] Selenocyanation using elemental selenium in combination with TMSCN is also reported.[12] Similar to selenocyanation, selenoether formation can also be achieved under different conditions.[13]

A comparison of a few recent methods for the construction of C−Se bonds in different moieties and our present protocol is shown in Scheme 1. Kachanov et al. reported selenocyanation of diketones by utilizing in situ generated triselenium dicyanide from malononitrile and selenium dioxide (Scheme 1a).[14] Redon et al. reported a direct method for the synthesis of 3-seleno cyanatoimidazo*[1,2-a]* pyridine derivatives by using in situ triselenium dicyanides (Scheme 1b).[15a] They also used the combination of SeO_2 and malononitrile in other transformations.[15b−d] Xiao et al. developed a method for selenocyanation of enolizable carbonyl compounds by employing selenocyano-benziodoxolone (BI-SeCN), a hypervalent iodine reagent, under solvent and oxidant-free grinding reaction conditions (Scheme 1c).[16] Sun et al. reported oxidative selenocyanation of aromatic ketones by using KSeCN, a catalytic amount of molecular iodine, and TBHP

Received: April 22, 2023
Accepted: June 16, 2023
Published: July 5, 2023

https://doi.org/10.1021/acsomega.3c02769
ACS Omega 2023, 8, 25349−25357

Scheme 1. Comparison of Some Reported Methods for Selenocyanation with Our Work (a–h)



as an oxidizing agent (Scheme 1d).[17] Yang et al. synthesized selenocyanates of pyrrolo[1,2-a]quinoxaline in the presence of 1.5 equivalent of NCS as an oxidant (Scheme 1e).[18] Zhu et al. reported temperature-dependent iodine-catalyzed chalcocyanation and chalcogenation of imidazopyridines by using KSeCN and KSCN as a source of chalcogens and a

https://doi.org/10.1021/acsomega.3c02769
ACS Omega 2023, 8, 25349−25357

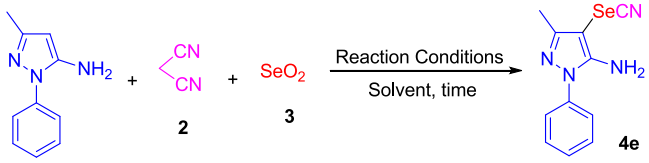
stoichiometric amount of PIDA as an oxidant (Scheme 1f).[19] Myrboh and co-workers reported selenocyanation of enolizable ketones and chalcones using in situ triselenium dicyanide obtained from malononitrile and selenium dioxide (Scheme 1g).[20] Herein, we report a straightforward method using in situ triselenium dicyanide obtained from malononitrile and selenium dioxide for the preparation of selenocyanates and selenoethers of amino pyrazole and amino uracils (Scheme 1h).

Recently, we reported a H_2O_2-mediated thiocyanation of amino pyrazole and amino uracil moiety,[21] and rose Bengal-catalyzed phenylselenylation of amino pyrazole and amino uracils in the presence of visible light.[21] In continuation of our work on sp^2 C−H functionalization, especially on C−S and C−Se bond-forming reactions, we turned our attention toward developing an efficient and straightforward method for the functionalization of amino pyrazole and amino uracil derivatives. Triselenodicyanide is considered as an ideal electrophilic source, especially considering its simple and easy generation from malononitrile and selenium dioxide. However, to the best of our knowledge, this has not been explored for the synthesis of selenocyanates and selenoethers of amino pyrazole and amino uracils. Thus, we wanted to investigate and explore the reactivity of triselenodicyanides for selenocyanation of various pyrazole and uracil moieties.

RESULTS AND DISCUSSION

We started our preliminary investigation on selenocyanation by choosing 5-amino-3-methyl-1-phenyl-1*H*-pyrazole (**1e**) as a model substrate. The reaction of **1e** with selenium dioxide (**3**) and malononitrile (**2**) under various reaction conditions was performed to find out the optimum reaction conditions for this transformation (Table 1). Initially, a reaction using 0.5 mmol of 5-amino-3-methyl-1-phenyl-1H- pyrazole (**1e**), 0.75 mmol (1.5 equiv) of malononitrile (**2**), and 1.5 mmol of selenium dioxide (**3**) in 2.0 mL of DMSO was tried keeping the reaction temperature at 40 °C. To our delight, an 80% yield of our desired corresponding selenocyanated product **4e** was obtained within a short reaction time (entry 1, Table 1). It is noteworthy to mention that we did not observe any oxidation of amine functionality in this reaction. Next, the same reaction was tried at 25 °C, and to our surprise, the reaction provided only 15% yield even after a 12 h reaction time (Table 1, entry 2). We also varied the stoichiometry of malononitrile and SeO_2 keeping the solvent DMSO and the temperature at 40 °C (fixed) to check their effect on the observed yield. Only 43% yield was observed using 1.0 equiv of malononitrile and 1.0 equiv of SeO_2 (entry 3, Table 1). Interestingly, in the presence of 1.0 equiv of malononitrile and 2.0 equiv of SeO_2, a slightly better result was observed (entry 4, Table 1). Next, we performed the reaction for a longer reaction time (3 h) and ended up with lower yields. Similarly, another reaction was investigated at a slightly higher temperature (55 °C); in this case also relatively lower yield was observed (entry 6, Table 1). When the same reaction was performed in DMF medium instead of DMSO, only 47% yield was observed. Solvents like water, acetonitrile, THF, and toluene were not found suitable for this transformation (Table 1, entries 8−11).

Table 1. Optimization of the Reaction Conditions for the Synthesis of 4e[a]



1e 2 3 4e

entry	substrate 2 (equiv)	SeO_2 (equiv)	solvent	temp (°C)	time	yield[b] (%)
1	**1.5**	**3**	**DMSO**	**40**	**30 min**	**80**
2	1.5	3	DMSO	25	12 h	15
3	1	1	DMSO	40	2 h	43
4	1	2	DMSO	40	2 h	61
5	1.5	3	DMSO	40	3 h	62
6	1.5	3	DMSO	55	30 min	73
7	1.5	3	DMF	40	30 min	47
8	1.5	3	H_2O	40	30 min	Traces
9	1.5	3	acetonitrile	40	30 min	Traces
10	1.5	3	THF	40	30 min	Traces
11	1.5	3	toluene	40	30 min	Traces

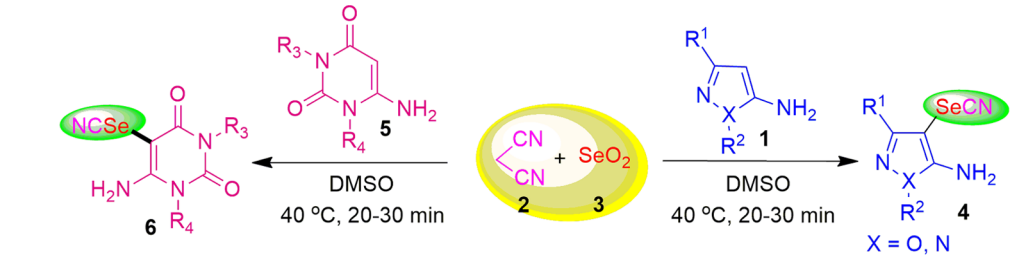
[a]Reaction conditions **1e** (0.5 mmol,1.0 equiv). [b]Yield of the isolated product.

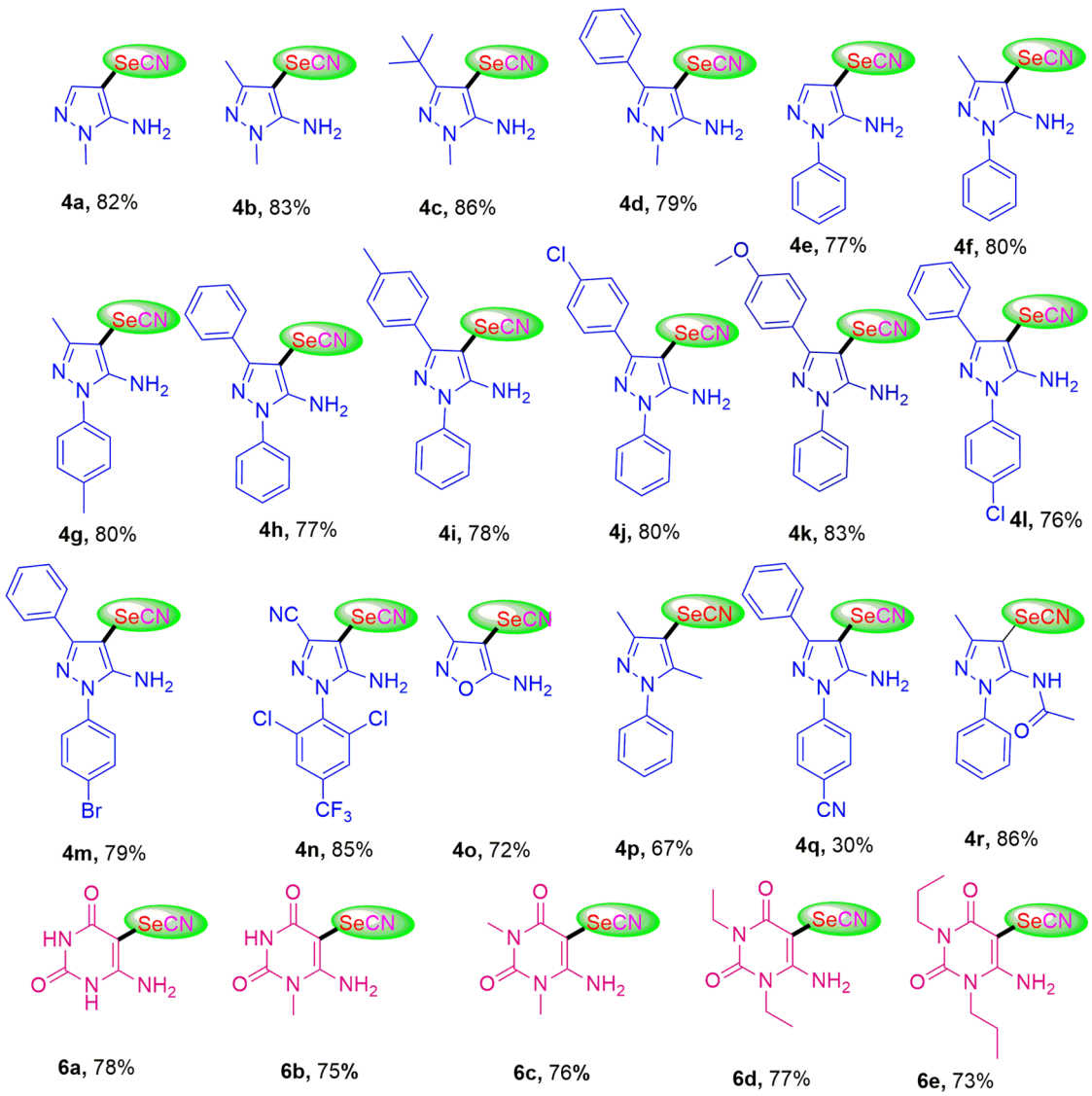
Among all of the screened solvents, DMSO was found to be the most suitable solvent for the synthesis of selenocyanates using this method. From this investigation, it was realized that 1.0 equiv of 5-amino-3-methyl-1-phenyl-1H-pyrazole (**1e**), 1.5 equiv of malononitrile (**2**), and 3.0 equiv of selenium dioxide (**3**) in DMSO medium at 40 °C provide the optimum yield for the selenocyanated product (**4e**). With this optimal reaction condition in hand, we further turned our attention to checking the generality and scope of this selenocyanation methodology. A wide variety of amino pyrazole derivatives with R^1 = H, CN, Me, $C(CH_3)_3$, Ph, 4-Me-Ph, 4-OMe-Ph, 4-Cl-Ph groups and R^2 = Me, Ph, 4-Cl-Ph, 4-Br-Ph, and 2,6-dichloro-4-trifluoromethylphenyl groups were found suitable for selenocyanation and the corresponding selenocyanates were obtained in good to very good yields (Table 2). A relatively lower yield of **4q** was obtained and it took a longer reaction time (6 h), which may be due to the presence of an electron-withdrawing group -CN in the Phenyl ring tethered with N1. Amino pyrazole derivatives having NH−Ac group also provided the corresponding selenocyanated product **4r** without affecting the protecting group.

After the successful application of this methodology for selenocyanation of amino pyrazoles, next, we turned our attention to explore this method for selenocyanation of amino uracil derivatives. Under standard reaction conditions, it was observed that 6-amino uracil provides the corresponding selenocyanated product **6a** in 78% yield. Likewise, mono-substituted and disubstituted 6-amino uracils with methyl groups were reacted, and the corresponding selenocyanated products **6b** and **6c** were obtained in very good yields (75−76%). Likewise, 6-amino uracil having diethyl and dipropyl groups also provided selenocyanated products **6d** and **6e** in 77 and 73% yield, respectively, under standard reaction conditions. Next, we turned out our attention on the synthesis of selenium-bridged symmetrical selenoethers of 5-amino pyrazole derivatives. For this purpose, we initially carried out a one-pot two-step procedure. First, we carried out selenocyanation of 5-amino-3-methyl-1-phenyl-1-H-pyrazole (**1e**) under standard reaction conditions. After the full consumption of **1e** as monitored by the TLC, we added one more equivalent of **1e**, and the resultant reaction mixture was

https://doi.org/10.1021/acsomega.3c02769
ACS Omega 2023, 8, 25349−25357

Table 2. Substrate Scope for Selenocyanation of Amino pyrazole 1 and Amino uracil Derivatives 5[a,b]





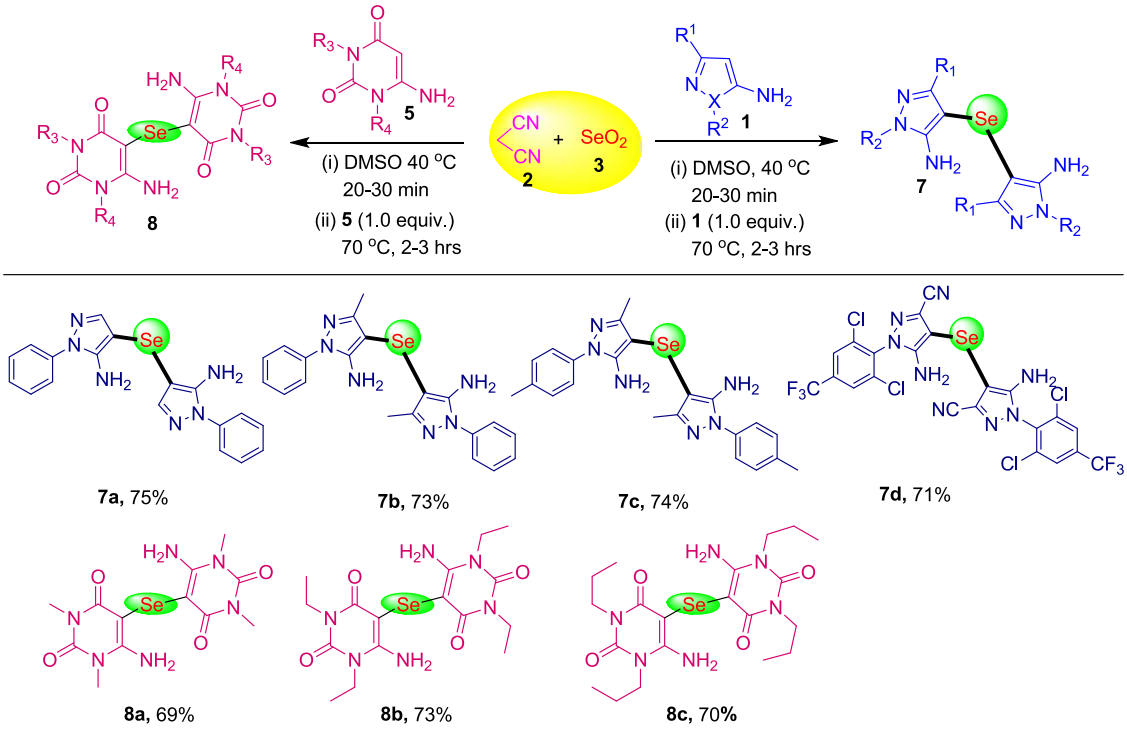
[a]Reaction conditions: **1** or **5** (0.5 mmol), **2** (0.75 mmol), and SeO_2 (1.5 mmol) in DMSO (2.0 mL), 40 °C, 15−30 min. [b]Yield of the isolated product.

stirred for 2 h at 70 °C until the selenocyanated product was fully consumed (monitored by TLC). Interestingly, in this reaction, the corresponding symmetrical selenoether **7b** was obtained in 73% yield (Table 3). After this, following this one-pot two-step strategy and just varying amino pyrazole derivatives, we prepared other symmetrical selenoethers **7a**, **7c**, and **7d** in good yields, and the results are summarized in Table 3.

All of these products were fully characterized by recording ^{1}H and ^{13}C NMR and HRMS. In addition to these, the structure of **7d** was further unambiguously confirmed by single-crystal XRD as shown in Figure 1. Next, to generalize this method, we also applied the same one-pot two-step procedure for the synthesis of symmetrical selenoethers of amino uracil derivatives, i.e., selenocyanation followed by the addition of one more equivalent amino uracil derivatives under standard reaction conditions at 70 °C. Interestingly, amino uracil derivatives having methyl, ethyl and propyl groups were also found suitable for this one-pot symmetrical selenoether

https://doi.org/10.1021/acsomega.3c02769
ACS Omega 2023, 8, 25349−25357

Table 3. Substrate Scope for the Synthesis of Symmetrical Selenoethers of Amino pyrazole 7a−7d and Amino uracil Derivatives 8a−8c[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), and SeO_2 (1.5 mmol) in DMSO (2.0 mL), at 40 °C, 15−30 min. After 30 min again **1** or **5** (1.0 equiv) was added. [b]Yield of the isolated product.

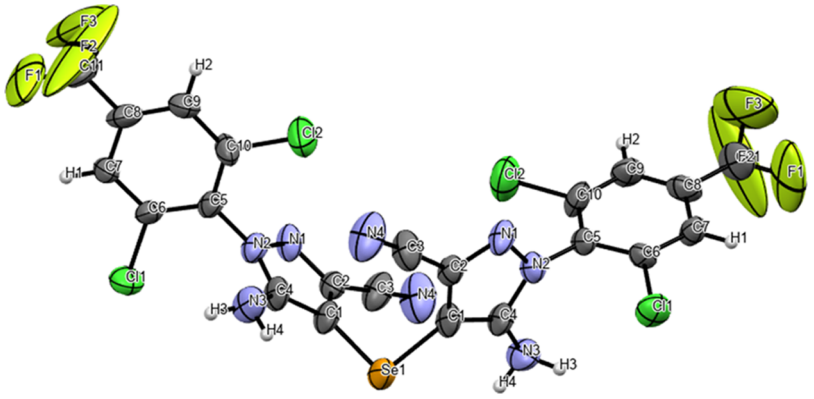


Figure 1. Single-crystal X-ray structure of **7d** (**CCDC 2256632**).

formation reaction and the corresponding symmetrical selenoethers **8a−8c** were prepared in good to very good yields.

The feasibility of gram-scale synthesis of selenocyanated products by this method was also determined. For this purpose, we took amino pyrazole **1e** in 5.0 mmol and 7.5 mmol malononitrile and 15.0 mmol selenium dioxide in 20.0 mL of DMSO, and the reaction mixture was stirred under standard reaction conditions for 40 min. After completion of the reaction, the corresponding selenocyanated product **4e** was obtained in 78% yield as shown in Scheme 2. Similarly, selenocyanate **6c** was prepared in a 5.0 mmol scale.

Finally, we tried to utilize our selenocyanated products for the synthesis of alkynyl selenides tethered with amino pyrazole moiety. From the literature, we found that alkynyl sulfides can be prepared by utilizing copper catalysis using thiocyanates and alkynes at ambient temperature.[22] However, to the best of our knowledge, to date, synthesis of alkynyl selenides tethered with amino pyrazole is not known. Thus, we carried out the reaction by taking selenocyanates **4e** (0.3 mmol), phenylacetylene **9** (1.5 equiv), Cs_2CO_3 (1.0 equiv), and CuI (20.0 mol %) in 4.0 mL of acetonitrile in a 10 mL round-bottom flask and the reaction was performed under a nitrogen atmosphere. Interestingly, after stirring for 2 h at room temperature, the corresponding alkynyl selenoether **10e** was obtained in 71% yield. Next, we tried to optimize this reaction by using different organic solvents such as THF, DCE, toluene, DCM, ethanol, and DMSO at room temperature conditions; among all of the screened solvents, acetonitrile provided the best result. Thus, using selenocyanate **4l** and phenyl acetylene under standard reaction conditions, we prepared the corresponding alkynyl selenides **10b** in 67% yield as shown in Table 4.

https://doi.org/10.1021/acsomega.3c02769
ACS Omega 2023, 8, 25349−25357

Scheme 2. Gram-Scale Synthesis of 4e and 6c

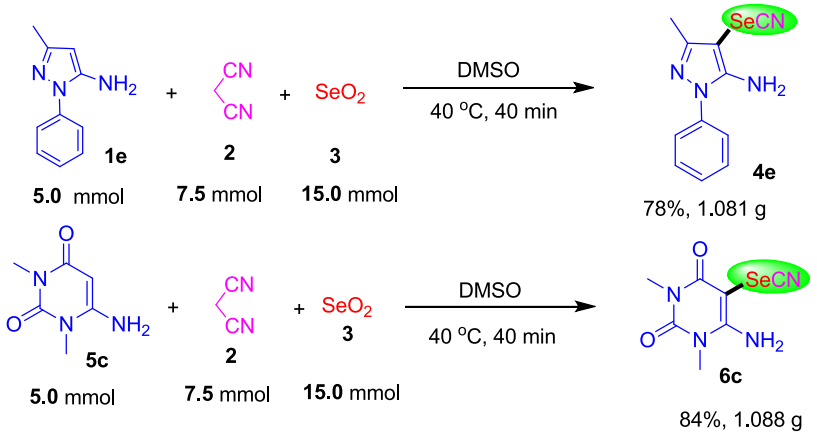
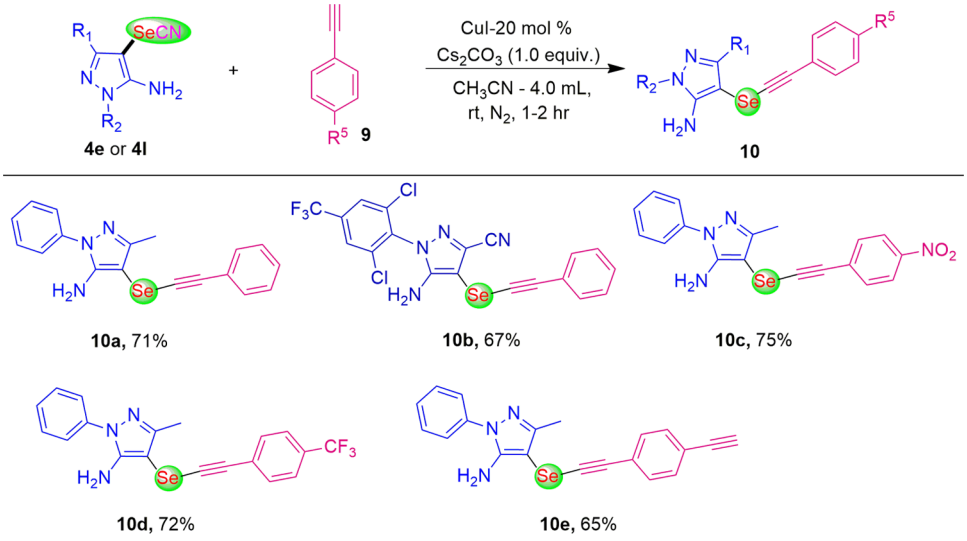


Table 4. Substrate Scope for the Synthesis of Alkynyl Selenides 10a−10e[a,b]



[a]Reaction conditions: **4e** or **4l** (0.3 mmol, 1.0 equiv), phenylacetylene derivative **9** (1.5 equiv), Cs_2CO_3 (1.0 equiv), and CuI (20.0 mol %) in 4.0 mL of CH_3CN, N_2, rt. [b]Yield of the isolated product.

Phenyl acetylene derivatives having substituents such as 4-NO_2 and 4-CF_3 also reacted with **4e** to provide corresponding alkynyl selenoethers **10c** and **10d** in good yields under standard reaction conditions. In the case of 1,4-diethynylbenzene under standard reaction conditions, we only obtained mono alkynyl selenide **10e** in a satisfactory yield.

The plausible reaction mechanism for the formation of selenocyanate and selenoether is shown in Scheme 3. Based on the literature reports on preparation and application of triselenium dicyanide in organic synthesis,[12,13,18] we proposed the mechanism for this reaction. It is believed that amino pyrazoles act as a C-nucleophile due to enamine-like properties and attack the in situ generated electrophilic selenocyanating reagent triselenium dicyanide (I) to give intermediate II. Next, deprotonation of intermediate II provides the desired selenocyanated product **4e**. Formation of selenoether **8a** goes via a nucleophilic substitution of cyanamide from **4e** by another molecule of amino pyrazole as shown in Scheme 3. Likewise, alkynyl selenides form via the formation of an organo copper intermediate, which acts as a nucleophile for the substitution of CN^- from **4e**.

CONCLUSIONS

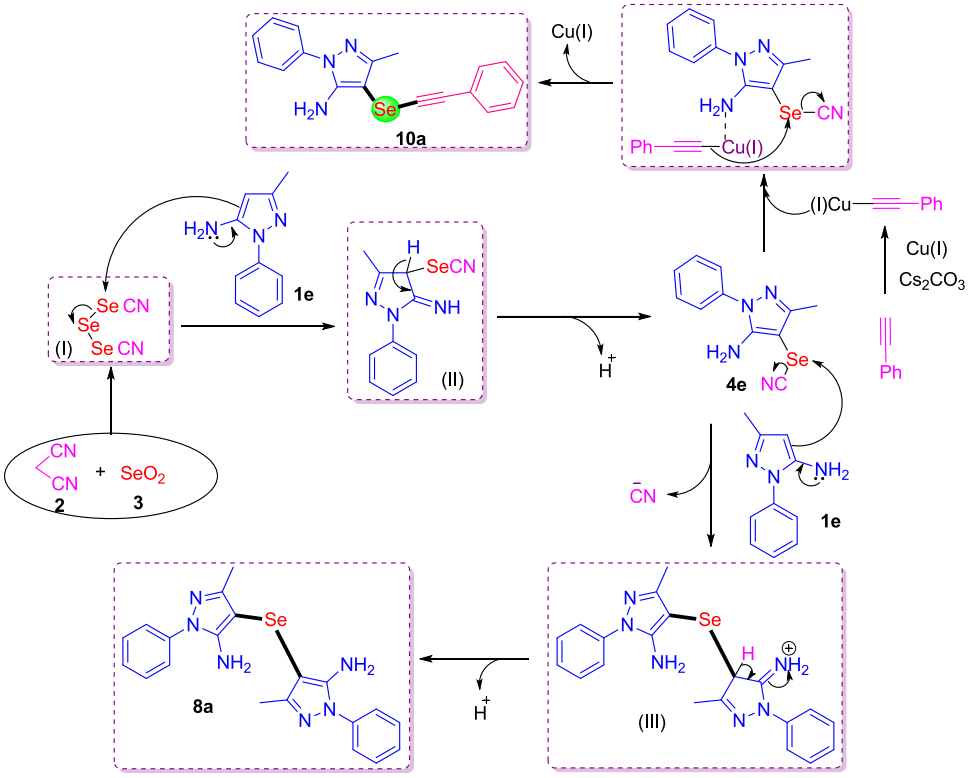
In summary, we developed an efficient method for selenocyanation of amino pyrazole, amino isoxazole, and amino uracil derivatives as well as symmetrical selenoethers of amino pyrazole and amino uracils using in situ triselenium dicyanide from the combination of SeO_2 and malononitrile. The salient features of this method are: inexpensive starting materials, shorter reaction time, wide substrate scope, and applicable for gram-scale synthesis. The prepared selenocyanates of amino pyrazoles have been converted to alkynyl selenides using copper catalysis.

EXPERIMENTAL SECTION

Experimental Procedure. *General Procedure for the Synthesis of **4a−4r** and **6a−6e**.* In a 10.0 mL round-bottom flask, malononitrile (50 mg, 0.75 mmol, 1.5 equiv), SeO_2 (166 mg, 1.5 mmol, 3.0 equiv), and 2.0 mL of DMSO were transferred and the resulting mixture was stirred for five minutes at 40 °C. Then, amino pyrazole/amino isoxazole/amino uracil (0.5 mmol, 1.0 equiv) was transferred to this mixture and again stirred for 30 minutes. The progress of the reaction was monitored by TLC. After completion of reaction,

https://doi.org/10.1021/acsomega.3c02769
ACS Omega 2023, 8, 25349−25357

Scheme 3. : Plausible Reaction Mechanism for the Formation of Selenocyanate 4e and Selenoethers 8a and 10a



the reaction mixture was transferred to a separating funnel and 10.0 mL of water was added and extracted three times with ethyl acetate (3 × 10.0 mL). The resultant organic layer was dried over anhydrous sodium sulfate and concentrated by using a rotavap. The crude product was purified by silica-gel column chromatography to get the pure products **4a**−**4p**, while the selenocyanated products **6a**−**6e** were obtained by addition of water followed by simple filtration and column chromatography.

*General Procedure for the Synthesis of Symmetrical Selenoethers **7a**−**7d** and **8a**−**8c**.* In a 10.0 mL round-bottom flask, malononitrile (50 mg, 0.75 mmol, 1.5 equiv), SeO_2 (166 mg, 1.5 mmol 3.0 equiv), and 2.0 mL DMSO were transferred. The resulting mixture was stirred for five minutes at 40 °C. Then, amino pyrazole/amino uracil (0.5 mmol, 1.0 equiv) was added to this mixture and again stirred for 30 minutes. After the completion of the reaction, one equivalent of amino pyrazole/amino uracil (0.5 mmol, 1.0 equiv) was added and the reaction mixture was kept under heating condition (at 70 °C) with constant stirring for 2−3 h. After completion of the reaction, 10.0 mL of water was added to the reaction mixture and extracted three times with ethyl acetate (3 × 10.0 mL).The resultant organic layer was dried over anhydrous sodium sulfate and concentrated by using a rotavap. The pure product was isolated by column chromatography.

*General Procedure for the Synthesis of Alkynyl Selenides **10a**−**10e**.* In a 10.0 mL round-bottom flask, a mixture of selenocyanated product **4e** or **4l** (0.3 mmol, 1.0 equiv), phenylacetylene **9** (1.5 equiv), Cs_2CO_3 (1.0 equiv) and CuI (20.0 mol %) and 4.0 mL of acetonitrile was transferred and flushed with nitrogen gas to create an inert atmosphere. The reaction mixture was stirred for 2 h and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was passed through a pad of Celite and the filtrate was concentrated in reduced pressure. Then, 5.0 mL of water was added to the crude product and the mixture was transferred to a separating funnel and extracted three times with ethyl acetate (3 × 10.0 mL). The resultant organic layer was dried over anhydrous sodium sulfate and concentrated by using a rotavap. Finally, the crude product was purified by silica-gel column chromatography to get pure products **10a** to **10e**.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02769.

Characterization data (^{1}H NMR, ^{13}C NMR) for all the products along with ^{77}Se NMR of some products and XRD data (PDF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Lokman H. Choudhury − *Department of Chemistry, Indian Institute of Technology Patna, Patna 801106, India;* orcid.org/0000-0003-1735-1985; Email: lokman@iitp.ac.in, lokman.iitp@gmail.com

Authors

Danish Ali − *Department of Chemistry, Indian Institute of Technology Patna, Patna 801106, India;* orcid.org/0000-0003-4431-3757

https://doi.org/10.1021/acsomega.3c02769
ACS Omega 2023, 8, 25349−25357

Nurabul Mondal − *Department of Chemistry, Indian Institute of Technology Patna, Patna 801106, India*
Anoop Kumar Panday − *Department of Chemistry, Indian Institute of Technology Patna, Patna 801106, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c02769

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to IIT Patna for providing the general facilities and fundng to carry out this study. D.A. is thankful to IIT Patna for his research fellowship. The authors are also thankful to SAIF IIT Patna for the single-crystal XRD facility and for providing HRMS data.

■ REFERENCES

(1) (a) Mugesh, G.; duMont, W. W.; Sies, H. Chemistry of Biologically Important Synthetic Organoselenium Compounds. *Chem. Rev.* **2001**, *101*, 2125−2180. (b) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. Organoselenium and Organotellurium Compounds: Toxicology and Pharmacology. *Chem. Rev.* **2004**, *104*, 6255−6286. (c) Engman, L.; Cotgreave, I.; Angulo, M.; Taylor, C. W.; Paine-Murrieta, G. D.; Powis, G. Diaryl Chalcogenides as Selective Inhibitors of Thioredoxin Reductase and Potential Antitumor Agents. *Anticancer Res.* **1997**, *17*, 4599. (d) Woods, J. A.; Hadfield, J. A.; Mcgown, A. T.; Fox, B. W. Bioactivity and Molecular Modelling of Diphenylsulfides and Diphenylselenides. *Bioorg. Med. Chem.* **1993**, *1*, 333−340. (e) Engman, L.; Stern, D.; Frisell, H.; Vessman, K.; Berglund, M.; Ek, B.; Andersson, C. M. Synthesis, Antioxidant Properties, Biological Activity and Molecular Modelling of a Series of Chalcogen Analogues of the 5-lipoxygenase Inhibitor DuP 654. *Bioorg. Med. Chem.,* **1995**, *3*, 1255−1262. (f) Millois, C.; Diaz, P. Solution-Phase Synthesis of Diaryl Selenides Using Polymer-Supported Borohydride. *Org. Lett.,* **2000**, *2*, 1705−1708.

(2) (a) Barbosa, N. V.; Nogueira, C. W.; Nogara, P. A.; de Bem, A. F.; Aschner, M.; Rocha, J. B. T. Organoselenium Compounds as Mimics of Selenoproteins and Thiol Modifier Agents. *Metallomics* **2017**, *9*, 1703−1734. (b) Jantová, S.; Paulovičova′, E.; Paulovičova′, L.; Topoľska′, D.; Pa′nik, M.; Milata, V. Assessment of Immunomodulatory Activities and in vitro Toxicity of New Quinolone 7-ethyl 9-ethyl-6-oxo-6,9-dihydro[1,2,5]selenadiazolo[3,4-h]quinoline-7-carboxylate. *Immunol. Invest.* **2017**, *46*, 341−360.

(3) Rao, C. V.; Wang, C.-Q.; Simi, B.; Rodriguez, J. G.; Cooma, I.; El-Bayoumy, K.; Reddy, B. S. Chemoprevention of Colon Cancer by a Glutathione Conjugate of 1,4-Phenylenebis (methylene) selenocyanate, a Novel Organoselenium Compound with Low Toxicity. *Cancer Res.* **2001**, *61*, 3647−3652.

(4) (a) Shao, L.; Li, Y.; Lu, J.; Jiang, X. Recent Progress in Selenium-Catalyzed Organic Reactions. *Org. Chem. Front.* **2019**, *6*, 2999−3041. (b) Rathore, V.; Jose, C.; Kumar, S. Organoselenium Small Molecules as Catalysts for the Oxidative Functionalization of Organic Molecules. *New J. Chem.* **2019**, *43*, 8852−8864. (c) Wang, T.; Jing, X.; Chen, C.; Yu, L. Organoselenium-Catalyzed Oxidative C═C Bond Cleavage: A Relatively Green Oxidation of Alkenes into Carbonyl Compounds with Hydrogen Peroxide. *J. Org. Chem.* **2017**, *82*, 9342−9349. (d) Guo, R.; Huang, J.; Huang, H.; Zhao, X. Organoselenium-Catalyzed Synthesis of Oxygen- and Nitrogen-Containing Heterocycles. *Org. Lett.* **2016**, *18*, 504−507. (e) Kumar, A.; Rao, G. K.; Saleem, F.; Singh, A. K. Organoselenium Ligands in Catalysis. *Dalton Trans.* **2012**, *41*, 11949−11977.

(5) (a) Krief, A.; Dumont, W.; Delmotte, C. Reaction of Organic Selenocyanates with Hydroxides: The One-Pot Synthesis of Dialkyl Diselenides from Alkyl Bromides. *Angew Chem Int Ed.* **2000**, *39*, 1669−1672. (b) Nikolaienko, P.; Rueping, M. Trifluoromethylselenolation of Aryldiazonium Salts: A Mild and Convenient Copper-Catalyzed Procedure for the Introduction of the $SeCF_3$ Group. *Chem. Eu.r J.* **2016**, *22*, 2620−2623. (c) Mukherjee, N.; Kundu, D.; Ranu, B. C. Copper-Silver Dual Catalyzed Decyanative C−Se Cross-Coupling. *Adv. Synth. Catal.* **2017**, *359*, 329−338. (d) Redon, S.; Kosso, A. R. O.; Broggi, J.; Vanelle, P. Easy and Efficient Selenocyanation of Imidazoheterocycles Using Triselenodicyanide. *Tetrahedron Lett.* **2017**, *58*, 2771−2773.

(6) (a) Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. Pyrazole Containing Natural Products: Synthetic Preview and Biological Significance. *Eur. J. Med. Chem.* **2013**, *69*, 735−753. (b) Küçükgüzel, Ş.; Şenkardeş, S. Recent Advances in Bioactive Pyrazoles. *Eur. J. Med. Chem.* **2015**, *97*, 786−815.

(7) (a) Marinozzi, M.; Marcelli, G.; Carotti, A. *N*-Aryl-5-amino pyrazole: A Versatile Architecture in Medicinal Chemistry. *Mini-Rev. Med. Chem.* **2015**, *15*, 272−299. (b) Nitulescu, G. M.; Nedelcu, G.; Buzescu, A.; Olaru, O. T. Amino pyrazoles as Privileged Structures in Anticancer Drug Design- an *in silico* Study. *Bulg. Chem. Commun.* **2016**, *48*, 55−60.

(8) Kumar, A.; Rao, G. K.; Kumar, S.; Singh, A. K. Formation and role of palladium chalcogenide and other species in Suzuki−Miyaura and Heck C−C coupling Reactions Catalyzed with Palladium(II) Complexes of Organochalcogen Ligands: Realities and Speculations. *Organometallics* **2014**, *33*, 2921−2943.

(9) Hodage, A. S.; Phadnis, P. P.; Wadawale, A.; Priyadarsini, K. I.; Jain, V. K. Synthesis, Characterization and Structures of 2-(3,5-dimethylpyrazol-1-yl)ethylseleno Derivatives and Their Probable Glutathione Peroxidase (GPx) Like Cctivity. *Org. Biomol. Chem.* **2011**, *9*, 2992−2998.

(10) (a) Mohammadi Ziarani, G.; Nasab, N. H.; Lashgari, N. Synthesis of Heterocyclic Scaffolds Through 6-Amino uracil-Involved Multicomponent Reactions. *RSC Adv.* **2016**, *6*, 38827−38848. (b) Bharti, R.; Kumari, P.; Parvin, T.; Choudhury, L. H. Recent Advances of Aminopyrimidines in Multicomponent Reactions. *Curr. Org. Chem.* **2018**, *22*, 417−445.

(11) (a) Raji Reddy, C.; Ajaykumar, U.; Kolgave, D. Expeditious Access to Spiro-Fused 2,5-Cyclohexadienones via Thio(seleno)-cyanative ipso-Cyclization. *J. Org. Chem.* **2020**, *85*, 15521−15531. (b) Lu, L.-H.; Wang, Z.; Xia, W.; Cheng, P.; Zhang, B.; Cao, Z.; He, W-M. Sustainable Routes for Quantitative Green Selenocyanation of Activated Alkynes. *Chin. Chem. Lett.* **2019**, *30*, 1237−1240. (c) Lu, L.-H.; Zhou, S. -J.; He, W. -B.; Xia, W.; Chen, P.; Yu, X.; Xu, X.; He, W. -M. Metal-free Difunctionalization of Alkynes Leading to Alkenyl Dithiocyanates and Alkenyl Diselenocyanates at Room Temperature. *Org. Biomol. Chem.* **2018**, *16*, 9064−9068. (d) Maity, P.; Paroi, B.; Ranu, B. C. Transition-Metal-Free Iodine Catalyzed Selenocayanation of Styrenyl Bromides and an Easy Access to Benzoselenophenes via Intermediacy of Styrenyl Selenocyanate. *Org. Lett.* **2017**, *19*, 5748−5751. (e) Chen, J.; Wang, T.; Wang, T.; Lin, A.; Yao, H.; Xu, J. Copper-Catalyzed C5-Selective Thio/Selenocyanation of 8-Amino-quinolines. *Org. Chem. Front.* **2017**, *4*, 130−134. (f) Nair, V.; Augustine, A.; George, T. G. A Facile CAN-Mediated Synthesis of Selenocyanates from Arylalkenes and Heteroarenes. *Eur. J. Org. Chem.* **2002**, *14*, 2363−2366.

(12) (a) Feng, C.; Peng, Y.; Ding, G.; Li, X.; Chang, C.; Yan, Y. Catalyst and Additive-Free Regioselective Oxidative C−H Thio/Selenocyanation of Arenes and Heteroarenes with Elemental Sulfur/Selenium and TMSCN. *Chem. Commun.* **2018**, *54*, 13367−13370. (b) Zhang, X.; Huang, X. B.; Zhou, Y. B.; Liu, M. C.; Wu, H. Y. Metal-Free Synthesis of Aryl Selenocyanates and Selenaheterocycles with Elemental Selenium. *Chem.−Eur. J.* **2021**, *27*, 944−948. (c) Lu, L. -G.; Bi, K.; Huang, X. -B.; Liu, M. -C.; Zhou, Y. -B.; Wu, H. -Y. Catalyst and Additive-Free Selective Ring-Opening Selenocyanation of Heterocycles with Elemental Selenium and TMSCN. *Adv. Synth. Catal.* **2021**, *363*, 1346−1351. (d) Li, J. -C.; Gao, W. -X.; Liu, M. -C.; Zhou, Y. -B.; Wu, H.-Y. α-Selective C(sp^3)−H Thio/Selenocyanation of Ketones with Elemental Chalcogen. *J. Org. Chem.* **2021**, *86*, 17294−17306.

(13) (a) Ghosh, T.; Mukherjee, N.; Ranu, B. C. Transition Metal- and Oxidant-Free Base-Mediated Selenation of Bicyclic Arenes at

Room Temperature. *ACS Omega* **2018**, *3*, 17540−17546. (b) Lima, D. B.; Santos, P. H. V.; Fiori, P.; Badshah, G.; Luz, E. Q.; Seckler, D.; Rampon, D. S. Base-Promoted Direct Chalcogenylation of 2-Naphthols. *ChemistrySelect* **2019**, *4*, 13558−13563. (c) Saba, S.; Rafique, J.; Franco, M. S.; Schneider, A. R.; Espíndola, L.; Silvaa, D. O.; Braga, A. L. Rose Bengal Catalysed Photo-Induced Selenylation of Indoles, Imidazoles and Arenes: A Metal Free Approach. *Org. Biomol. Chem.* **2018**, *16*, 880−885. (d) Kumaraswamy, G.; Ramesh, V. G. M.; Gangadhar, M.; Vijaykumar, S. Catalyst and Sensitizer-Free Visible-Light-Induced C(sp^2)−H Chalcogenation of Arenes/ Heteroarenes with Dichalcogenides. *Asian J. Org. Chem.* **2018**, *7*, 1689−1697.

(14) Kachanov, A. V.; Slabko, O. Y.; Baranova, O. V.; Shilova, E. V.; Kaminskii, V. A. Triselenium Dicyanide from Malononitrile and Selenium dioxide. One-pot Synthesis of Selenocyanates. *Tetrahedron Lett.* **2004**, *45*, 4461−4463.

(15) (a) Redon, S.; Roly, A.; Kosso, O.; Broggi, J.; Vanelle, P. Easy and Efficient Selenocyanation of Imidazoheterocycles Using Triselenodicyanide. *Tetrahedron Lett.* **2017**, *58*, 2771−2773. (b) Kosso, A.; Broggi, J.; Redon, S.; Vanelle, P. Convenient and Rapid Synthesis of 3-Selenocyanato-4H-chromen-4-ones. *Synlett.* **2018**, *29*, 1215−1218. (c) Redon, S.; Kosso, A. R. O.; Broggi, J.; Vanelle, P. Metal-Free ipso-Selenocyanation of Arylboronic Acids Using Malononitrile and Selenium Dioxide. *Synthesis* **2019**, *51*, 3758−3764. (d) Redon, S.; Vanelle, P. Nucleophilic Selenocyanation from Selenium Dioxide and Malononitrile. *Synthesis* **2023**, *55*, 510−518.

(16) Xiao, J.-A.; Li, Y.-C.; Cheng, X.-L.; Chen, W.-Q.; Cui, J.-G.; Huang, Y.-M.; Huang, J.; Xiao, Q.; Su, W.; Yang, H. Selenocyanobenziodoxolone: A Practical Electrophilic Selenocyanation Reagent and its Application for Solid-state Synthesis of α-carbonyl Selenocyanates. *Org. Chem. Front.* **2019**, *6*, 1967−1971.

(17) Sun, K.; Lv, Y.; Chen, Y.; Zhou, T.; Xing, Y.; Wang, X. A Novel Metal-free Method for the Selenocyanation of Aromatic Ketones to Afford α-Carbonyl Selenocyanates. *Org. Biomol. Chem.* **2017**, *15*, 4464−4467.

(18) Yang, Z.; He, J.; Wei, Y.; Li, W.; Liu, P.; Zhao, J.; Wei, Y. NCS-promoted Thiocyanation and Selenocyanation of Pyrrolo*[1,2-a]* quinoxalines. *Org. Biomol. Chem.* **2020**, *18*, 9088−9094.

(19) Zhu, Y.-S.; Xue, Y.; Liu, W.; Zhu, X.; Hao, X.-Q.; Song, M. -P. Temperature-Controlled Chalcogenation and Chalcogenocyanation of Imidazopyridines in Water under Transition Metal-Free Conditions. *J. Org. Chem.* **2020**, *85*, 9106−9116.

(20) Marpna, I. D.; Wanniang, K.; Lipon, T. M.; Shangpliang, O. R.; Myrboh, B. elenocyanation of Aryl and Styryl Methyl Ketones in the Presence of Selenium Dioxide and Malononitrile: An Approach for the Synthesis of α-Carbonyl Selenocyanates. *J. Org. Chem.* **2021**, *86*, 1980−1986.

(21) (a) Ali, D.; Panday, A. K.; Choudhury, L. H. Hydrogen Peroxide-Mediated Rapid Room Temperature Metal-Free C(sp^2)-H Thiocyanation of Amino Pyrazoles, Amino Uracils, and Enamines. *J. Org. Chem.* **2020**, *85*, 13610−13620. (b) Ali, D.; Parvin, T.; Choudhury, L. H. Visible Light-Mediated C(sp^2)−H Selenylation of Amino Pyrazole and Amino Uracils in the Presence of Rose Bengal as an Organophotocatalyst. *J. Org. Chem.* **2022**, *87*, 1230−1239.

(22) Chandran, R.; Pise, A.; Shah, S. K.; Rahul, D.; Suman, V.; Tiwari, K. N. Synthesis of Alkynyl Sulfides by Copper-Catalyzed Thiolation of Terminal Alkynes Using Thiosulfonates. *Org. Lett.* **2020**, *22*, 6557−6561.

https://doi.org/10.1021/acsomega.3c02769
ACS Omega 2023, 8, 25349−25357