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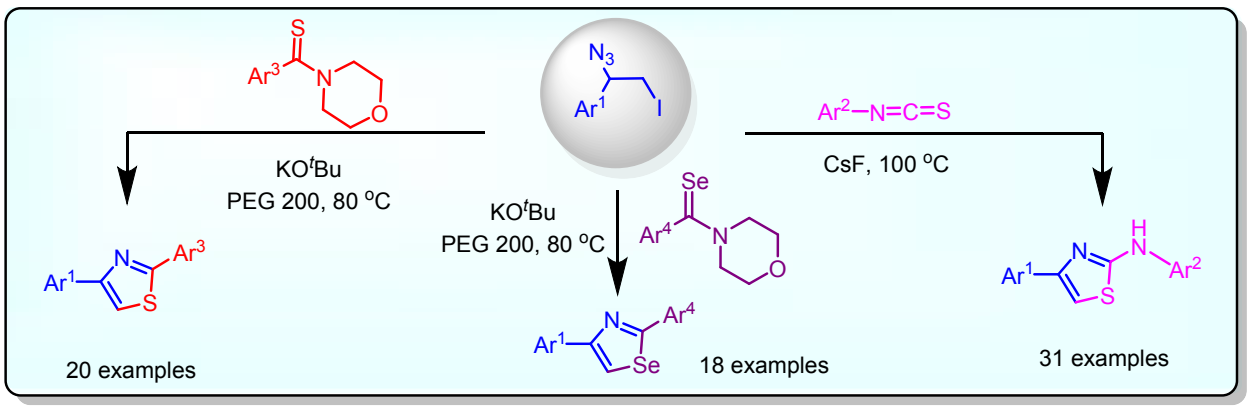

Aryliodoazide Synthons: A Different Approach for Diversified Synthesis of 2-Aminothiazole, 1,3-Thiazole and 1,3-Selenazole Scaffolds

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ABSTRACT: Several straightforward and practical processes have been established for the construction of 2-aminothiazoles, 1,3-thiazoles and 1,3-selenazoles from aryliodoazides. These strategies successfully proceed with a wide spectrum of substituted thioamides and its derivatives producing the resulting five-membered heterocycles obtained in satisfactory yields. The unique features of these protocols are operational simplicity, and highly functional group tolerance that make them convenient and practical routes for the preparation of various libraries of 2-aminothiazoles, 1,3-thiazoles and 1,3-selenazoles.

KEYWORDS: *Iodoazide; Isothiocyanate; 2-Aminothiazole; 1,3-Thiazole; 1,3-Selenazole; Thioamide; Selenoamide*

Over the past decade, 1,3-thiazoles especially 2-amino-1,3-thiazoles were widely recognized as a vital, five-membered heterocycles. The 1,3-thiazole motif is one of the backbones of many bioactive natural products, such as vitamin B1 (thiamine),[1] micrococcin,[2] and thiostrepton.[3] Thiazole containing compounds are known for their broad medicinal and biological activities, including antitumor,[4] anticancer,[5] antiviral,[6] anti-inflammatory,[7] antitubercular,[8] antibacterial,[9] antifungal,[10] antimalarial,[11] antihypertensive,[12] and anti-HIV (Figure **1, A**).[13]

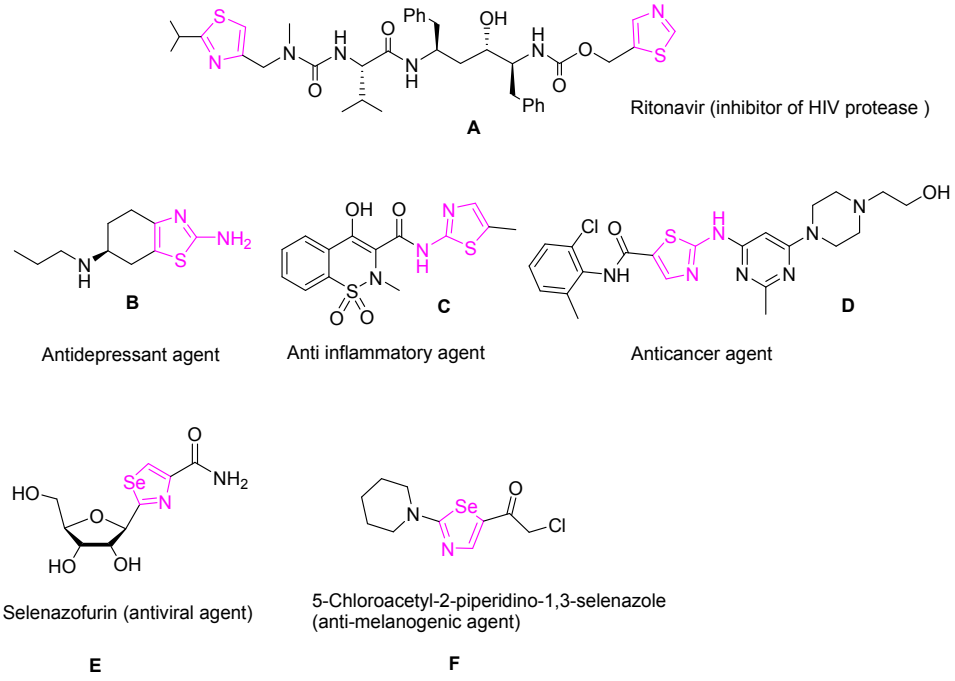


Figure 1. Selected examples of biologically active and medicinal thiazole and selenazole containing molecules.

Furthermore, 2-aminothiazole as a derivative of this azoles, exhibits various medicinal and biological activities which have been utilized widely in the treatment of depression (Figure **1**, **B**),[14] inflammation (Figure **1**, **C**),[15] schizophrenia,[16] tuberculosis,[17] Parkinson's disease,[18] ulcers,[19] and

HIV infections.[20] Moreover, some of them have shown potent anti-tumor and anti-cancer activities (Figure **1**, **D**).[21] On the other hand, 1,3-selenazoles, as seleno-analoges of 1,3-thiazoles, have also been studied extensively due to their potential pharmacological and biological behaviours including antibacterial,[22] antitumor,[23] anticancer,[24] antimicrobial,[25] antiviral,[26] and anti-melanogenic activity (Figure **1**, **E** and **F**).[27]

In spite of the significance and the unique behaviors of these compounds, limited synthetic approaches have been introduced for the preparation of these scaffolds in the literature.[28] Fundamentally, the Hantzsch reaction,[29] which consists of the condensation of α-halocarbonyl with thioamides or selenoamides, is the main path for the synthesis of these heterocycles. Despite widespread use of this approach, it suffers from utilizing hazardous solvents, harsh reaction conditions, low diversity and/or expensive starting materials.[28,29] Therefore, devising a new and practical alternative protocol for the synthesis of diverse thiazoles and its derivatives to overcome these problems is highly desirable.

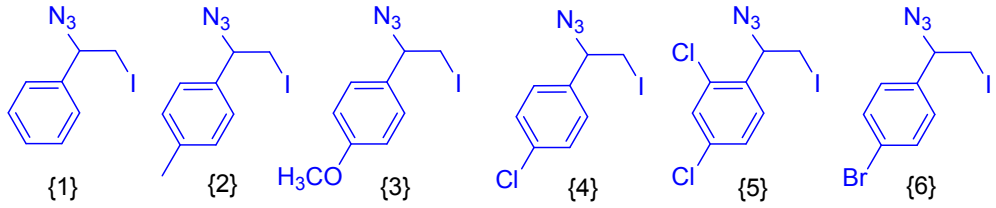
Among the numerous nitrogen sources, haloazides, specifically iodoazides, have attracted attention as an effective compound for the C–N bond formation. These precursors have been utilized as useful synthons to prepare a new class of nitrogen-containing molecules such as vinyl azides,[30] triazoles,[31] *N*-vinyl amides,[32] pyrroles and pyridines.[33] The iodoazide scaffold could be obtained via azidoiodination of olefins utilizing I_2–NaN_3,[34] $PhI(OAc)_2/TMSN_3/Et_4NI$,[35] $IPy_2BF_4/TMSN_3$,[36] NaN_3/NaI/CAN[37] and NaN_3/KI/oxone/wet Al_2O_3.[38]

To circumvent the challenges of the current synthetic methods of these useful heterocycles, we developed a practical strategy for the preparation of azoles through a base-promoted reaction of aryliodoazides.

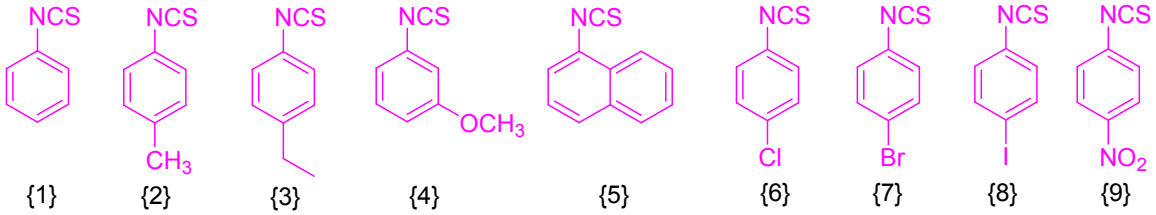
The synthesis of 2-aminothiazoles was the first target. The simplest aryliodoazide, 1-(1-azido-2-iodoethyl)benzene **1**{*1*}, and phenyl isothiocyanate **2**{*1*} were used to optimize reaction conditions and screen solvent and base effects (**SI**, Table S1).

With the optimized reaction conditions in hand, we probed the efficiency and generality of this protocol using a series of aryl iodoazides and isothiocyanates as shown in Figure 2.

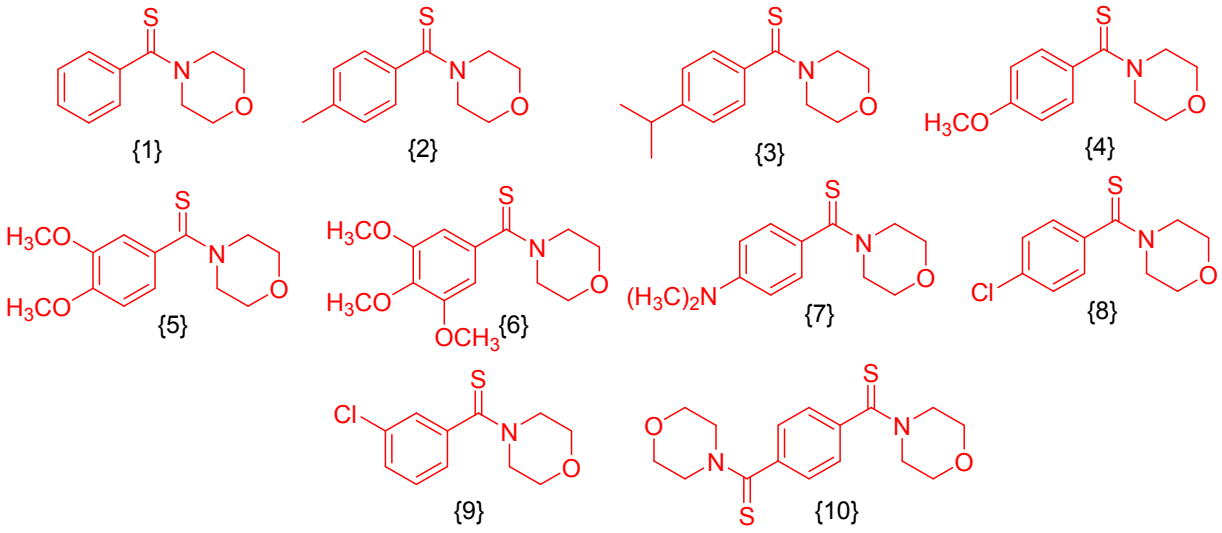
Iodoazides 1:



Isothiocyanates 2:



Thioamides 4:



Selenoamides 5:

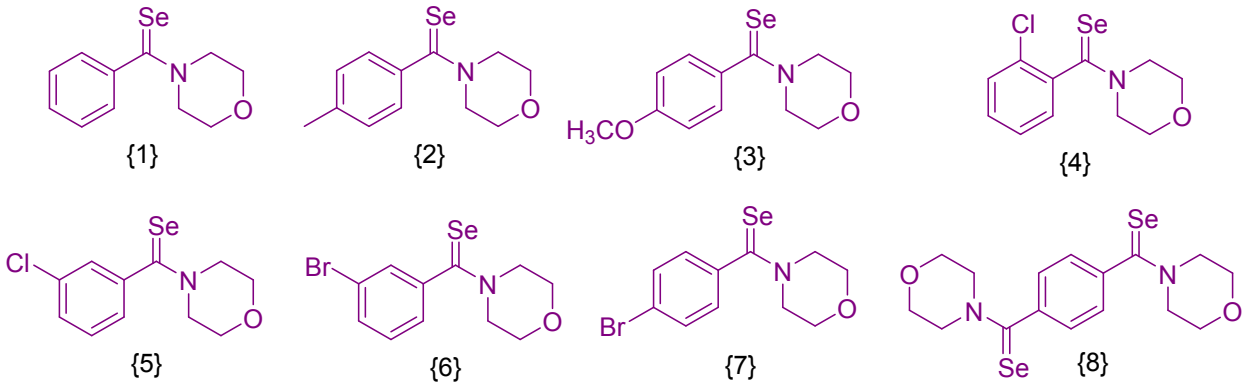
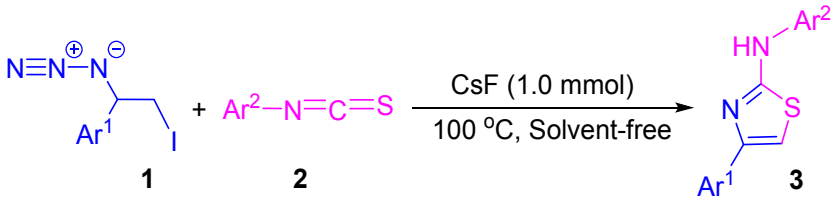


Figure 2. The diversity of reagents screened.

As shown in Table 1, various aryliodozides **1** with functionalized Ar^1 were applied to study the substrate scope. Although both electron-withdrawing and electron-donating moieties on the iodoazide had little effect on the overall reaction, better results were achieved in the presence of electron-rich substituents. Additionally, it was observed that regardless of the presence of either electron-donating or electron-withdrawing groups all arylisothiocyanates screened produced the desired product in good yields.

Table 1. Synthesis of 2-Aminothiazoles from Various Iodoazides and Isothiocyanates[a]



Entry	Compounds	Ar^1	Ar^2	Yield[b] (%)
1	**3**{*1,1*}	C_6H_5	C_6H_5	67
2	**3**{*1,2*}	C_6H_5	4-MeC_6H_4	65
3	**3**{*1,6*}	C_6H_5	4-ClC_6H_4	69
4	**3**{*1,7*}	C_6H_5	4-BrC_6H_4	70
5	**3**{*1,9*}	C_6H_5	4-$NO_2C_6H_4$	72
6	**3**{*2,2*}	4-MeC_6H_4	4-MeC_6H_4	65
7	**3**{*3,1*}	4-$MeOC_6H_4$	C_6H_5	69

8	**3**{*3,2*}	4-$MeOC_6H_4$	4-MeC_6H_4	68
9	**3**{*3,4*}	4-$MeOC_6H_4$	3-$MeOC_6H_4$	66
10	**3**{3,6}	4-$MeOC_6H_4$	4-ClC_6H_4	70
11	**3**{3,7}	4-$MeOC_6H_4$	4-BrC_6H_4	72
12	**3**{*4,1*}	4-ClC_6H_4	C_6H_5	64
13	**3**{*4,2*}	4-ClC_6H_4	4-MeC_6H_4	63
14	**3**{*4,3*}	4-ClC_6H_4	4-EtC_6H_4	61
15	**3**{*4,4*}	4-ClC_6H_4	3-$MeOC_6H_4$	60
16	**3**{*4,5*}	4-ClC_6H_4	1-Naphthyl	57
17	**3**{*4,6*}	4-ClC_6H_4	4-ClC_6H_4	66
18	**3**{*4,7*}	4-ClC_6H_4	4-BrC_6H_4	67
19	**3**{*5,1*}	2,4-$Cl_2C_6H_3$	C_6H_5	63
20	**3**{*5,2*}	2,4-$Cl_2C_6H_3$	4-MeC_6H_4	61
21	**3**{*5,3*}	2,4-$Cl_2C_6H_3$	4-EtC_6H_4	60
22	**3**{*5,5*}	2,4-$Cl_2C_6H_3$	1-Naphthyl	54
23	**3**{*5,6*}	2,4-$Cl_2C_6H_3$	4-ClC_6H_4	65
24	**3**{*5,7*}	2,4-$Cl_2C_6H_3$	4-BrC_6H_4	66
25	**3**{*6,1*}	4-BrC_6H_4	C_6H_5	63
26	**3**{*6,2*}	4-BrC_6H_4	4-MeC_6H_4	62
27	**3**{*6,3*}	4-BrC_6H_4	4-EtC_6H_4	60
28	**3**{*6,5*}	4-BrC_6H_4	1-Naphthyl	55
29	**3**{*6,6*}	4-BrC_6H_4	4-ClC_6H_4	65
30	**3**{*6,7*}	4-BrC_6H_4	4-BrC_6H_4	67
31	**3**{*6,8*}	4-BrC_6H_4	4-IC_6H_4	66

[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), CsF (1 mmol), were heated at 100 ^oC for 10 h. [b]Yield of isolated product.

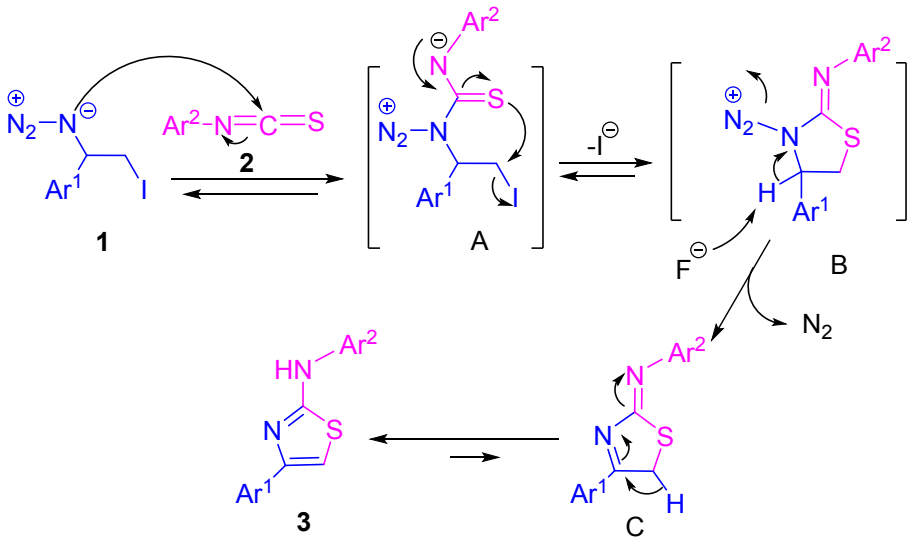
It is noteworthy that 1-naphthyl group as bulky aryl-substituents was also found to be suitable for this conversion and an acceptable quantity of the corresponding products was obtained (compounds **3**{*4,5*}, **3**{*5,5*}, and **3**{*6,5*}).

In order to investigate the selectivity in the synthesis of 2-aminothiazoles, the competition between aliphatic and aromatic isothiocyanates was also examined. Phenyl isothiocyanate, as the aromatic derivative, and benzyl isothiocyanate, as the aliphatic derivative, were reacted with 1-(1-azido-2-iodoethyl)benzene in an equimolar ratio. Under both optimal and increased temperature or reaction time, the benzyl isothiocyanate derived product was not produced. Furthermore, to explore the full scope of this procedure, we substituted phenyl isothiocyanate with phenyl isocyanate and found that the reaction failed and the phenyl isocyanate was recovered entirely. Both of these competition

reactions confirm that the electrophilicity of the *sp*-carbon could be a key factor for this transformation.

Based on the observed results, a plausible mechanism was suggested in Scheme 1. First, the azide group of iodoazide **1** attacks to isothiocyanate **2** to form intermediate **A** which undergoes an intramolecular addition generating intermediate **B**. Subsequently, intermediate **B** is converted to intermediate **C** by releasing N_2 via the abstraction of benzylic hydrogen with F^- as a base. Eventually, the desired product is generated by tautomerization of **C**.

Scheme 1. Proposed Mechanism for the Synthesis of 3.

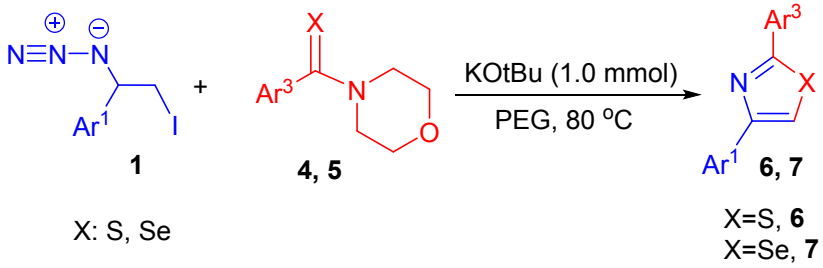


Inspired by these results, we envisioned the investigation into the synthesis of other 1,3-thiazoles as well as corresponding 1,3-selenazoles. Accordingly, the reaction of iodoazide **1**{*1*} with thioamide **4**{*1*} in the presence of base was chosen as the model reaction. Optimization of the reaction parameters is summarized in **SI**, Table S2.

Based on the results, we focused our attention on the investigation of substituent influence in this transformation. Thioamides bearing a variety of substituents (Figure 2) were reacted with three

types of iodoazide in PEG-200 using KO^{t}Bu as the base and the corresponding products were obtained in good to excellent yields (Table 2). In this reaction, the electron density on the phenyl ring of thioamides slightly affected their reactivity. As expected, thioamides with electron-donating group showed more reactivity than those electron-withdrawing groups. The best result was observed when electron-donating groups like –$CH(CH_3)_2$, –OCH_3 and –$N(CH_3)_2$ were placed in the *para* position of phenyl moiety (compounds **6**{*1,3*}, **6**{*1,4*} and **6**{*1,7*} respectively).

Table 2. Synthesis of Thiazole and Selenazole Derivatives [a]



Entry	Compounds	Ar^1	Ar^3	Yield[b] (%)
1	**6**{*1,1*}	C_6H_5	C_6H_5	83
2	**6**{*1,2*}	C_6H_5	4-MeC_6H_4	85
3	**6**{*1,3*}	C_6H_5	4-$CH(CH_3)_2C_6H_4$	84
4	**6**{*1,4*}	C_6H_5	4-$MeOC_6H_4$	88
5	**6**{*1,5*}	C_6H_5	3,4-$(MeO)_2C_6H_3$	86
6	**6**{*1,6*}	C_6H_5	3,4,5-$(MeO)_2C_6H_3$	87
7	**6**{*1,7*}	C_6H_5	4-$N(CH_3)_2C_6H_4$	88
8	**6**{*1,8*}	C_6H_5	4-ClC_6H_4	79
9	**6**{*1,9*}	C_6H_5	3-ClC_6H_4	76
10	**6**{*1,10*}	C_6H_5	$O(CH_2CH_2)_2NCSC_6H_4$	79
11	**6**{*3,1*}	4-$MeOC_6H_4$	C_6H_5	87
12	**6**{*4,1*}	4-ClC_6H_4	C_6H_5	80
13	**6**{*4,2*}	4-ClC_6H_4	4-MeC_6H_4	81
14	**6**{*4,3*},	4-ClC_6H_4	4-$CH(CH_3)_2C_6H_4$	83
15	**6**{*4,4*}	4-ClC_6H_4	4-$MeOC_6H_4$	85
16	**6**{*4,5*}	4-ClC_6H_4	3,4-$(MeO)_2C_6H_3$	83
17	**6**{*4,6*}	4-ClC_6H_4	3,4,5-$(MeO)_2C_6H_3$	84
18	**6**{*4,7*}	4-ClC_6H_4	4-$N(CH_3)_2C_6H_4$	85
19	**6**{*4,8*}	4-ClC_6H_4	4-ClC_6H_4	74
20	**6**{*4,9*}	4-ClC_6H_4	3-ClC_6H_4	73
21	**6**{*1,1*}	C_6H_5	C_6H_5	88
22	**7**{*1,2*}	C_6H_5	4-MeC_6H_4	89

23	**7**{*1,3*}	C_6H_5	4-$MeOC_6H_4$	91
24	**7**{*1,4*}	C_6H_5	2-ClC_6H_4	81
25	**7**{*1,5*}	C_6H_5	3-ClC_6H_4	82
26	**7**{*1,6*}	C_6H_5	3-BrC_6H_4	84
27	**7**{*1,7*}	C_6H_5	4-BrC_6H_4	85
28	**7**{*1,8*}	C_6H_5	$O(CH_2CH_2)_2NCSC_6H_4$	80
29	**7**{*3,2*}	4-$MeOC_6H_4$	4-MeC_6H_4	91
30	**7**{*3,3*}	4-$MeOC_6H_4$	4-$MeOC_6H_4$	94
31	**7**{*3,5*}	4-$MeOC_6H_4$	3-ClC_6H_4	87
32	**7**{*4,1*}	4-ClC_6H_4	C_6H_5	83
33	**7**{*4,2*}	4-ClC_6H_4	4-MeC_6H_4	84
34	**7**{*4,3*},	4-ClC_6H_4	4-$MeOC_6H_4$	90
35	**7**{*4,4*},	4-ClC_6H_4	2-ClC_6H_4	80
36	**7**{*4,5*},	4-ClC_6H_4	3-ClC_6H_4	81
37	**7**{*4,6*},	4-ClC_6H_4	3-BrC_6H_4	83
38	**7**{*4,7*},	4-ClC_6H_4	4-BrC_6H_4	85

[a]Reaction conditions: 1 mmol of **1** and 1 mmol of **4** or **6** in the presence of 1mmol of KO^{t}Bu in 2ml of PEG-200 as solvent at 80^{o}C for 7 h .[b] Yield of isolated product.

To better distinguish the substitution effect on the reaction, we decided to carry out a set of additional examination. As illustrated in Table 2, by utilizing of **4**{*10*} as a *di*-thioamide substrate, only **6**{*1,10*} was obtained selectively. Next, we decided to extend the scope of this protocol through the synthesis of selenazoles by utilizing selenoamides (Figure 2) instead of thioamides with the previously optimized reaction conditions (Table 2).

As depicted in Table 2, the reaction of iodoazides **1** with the variety of selenoamides **5** proceeded efficiently utilizing KO^{t}Bu as the base in PEG-200 to obtain the corresponding products in good to excellent yields.

As shown in Table 2, similar to the thioamides, the reactivity of the selenoamides was influenced slightly by the substituted effects on the phenyl ring. Also, it was illustrated that by utilizing **5**{*8*}, **7**{*1,8*} as a mono-selenazole was obtained selectively in high yield. During our investigation, we found that selenoamides perform similar to the corresponding thioamides with more reactivity. Meanwhile, investigating the reactivity of iodoazides revealed that the electron-donating groups

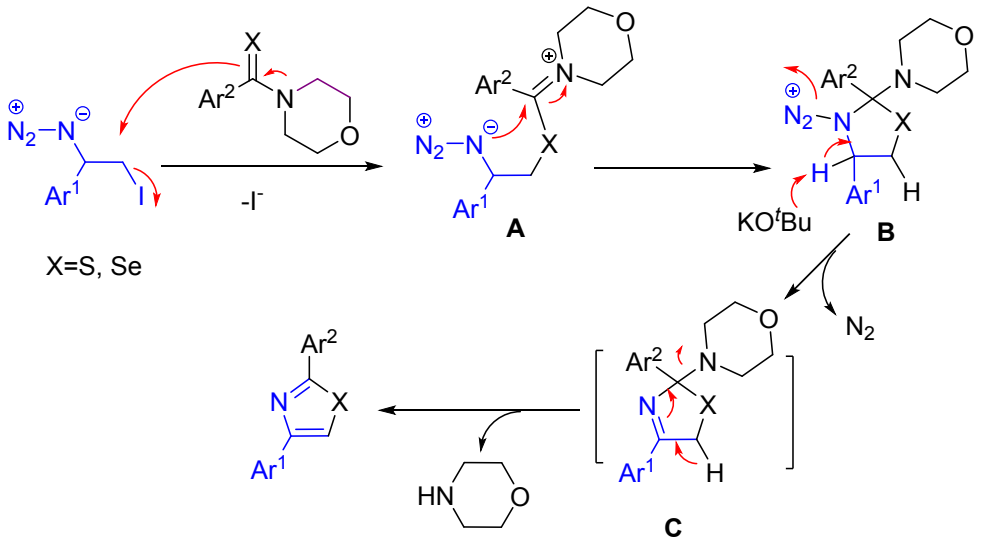
(e.g. OCH_3) increased the efficiency of the reaction (compounds **7** {*3,2*},**7** {*3,3*} and **7** {*3,5*} respectively).

In order to develop the scope of this reaction, we decided to employ this method in the synthesis of 1,3-oxazoles and 1,3-imidazoles. The reaction of iodoazide **1**{*1*} with two types of substrates: morpholino(phenyl)methanone (X=O) and morpholino (phenyl) methanimine (X=NH) was carried out under the optimized condition (**SI**, Scheme S1). Unfortunately, these reactions did not proceed to form the desired products. These results demonstrated that the progress of this reaction was directly related to the nucleophilicity of the substrates.

Finally, to expand the utility of this method, the selectivity was studied more by carrying out the competitive reaction of 1-(1-azido-2-iodoethyl)benzene **1**{*1*} with morpholino(phenyl)methanethione **4**{*1*} and morpholino(phenyl)methaneselenone **5**{*1*} in equimolar ratios under optimized condition (**SI**, Scheme S2). This investigation illustrated the increased reactivity of selenoamides in comparison to thioamides and the corresponding selenazole was produced in good selectivity. This observation may be due to the more nucleophilicity of the selenoamide in contrast to the thioamide. Moreover, this result indicated that the strength of the nucleophile was the key factor in this transformation.

Based on the aforementioned results, the plausible mechanism is proposed in Scheme 2. Initially, the thio/selenoamide reacts with the iodoazide via S_N2 reaction to form **A**. Subsequently, via 5-*exo-dig* reaction through azide attack on iminium part, the intermediate **B** is achieved. Through abstraction of proton by KO^{t}Bu and releasing nitrogen gas, **C** is produced. Finally, by aromatization of **C** and the elimination of morpholine molecule the desired product is obtained.

Scheme 2. Proposed Reaction Mechanism



In conclusion, we designed practical strategy to access diversified 2-aminothiazole, 1,3-thiazole and 1,3-selenazole scaffolds. The significant feature of these methods is utilizing aryliodoazides as the versatile reagent, which can participate in the reaction with a wide variety of aryl isothiocyanates, thioamides or selenoamides. Utilizing solvent free conditions for the synthesis of 2-aminothiazoles or PEG-200 as a non-toxic solvent for 1,3-thiazole and 1,3-selenazole preparations could be considered as advantages of these protocols. In addition, high diversity in the presented methodologies and the use of inexpensive starting materials are other significant advantages. These new procedures give promising approaches

to attain useful 5-membered nitrogen containing heterocycles. Furthermore, we envision that the protocols with aryliodoazides are capable to furnish various *N*-heterocycles with medicinal and biological activities.

■ ASSOCIATED CONTENT

Supporting Information

Typical experimental procedures, antimicrobial assay and characterization data, including ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes: The authors declare no competing financial interest.

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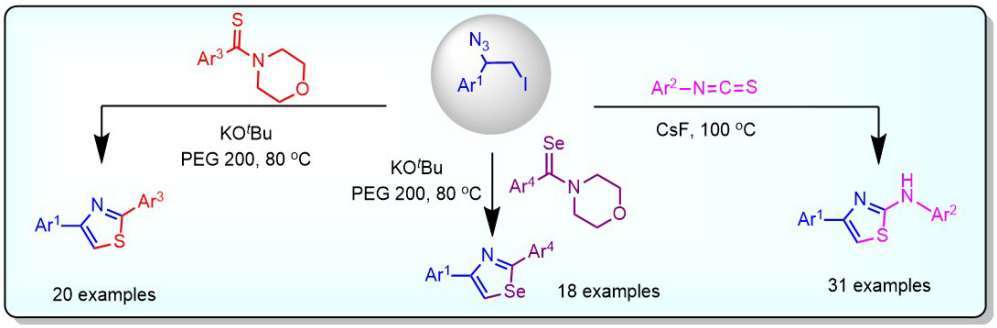
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PEG 200, 80 °C
KO^{t}Bu
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Ar^2–N=C=S
CsF, 100 °C
20 examples
18 examples
31 examples