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Synthesis of 4-Functionalized Pyrazoles via Oxidative Thio/selenocyanation Mediated by $PhICl_2$ and NH_4SCN/KSeCN

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Abstract

A series of 4-thio/selenocyanated pyrazoles were conveniently synthesized from 4-unsubstituted pyrazoles using NH_4SCN/KSeCN as thio/selenocyanogen sources and $PhICl_2$ as the hypervalent iodine oxidant. This metal-free approach was postulated to involve the *in situ* generation of the reactive thiocyanogen chloride (Cl-SCN/SeCN) from the reaction of $PhICl_2$ and NH_4SCN/KSeCN, followed by an electrophilic thio/selenocyanation of pyrazole skeleton.

Keywords

$PhICl_2$; pyrazoles; thiocyanation, selenocyanation, thiocyanogen chloride

Introduction

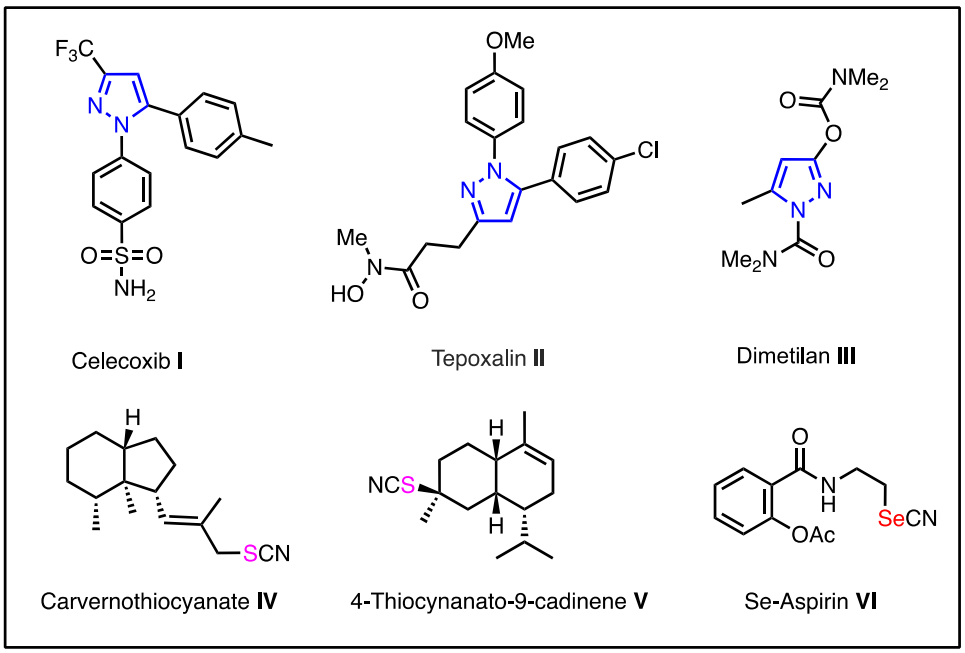
Pyrazoles and their derivatives are an important class of five-membered heterocyclic compounds [1-5] that have drew increasing attention from organic chemists, due to their potential biological and pharmaceutical properties including anti-inflammatory [6], antiviral [7], antibacterial [8], antifungal [9], cytotoxic [10], antioxidant [11] and analgesic [12] activities. For instance, Celecoxib (**I**, Scheme 1) (for treating rheumatoid arthritis and osteoarthritis), Tepoxalin (**II**, Scheme 1) (a veterinary painkiller used to relieve pain from muscle and bone diseases), Dimetilan (**III**, Scheme 1) (demonstrating excellent insecticidal effect) [13-15] all possess pyrazole framework in their respective chemical structure. Considering the pharmaceutical significance of pyrazole compounds, there has been growing interest in the development of efficient strategies for accessing functionalized pyrazole derivatives.

Thio/selenocyano are important functional groups widely existing in the core structural motifs of various natural products and pharmaceutical agents [16-20]. Many S/SeCN-containing bioactive small molecules have been proved to possess wide-ranging biological activities. Specifically, representative examples include cadinene (**V** Scheme 1) and carvernothiocyanate (**IV** Scheme 1), which are both isolated from marine natural products and possess significant antifungal and antifouling effects on *Barnacle Larvae* [21-22]. In addition, Se-Aspirin (**VI** Scheme 1) has been used as an effective anti-inflammatory pharmaceuticals [23]. On the other hand, organic thiocyanates usually are served as useful synthetic intermediates that could be conveniently converted to sulfur-containing derivatives including sulfides [24],

disulfides [25], thiocarbamates [26] and trifluoromethyl thioethers [27]. Likewise, selenocyanates can be used as versatile precursors for the synthesis of a variety of selenium-containing compounds [28-32].

As the S/SeCN-containing organic compounds play an important role in organic and medicinal chemistry, organic chemists have devoted a great deal of efforts to developing efficient thio/selenocyanation approaches [33-41]. Specifically, a plethora of synthetic strategies have been reported for thiocyanation of heteroaromatic compounds including arenes, indoles, carbazoles, pyrroles and imidazopyridines [42-45]. However, the electrophilic thiocyanation of the biologically important pyrazoles have been less explored [46-48]. Among them, the majority of the reported methods underwent the radical pathway, with the SCN radical generated by the reaction of the thiocyanate source with the corresponding oxidant (Scheme 2a-c) [49]. For examples, Xu reported that a series of 4-thiocyanated 5-hydroxy-1*H*-pyrazoles were synthesized by $K_2S_2O_8$-promoted direct thiocyanation of pyrazolin-5-ones at room temperature, using NH_4SCN as thiocyanogen source (Scheme 2a) [20]. Similarly, utilizing NH_4SCN and $K_2S_2O_8$, Yotphan and colleagues realized direct thiocyanation of *N*-substituted pyrazolones under metal-free conditions [49]. Besides, Choudhury and co-workers developed an additive- and metal-free methodology for the C-H thiocyanation of amino pyrazoles, using H_2O_2 as a benign oxidizing agent (Scheme 2b) [41]. Pan presented a method for C-H thiocyanation of pyrazoles by using a sustainable catalyst of graphite-phase carbon nitride (*g*-C_3N_4) under visible light irradiation (Scheme 2c) [2]. Furthermore, Yao harnessed an electrochemical approach to form the electrophilic SCN^+ intermediate, which reacted with pyrazoles to give the corresponding thiocyanated pyrazoles (Scheme 2d) [50]. However, to our knowledge, there is few reports on the electrophilic selenocyanation of heterocycles [51-53] including the

biologically important pyrazoles. In this regard, it should be highly desirable to develop an efficient method for a smooth selenocyanation of pyrazole compounds.

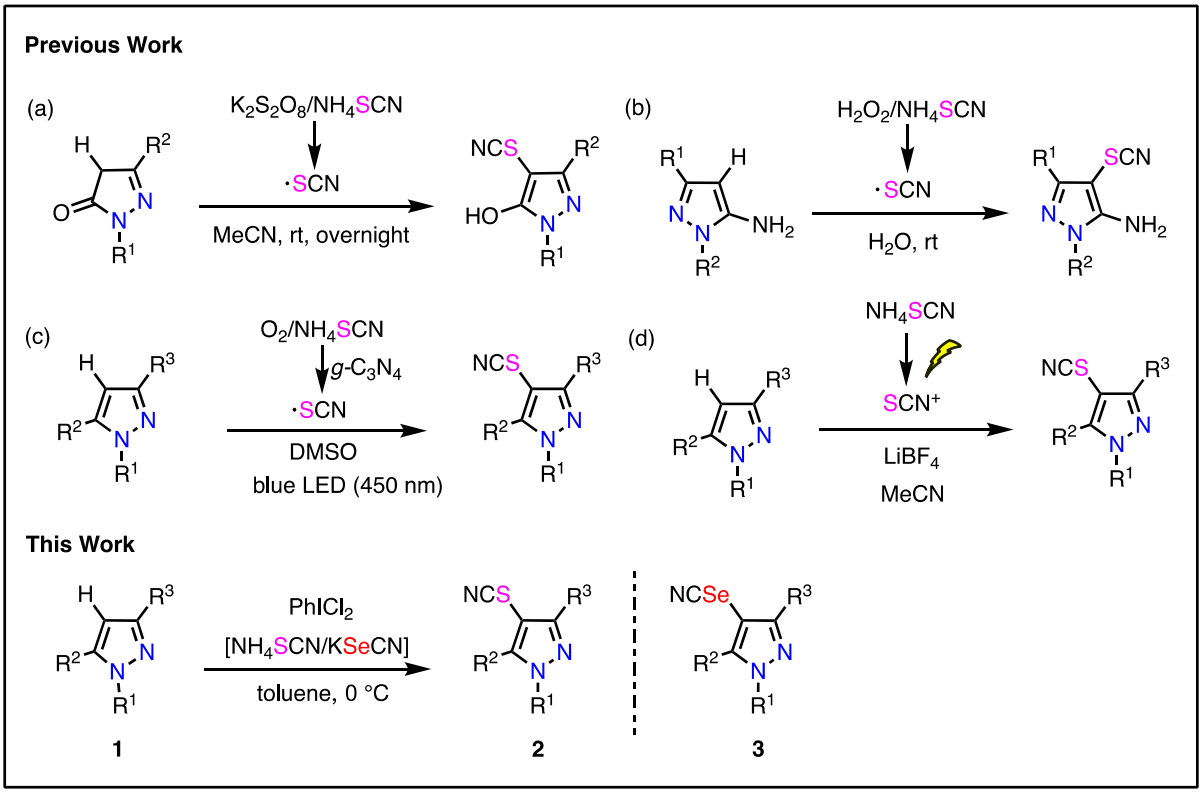


Scheme 1: Representative Pyrazoles with Pharmacological Activities and S/Se-Containing Pharmaceuticals Molecule.

Results and Discussion

Our previous work reported that regioselective C-5 thiocyanation of the 2-pyridone skeleton could be realized via a $PhICl_2$-mediated electrophilic thiocyanation approach [54]. Inspired by this previous work, we were interested at investigating whether a direct C-4 selenocyanation as well as thiocyanation of pyrazole skeleton could be realized using the same protocol. At the outset of the study, 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**1a**) (1 equiv) was chosen as the model substrate to react with NH_4SCN (1 equiv) and $PhICl_2$ (1 equiv) in THF at 0 ^oC under N_2 atmosphere. To our delight, the desired thiocyanated product **2a** was obtained in 68% yield (Table 1, entry 1). Encouraged by this result, we proceeded to investigate the other parameters that would possibly affect the efficiency of the reaction. First, upon a comparison of different reaction

temperatures, we found that the reaction operating at 0 °C gave the best result (Table 1, entries 1-3). Then, other SCN-containing inorganic salts including KSCN, AgSCN and CuSCN were screened, and the results showed that none of them gave better results than NH_4SCN (Table 1, entries 4-6). Next, the other oxidants including phenyliodine(III) diacetate (PIDA), phenyliodine(III) bis(trifluoroacetate) (PIFA), iodosobenzene (PhIO) and NCS were applied, the results indicated that $PhICl_2$ was

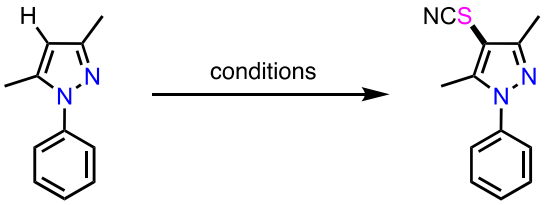


Scheme 2: Approaches for Thio/selenocyanation of Pyrazole Skeleton.

the most effective one (Table 1, entries 7-10). Later on, when the dosage of $PhICl_2$ and NH_4SCN was increased to 2.0 equivalents, the yield of product **2a** could increase significantly to 82% (Table 1, entry 11). However, while the loading of $PhICl_2$ and NH_4SCN were further improved to 3.0 equivalents, the reaction did not afford a better outcome (Table 1, entry 12). Furthermore, solvent screening showed that toluene was the most appropriate solvent, while the reaction led to a much lower yield in each case when DMF, MeOH, MeCN and DCM were used as solvents (Table 1, entries 13-17).

On the basis of the above experimental results, the optimized conditions for the thiocyanation of the model substrate were concluded to be: 2.0 equivalents of $PhICl_2$ and NH_4SCN in toluene at 0 ^oC, under N_2 atmosphere (Table 1, entry 17).

Table 1: Optimization of oxidative thiocyanation of pyrazole.[a]

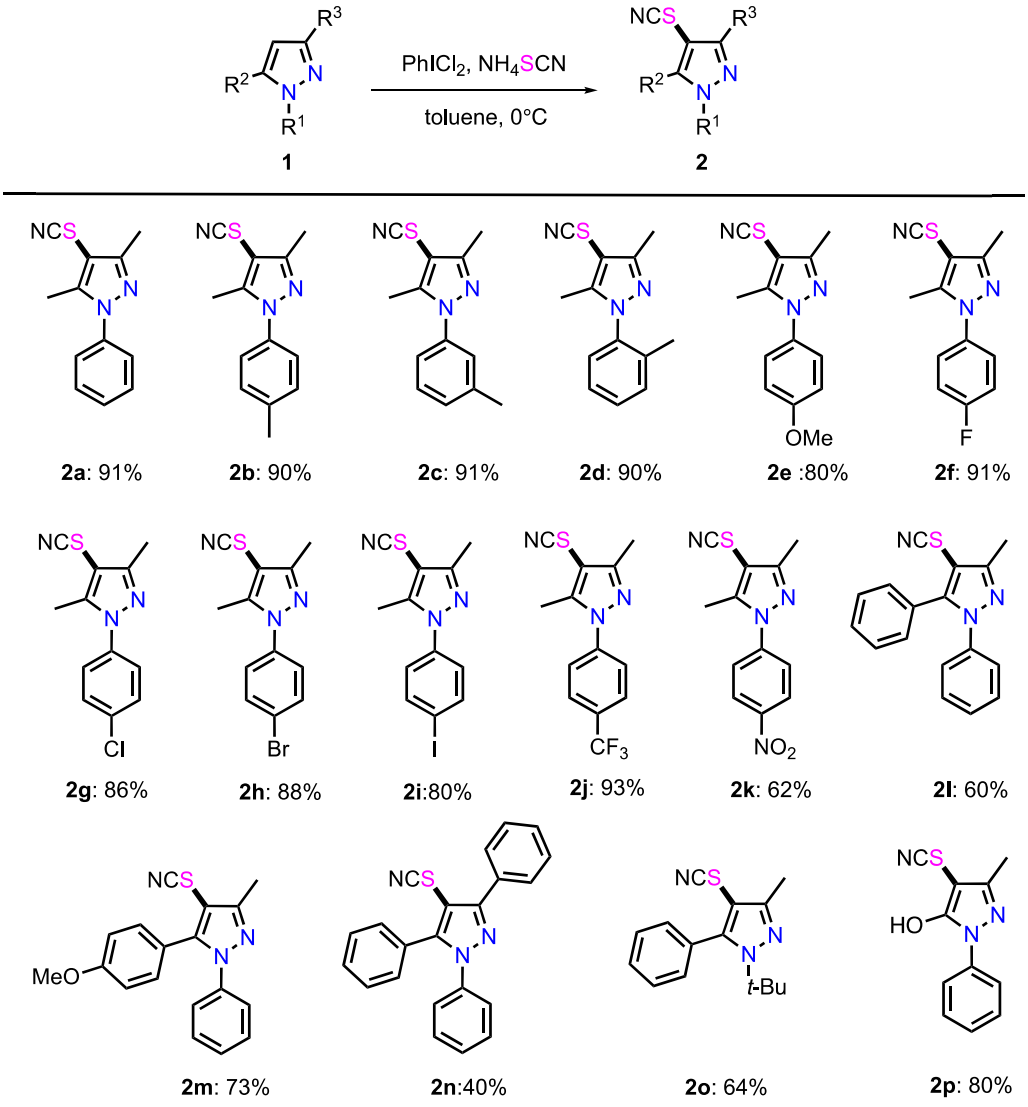


1a **2a**

Entry	Oxidant (equiv)	[SCN] (equiv)	Solvent	T (^oC)	Yield(%)[b]
1	$PhICl_2$ (1.0)	NH_4SCN (1.0)	THF	0	68
2	$PhICl_2$ (1.0)	NH_4SCN (1.0)	THF	25	43
3	$PhICl_2$ (1.0)	NH_4SCN (1.0)	THF	40	40
4	$PhICl_2$ (1.0)	KSCN (1.0)	THF	0	10
5	$PhICl_2$ (1.0)	AgSCN (1.0)	THF	0	15
6	$PhICl_2$ (1.0)	CuSCN (1.0)	THF	0	12
7	PIDA (1.0)	NH_4SCN (1.0)	THF	0	NR[c]
8	PIFA (1.0)	NH_4SCN (1.0)	THF	0	NR
9	PhIO (1.0)	NH_4SCN (1.0)	THF	0	NR
10	NCS (1.0)	NH_4SCN (1.0)	THF	0	ND[d]
11	$PhICl_2$ (2.0)	NH_4SCN (2.0)	THF	0	82
12	$PhICl_2$ (3.0)	NH_4SCN (3.0)	THF	0	80
13	$PhICl_2$ (2.0)	NH_4SCN (2.0)	DMF	0	NR
14	$PhICl_2$ (2.0)	NH_4SCN (2.0)	MeOH	0	10
15	$PhICl_2$ (2.0)	NH_4SCN (2.0)	MeCN	0	58
16	$PhICl_2$ (2.0)	NH_4SCN (2.0)	DCM	0	55
17	**$PhICl_2$ (2.0)**	**NH_4SCN (2.0)**	**toluene**	**0**	**91**

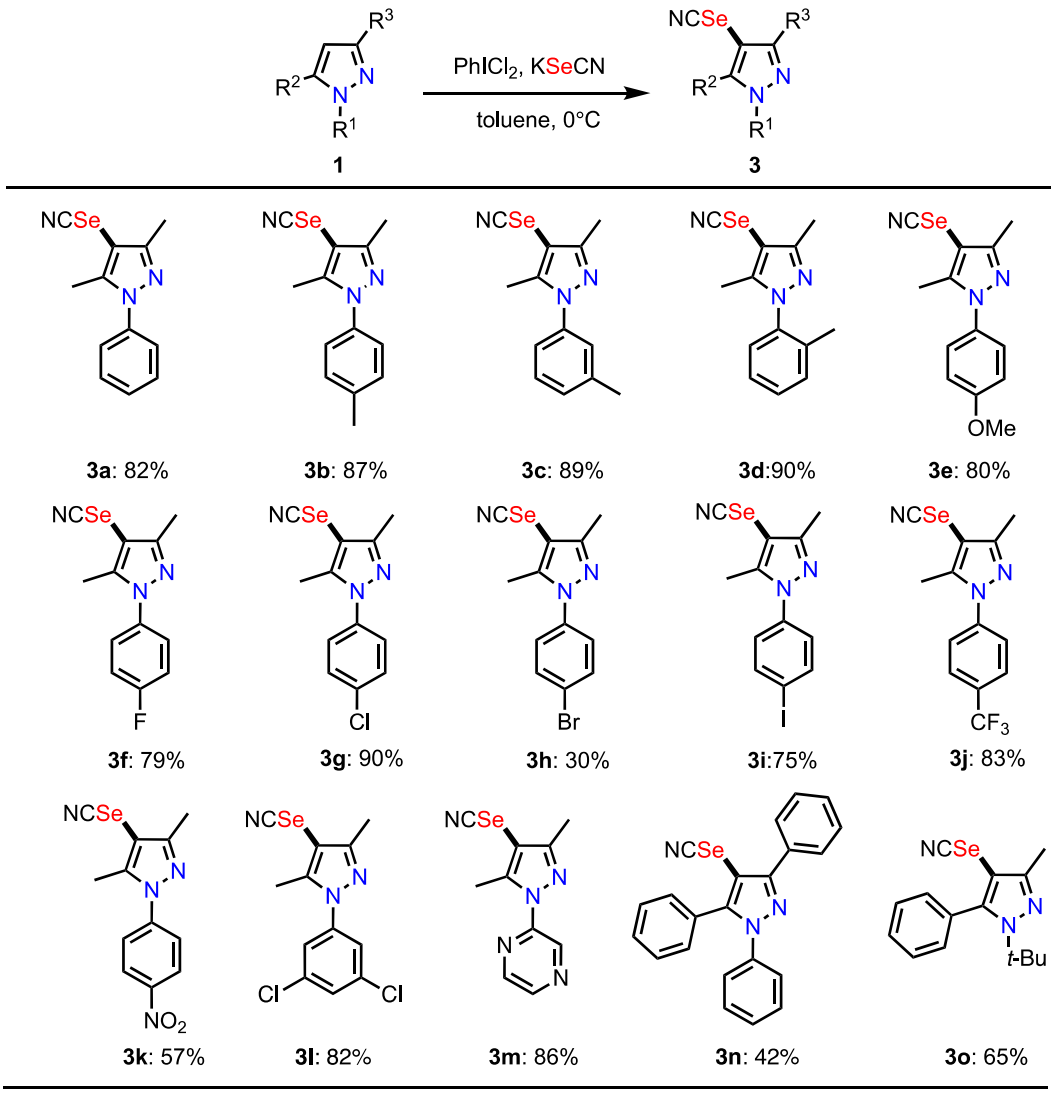
[a] Reaction conditions: under N_2 atmosphere, a mixture of oxidant and [SCN] in solvent (2 mL) was stirred at 0 °C for 0.5 h, then **1a** (0.20 mmol) was added, stirred at 0 °C for 8 h. [b] Yield of the isolated product. [c] NR = no reaction. [d] ND = no desired product.

With the optimized reaction conditions in hand, the substrate scope of this thiocyanation approach was first investigated (Scheme 3). The results showed that the newly established $PhICl_2$/NH_4SCN protocol was suitable for a wide range of substrates. Specifically, when *N*-aryl substrates containing electron-donating groups (-Me, -OMe) were subjected to the standard reaction conditions, the corresponding products (**2b-e)** were obtained in good yields (80-91%). It was found that there was no significant influence on the outcome of the reactions of various *N*-aryl substituted pyrazoles with



Scheme 3: $PhICl_2$/NH_4SCN-Mediated Thiocyanation of Pyrazoles. Reaction conditions: under N_2 atmosphere, a mixture of $PhICl_2$ (2.00 mmol) and NH_4SCN (2.00 mmol) in toluene (5 mL) was stirred at 0 °C for 0.5 h, then **1a** (1.00 mmol) was added, stirred at 0 °C for 8 h. Isolated yields are given.

the methyl group substituted at the *ortho*-, *meta*- or *para*- positions of the phenyl group. Next, *N*-aryl substrates bearing electron-withdrawing groups (-F, -Cl, -Br, -I, $-CF_3$, $-NO_2$) were tested, and the desired products **2f-k** could be conveniently obtained in moderate to good yield. Notably, the reaction of substrate bearing $-CF_3$ group afforded the corresponding product in 93% yield **2j**. However, substrate possessing a $-NO_2$ substituent gave an inferior yield **2k**. Then, we proceeded to investigate the effects of



Scheme 4: $PhICl_2$/KSeCN-Mediated Thiocyanation of Pyrazoles. Reaction conditions: under N_2 atmosphere, a mixture of $PhICl_2$ (2.00 mmol) and KSeCN (2.00 mmol) in toluene (5 mL) was stirred at 0 °C for 0.5 h, then **1a** (1.00 mmol) was added, stirred at 0 °C for 8 h. Isolated yields are given.

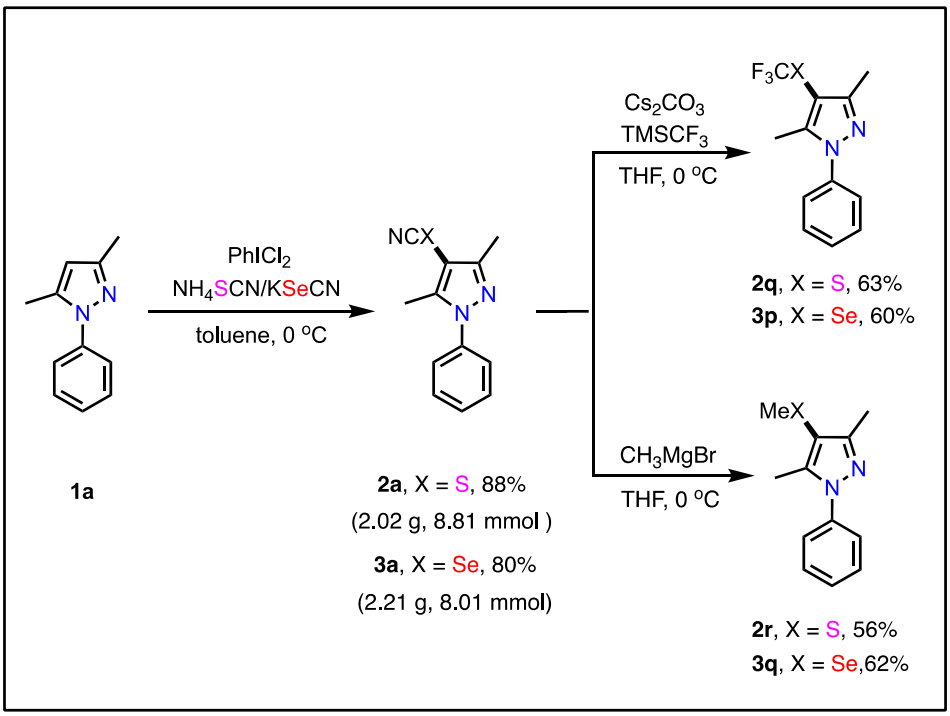
different R^2 substituent. When the methyl substituent (R^2) was replaced with an aryl group, the corresponding thiocyanated products **2l-o** could be afforded in acceptable to moderate yield. On the other hand, the method was equally applicable to substrate bearing two aryl substituents (R^2 & R^3), albeit the reaction afforded product **2n** in a much lower yield, possibly caused by the steric congestion. In addition, when the aryl

substituent of R^1 was replaced with a *tert*-butyl group, this method also worked well to give product **2o** in moderate yield. Strikingly, the thiocyanation of the pharmaceutically active edaravone could also be realized by the method, affording the corresponding product **2p** in good yield.

Next, we turned our attention to the feasibility of applying this protocol for the selenocyanation of pyrazole skeleton (Scheme 4). Gratifyingly, the method was equally applicable to selenocyanation of pyrazoles bearing various substituent, with the corresponding selenocyanated products **3a-o** achieved in acceptable to good yields. Disappointingly, the method was not effective for selenocyanation of edaravone as the reaction did not occur under the standard conditions (not shown).

The utility of this approach was further demonstrated by the scale-up experiment. When 10.0 mmol of compound **1a** was treated 20.0 mmol of NH_4SCN/KSeCN and $PhICl_2$ under the standard reaction conditions, the desired product **2a** and **3a** were afforded in 88% and 80% yield respectively (Scheme 5).

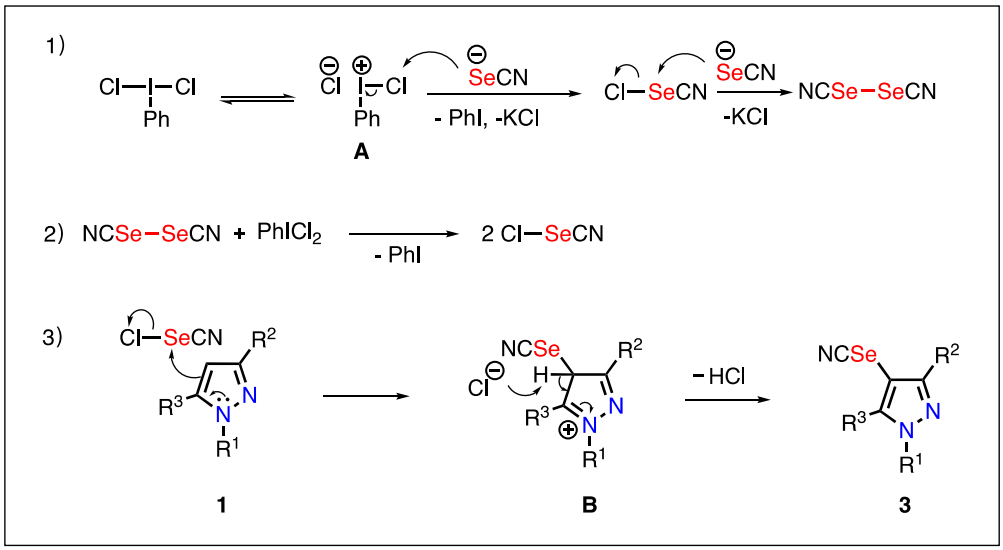
The obtained 4-thio/selenocyanated pyrazoles could be further derivatized by the known approaches. Specifically, products **2a** and **3a** could react with $TMSCF_3$ in the presence of Cs_2CO_3 [55] to give the corresponding SCF_3- and $SeCF_3$-containing compounds **2q** and **3p** in moderate yields. Moreover, products **2a** and **3a** could be



Scheme 5: Gram-Scale Synthesis and Derivatization of **2a**, **3a**.

conveniently transformed into thiomethyl and selenomethyl substituted pyrazole derivatives **2r** and **3q** by treatment with CH_3MgBr in THF [56] (Scheme 5).

Based on the previous reports [54,57-58], a possible mechanism of this selenocyanation reaction was proposed (Scheme 6). First, the reaction of $PhICl_2$ with KSeCN produced selenocyanogen chloride (Cl-SeCN), which further reacted with thiocyanate to give $(SeCN)_2$. Next, $(SeCN)_2$ was converted to reactive selenocyanogen chloride (Cl-SeCN) by reacting with $PhICl_2$. Subsequently, selenocyanogen chloride underwent an electrophilic addition reaction with pyrazole **1** to give intermediate **B**, which underwent deprotonative rearomatization to give 4-selenocyanated pyrazole **3**.



Scheme 6: Plausible Reaction Mechanism.

Conclusion

In conclusion, we have accomplished the synthesis of a series of C-4 thio/selenocyanated pyrazoles via a hypervalent iodine-mediated electrophilic thio/selenocyanation approach under mild reaction conditions. Furthermore, the obtained S/SeCN-containing pyrazoles can be converted to S/$SeCF_3$- and S/SeMe-containing pyrazole derivatives. Further investigation on the synthetic utility of this approach is still ongoing in our lab.

Supporting Information

Supporting Information File 1: Synthetic details and compound characterization data.

Acknowledgements

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References

1. Sangani, C. B.; Mungra, D. C.; Patel, M. P.; Patel, R. G. *Chin. Chem. Lett.* **2012,** *23*, 57-60.
2. Pan, J.; Liu, C.; Wang, J.; Dai, Y.; Wang, S.; Guo, C. *Tetrahedron Lett.* **2021,** *77*, 153253.
3. Mamaghani, M.; Hossein Nia, R.; Shirini, F.; Tabatabaeian, K.; Rassa, M. *Med. Chem. Res.* **2015,** *24*, 1916-1926.
4. El-Sabbagh, O. I.; Baraka, M. M.; Ibrahim, S. M.; Pannecouque, C.; Andrei, G.; Snoeck, R.; Balzarini, J.; Rashad, A. A. *Eur. J. Med. Chem.* **2009,** *44*, 3746-3753.
5. Li, G.; Cheng, Y.; Han, C.; Song, C.; Huang, N.; Du, Y. *RSC Med. Chem.* **2022,** *13*, 1300-1321.
6. Gawad, N. M. A.-E.; Georgey, H. H.; Ibrahim, N. A.; Amin, N. H.; Abdelsalam, R. M. *Arch. Pharm. Res.* **2012,** *35*, 807-821.
7. Ouyang, G.; Cai, X.-J.; Chen, Z.; Song, B.-A.; Bhadury, P. S.; Yang, S.; Jin, L.-H.; Xue, W.; Hu, D.-Y.; Zeng, S. *J. Agric. Food Chem.* **2008,** *56*, 10160-10167.
8. Lupsor, S.; Aonofriesei, F.; Iovu, M. *Med. Chem. Res.* **2012,** *21*, 3035-3042.
9. Mert, S.; Kasımoğulları, R.; İça, T.; Çolak, F.; Altun, A.; Ok, S. *Eur. J. Med. Chem.* **2014,** *78*, 86-96.
10. Hassan, G. S.; Kadry, H. H.; Abou-Seri, S. M.; Ali, M. M.; Mahmoud, A. E. E.-D. *Bioorg. Med. Chem.* **2011,** *19*, 6808-6817.
11. Rangaswamy, J.; Kumar,V. H.; Harini, S. T.; Naik, N. *Bioorg. Med. Chem. Lett.* **2012,** *22*, 4773-4777.

12. Palaska, E.; Aytemir, M.; Uzbay, İ. T.; Erol, D. *Eur. J. Med. Chem.* **2001,** *36*, 539-543.
13. Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013,** *113*, 2958-3043.
14. Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman, S. *New J. Chem.* **2017,** *41*, 16-41.
15. Kang, E.; Kim, H. T.; Joo, J. M. *Org. Biomol. Chem.* **2020,** *18*, 6192-6210.
16. Yasman; Edrada, R. A.; Wray, V.; Proksch, P. *J. Nat. Prod.* **2003,** *66*, 1512-1514.
17. Brown, S. P.; Smith, A. B. *J. Am. Chem. Soc.* **2015,** *137*, 4034-4037.
18. Lawson, A. P.; Long, M. J. C.; Coffey, R. T.; Qian, Y.; Weerapana, E.; El Oualid, F.; Hedstrom, L. *Cancer Res.* **2015,** *75*, 5130-5142.
19. Yang, H.; Duan, X.-H.; Zhao, J.-F.; Guo, L.-N. *Org. Lett.* **2015,** *17*, 1998-2001.
20. Mao, X.; Ni, J.; Xu, B.; Ding, C. *Org. Chem. Front.* **2020,** *7*, 350-354.
21. He, H. Y.; Faulkner, D. J.; Shumsky, J. S.; Hong, K.; Clardy, J. *J. Org. Chem.* **1989,** *54*, 2511-2514.
22. Hirota, H.; Tomono, Y.; Fusetani, N. *Tetrahedron* **1996,** *52*, 2359-2368.
23. Plano, D.; Karelia, D. N.; Pandey, M. K.; Spallholz, J. E.; Amin, S.; Sharma, A. K. *J. Med. Chem.* **2016,** *59*, 1946-1959.
24. Nguyen, T.; Rubinstein, M.; Wakselman, C. *J. Org. Chem.* **1981,** *46*, 1938-1940.
25. Prabhu, K. R.; Ramesha, A. R.; Chandrasekaran, S. *J. Org. Chem.* **1995,** *60*, 7142-7143.
26. Riemschneider, R.; Wojahn, F.; Orlick, G. *J. Am. Chem. Soc.* **1951,** *73*, 5905-5907.
27. Goossen, L.; Matheis, C.; Wang, M.; Krause, T. *Synlett* **2015,** *26*, 1628-1632.
28. Hiroyuki, H.; Tetsuo, O.; Fumio, O.; Hachiro, Y.; Yoshiteru, S.; Soichi, M. *Bull. Chem. Soc. Jpn.* **1982,** *55*, 182-187.
29. Mullen, G. P.; Luthra, N. P.; Dunlap, R. B.; Odom, J. D. *J. Org. Chem.* **1985,** *50*, 811-816.
30. Krief, A.; Dumont, W.; Delmotte, C. *Angew. Chem. Int. Ed.* **2000,** *39*, 1669-1672.

31. Yu, F.; Li, C.; Wang, C.; Zhang, H.; Cao, Z.-Y. *Org. Lett.* **2021,** *23*, 7156-7160.
32. Tao, S.; Jiang, L.; Du, Y. *Asian. J. Org. Chen.* **2022,** *11*, e202200595.
33. Barbero, M.; Degani, I.; Diulgheroff, N.; Dughera, S.; Fochi, R. *Synthesis* **2001,** *2001*, 0585-0590.
34. Sun, N.; Che, L.; Mo, W.; Hu, B.; Shen, Z.; Hu, X. *Org. Biomol. Chem.* **2015,** *13*, 691-696.
35. Fujiki, K.; Yoshida, E. *Synth. Commun.* **1999,** *29*, 3289-3294.
36. Takagi, K.; Takachi, H.; Sasaki, K. *J. Org. Chem.* **1995,** *60*, 6552-6556.
37. Teng, F.; Yu, J.-T.; Yang, H.; Jiang, Y.; Cheng, J. *Chem. Commun.* **2014,** *50*, 12139-12141.
38. Yang, X.; She, Y.; Chong, Y.; Zhai, H.; Zhu, H.; Chen, B.; Huang, G.; Yan, R. *Adv. Synth. Catal.* **2016,** *358*, 3130-3134.
39. Zhang, X.-Z.; Ge, D.-L.; Chen, S.-Y.; Yu, X.-Q. *RSC Adv.* **2016,** *6*, 66320-66323.
40. Jiang, G.; Zhu, C.; Li, J.; Wu, W.; Jiang, H. *Adv. Synth. Catal.* **2017,** *359*, 1208-1212.
41. Ali, D.; Panday, A. K.; Choudhury, L. H. *J. Org. Chem.* **2020,** *85*, 13610-13620.
42. Khalili, D. *New J. Chem.* **2016,** *40*, 2547-2553.
43. Fotouhi, L.; Nikoofar, K. *Tetrahedron Lett.* **2013,** *54*, 2903-2905.
44. Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004,** *45*, 2951-2954.
45. Yadav, J. S.; Reddy, B. V. S.; Krishna, A. D.; Reddy, C. S.; Narsaiah, A. V. *Synthesis* **2005,** *2005*, 961-964.
46. Thiruvikraman, S. V.; Seshadri, S. *Bull. Chem. Soc. Jpn.* **1985,** *58*, 785-786.
47. Kokorekin, V. A.; Sigacheva, V. L.; Petrosyan, V. A. *Tetrahedron Lett.* **2014,** *55*, 4306-4309.
48. Finar, I. L.; Godfrey, K. E. *J. Am. Chem. Soc.* **1954**, 2293-2298.

49. Kittikool, T.; Yotphan, S. *Eur. J. Org. Chem.* **2020,** *2020*, 961-970.
50. Zhang, Y.; Xu, S.; Zhu, Y.; Xu, Q.; Gao, H.; Liang, Z.; Yao, X. *Eur. J. Org. Chem.* **2023,** *26*, e202201278.
51. Dey, A.; Hajra, A. *Adv. Synth. Catal.* **2019,** *361*, 842-849.
52. Chen, X.-Y.; Kuang, X.; Wu, Y.; Zhou, J.; Wang, P. *Chin. J. Chem.* **2023,** *41*, 1979-1986.
53. Zhang, X.; Wang, C.; Jiang, H.; Sun, L. *RSC Adv.* **2018,** *8*, 22042-22045.
54. Tao, S.; Xiao, J.; Li, Y.; Sun, F.; Du, Y. *Chin. J. Chem.* **2021,** *39*, 2536-2546.
55. Jouvin, K.; Matheis, C.; Goossen, L. J. *Chem. Eur. J.* **2015,** *21*, 14324-14327.
56. Adams, R.; Bramlet, H. B.; Tendick, F. H. *J. Am. Chem. Soc.* **1920,** *42*, 2369-2374.
57. Ito, Y.; Touyama, A.; Uku, M.; Egami, H.; Hamashima, Y. *Chem. Pharm. Bull.* **2019,** *67*, 1015-1018.
58. Tao, S.; Huo, A.; Gao, Y.; Zhang, X.; Yang, J.; Du, Y. *Front. Chem.* **2022,** *10*, 859995.