A Synthetic and Structural Study of Arylselenoamides and 2,4-Diaryl-1,3-Selenazoles

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Abstract: The systematic preparation of 2,4-diaryl-1,3-selenazoles was carried out by two-component cyclization of the primary selenoamides with α-halo ketones. Selenoamides were obtained from the reaction of Woollins' reagent with arylnitrile, followed by hydrolysis with water. Three selenoamides have close structural similarities along with intermolecular interactions such as the strong N–H···O hydrogen bonding, the weak N–H···Se, C–H···O/N/Se intermolecular interactions and π–π stacking interactions; meanwhile, the newly formed five-membered N–C–Se–C–C rings in ten 2,4-diaryl-1,3-selenazoles have either planar or near-planar conformations along with the weak C–H···O/N/Se/Br/Cl intermolecular interactions and π–π stacking interactions. In addition, the weak Se···Se close contacts in four cases and the C–H···N intramolecular interactions in two structures were also observed within the all solid structures.

Key words: selenoamides, 1,3-selenazoles, Woollins' reagent, X-ray crystal structures, α-halo ketones

Selenium-containing heterocyclic compounds have received considerable attention in recent years due to their interesting reactivity and their potential pharmaceutical applications,[1,2] their uses in new materials,[3] as well as reagents and catalysts.[4] Among them, the selenazole derivatives are of marked interest because of their antitumor, antibacterial, and other notable activities.[5–9] Therefore, many synthetic approaches to selenazole derivatives have been extensively developed.[10,11] However, encountering major problem is the availability of the starting material, primary selenoamides, for the preparation of selenazoles. Many synthetic strategies for the preparation of primary selenoamides have been documented so far, for example, by reaction of nitriles with the highly toxic selenating reagents H_2Se or NaSeH, generated in situ from $NaBH_4$/Se,[12] LiAlHSeH, formed in situ from $LiAlH_4$/Se,[13] Se/CO,[14] P_2Se_5/H_2O,[15] and tris(trimethylsily)monoselenophosphate.[16] In addition, although some alternative selenating reagents such as Al_2Se_3,[17] $(Me_3Si)_2Se$,[18] and 4-methylselenobenzoate[19] have also been applied in these preparations in recent years, almost all of these methods required prolonged reaction times, high temperature, and inconvenient reaction conditions or could not always be reproduced.[15] We have previously reported a highly efficient approach for the preparation of a series of primary arylselenoamides from the reaction of arylnitriles with 2,4-bis(phenyl)-1,3-diselenadiphosphetane-2,4-diselenide {[PhP(Se)(μ-Se)]$_2$, Woollins' reagent},[20–27] followed by treatment with water.[28] By using this method, a series of new primary selenoamides was prepared in excellent yields. Herein, we report a very simple route to prepare a series of novel 2,4-diaryl-1,3-selenazoles from arylnitriles, Woollins' reagent/water, and α-halo ketones. The new compounds have been fully characterized spectroscopically and by single-crystal X-ray structural studies.

Refluxing toluene solution of arylnitriles with an equimolar amount of Woollins' reagent, followed by hydrolysis with water afforded a series of arylselenoamides **1a–i**.[28] The reactions proceed at atmospheric pressure, and the primary arylselenoamides are obtained in good to excellent yields. The reaction can conveniently be performed on a 1.0 mmol or larger scale. Arylselenoamides **1a–i** were allowed to react further with an equivalent of α-halo ketones under nitrogen atmosphere with subsequent workup in air resulting in a series of the corresponding 2,4-diaryl-1,3-selenazoles **2a–q** in 83–99% yields (Table 1). It should be noted that arylselenoamides bearing highly substituted groups, for example, selenoamides **1d** and **1f** result in lower yields than other selenoamides with less or without any substituted group. The highest yield was found for selenoamide **1a** without any substituted group. As for as the synthesis of the 2,4-diaryl-1,3-selenazoles, the lowest yields were found in 2,4-diaryl-1,3-selenazoles **2g** and **2j**.

The formation of 2,4-diaryl-1,3-selenazoles **2a–q** can be explained considering the mechanism depicted in Scheme 1. The intermediate **A**, the addition product of selenoamides and α-halo ketones, further carried on the cyclization reaction resulting in another intermediate **B**, which subsequently lost one molecule of H_2O leading to the formation of compounds **2a–q**.

The synthesis, characterization, and X-ray single-crystal structures of arylselenoamides **1a–e** have been reported previously by us,[28] thus, we will not mention them again here. Arylselenoamides **1f–i** and 2,4-diaryl-1,3-selenazoles **2a–q** are stable to air or moisture for months without any signs of degradation occurring (e.g., including reddening of the powders due to the expulsion of elemental selenium which is accompanied by the evolution of foul-smelling gas). The characterization of arylselenoamides **1f–i** and 2,4-diaryl-1,3-selenazoles **2a–q** was performed by means of ^{1}H NMR, ^{13}C NMR, ^{77}Se NMR, and IR spectroscopy

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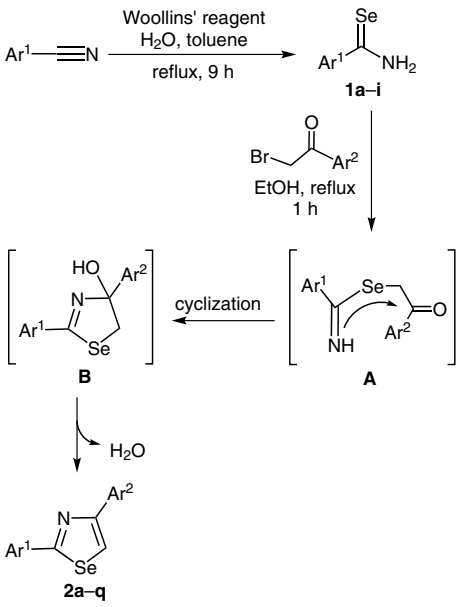
Table 1 Yields, Melting Points, and ^{77}Se NMR Data for Compounds **1a–i** and **2a–q**

Compd	X	Ar^1	Ar^2	Yield (%)	mp (°C)	^{77}Se NMR (δ, ppm)
1a		4-BrC_6H_4	–	91	137–139	647.2
1b		Ph	–	98	122–124	663.3
1c		3-MeC_6H_4	–	91	74–75	641.2
1d		3,4-$(MeO)_2C_6H_3$	–	67	177–179	578.8
1e		2,6-$Cl_2C_6H_3$	–	86	118–120	715.8
1f		2,4,6-$(MeO)_3C_6H_2$	–	83	168–170	657.8
1g		4-$F_3CC_6H_4$	–	90	140–141	741.0
1h		naphthalen-2-yl	–	86	146–148	686.2
1i		naphthalen-1-yl	–	89	118–119	762.2
2a	Br	4-BrC_6H_4	4-ClC_6H_4	91	142–144	723.2
2b	Br	Ph	4-ClC_6H_4	96	113–115	720.0
2c	Br	3-MeC_6H_4	4-ClC_6H_4	95	90–92	719.1
2d	Br	3-MeC_6H_4	4-BrC_6H_4	93	100–102	719.8
2e	Br	3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4	98	140–142	710.2
2f	Br	3,4-$(MeO)_2C_6H_3$	Ph	97	88–90	705.5
2g	Cl	3,4-$(MeO)_2C_6H_3$	4-BrC_6H_4	86	150–152	710.9
2h	Br	2,6-$Cl_2C_6H_3$	4-$O_2NC_6H_4$	97	96–98	798.8
2i	Br	2,6-$Cl_2C_6H_3$	4-ClC_6H_4	97	54–56	785.6
2j	Br	4-$F_3CC_6H_4$	4-BrC_6H_4	83	128–130	731.9
2k	Br	4-$F_3CC_6H_4$	4-$O_2NC_6H_4$	98	141–143	743.5
2l	Cl	naphthalen-2-yl	Ph	94	116–118	742.6
2m	Br	naphthalen-2-yl	4-ClC_6H_4	97	148–150	721.1
2n	Br	naphthalen-1-yl	4-ClC_6H_4	95	–	765.6
2o	Br	naphthalen-1-yl	3-$O_2NC_6H_4$	93	–	774.1
2p	Br	naphthalen-1-yl	4-MeC_6H_4	95	–	757.0
2q	Br	naphthalen-2-yl	4-MeC_6H_4	99	152–154	712.2

and mass spectrometry in conjunction with single-crystal X-ray crystallography.

All new compounds show the anticipated $[M + H]^+$ or $[M + Na]^+$ peak in their mass spectra, satisfactory accurate mass measurements and appropriate isotopic distributions. The IR spectra of arylselenoamides **1f–i** show strong bands ranging from 1587–1656 cm^{-1} resulting from the δ(N–H) accompanied with intense bands in the range of 680–654 cm^{-1} being characteristic for the C=Se group.[28–30] Furthermore, the ^{1}H NMR spectra exhibit all the expected peaks including broad singlet signals between δ = 7.88–8.80 ppm assigned to the (C=Se)–NH_2 group, which are in good agreement with literature values.[28–33] The ^{13}C NMR spectra have signals for the C=Se group at δ = 206.5–207.5 ppm along with the expected signals from the aromatic carbon backbones. The ^{77}Se NMR spectra of all compounds display singlet signals in the range δ = 657.8–741.0 ppm, comparable to the related selenoamides.[28–33] It is worth noting that arylselenoamides **1e** and **1g** bearing the electron-withdrawing substituted CF_3 and Cl groups on the phenyl ring have the bigger ^{77}Se NMR chemical shifts than arylselenoamide **1b** with nonsubstituted group, whilst arylselenoamides **1a**,**c–f** bearing the electron-releasing substituted Br, Me, and MeO groups show smaller ^{77}Se NMR chemical shifts than arylselenoamide **1b** with nonsubstituted group. In addition, the ^{77}Se NMR chemical shifts display the big difference in naphthalenylselenoamides **1h** and **1i**, indicating that the C(Se)–NH_2 position apparently affects the ^{77}Se NMR chemical shift value. Furthermore, these ^{77}Se NMR



Scheme 1 Synthesis of compounds **1a–i** and **2a–q** (X, Ar^1, and Ar^2 groups are defined in Table 1)

chemical shifts are significantly bigger than that in arylselenoamide **1b**, suggesting that the naphthalene ring behaves as an electron-withdrawing functional group.

The IR spectra of 2,4-diaryl-1,3-selenazoles **2a–q** reveal an absorption band between 1480–1702 cm^{-1} due to the ν(C–N) vibration whilst an absorption band in the range of 549–696 cm^{-1} can be assigned to the ν(Se–C) vibration.[11,34,35] The ^1H NMR spectra of 2,4-diaryl-1,3-selenazoles **2a–q** show singlet peaks in the range of δ = 8.06–8.81 ppm from the sole azole hydrogen atom present. In the ^{13}C NMR spectra of 2,4-diaryl-1,3-selenazoles **2a–q**, the chemical shifts for the selenazole ring fall in the range of δ = 170.7–190.1, 153.7–159.6, and 109.4–127.1 ppm, respectively. Interestingly, it is worth noting that ^{77}Se NMR chemical shifts in 2,4-diaryl-1,3-selenazoles **2a–q** are in the range of δ = 705.5–798.8 ppm, that is, at higher chemical shifts than in their precursor selenoamides **1f–i** (δ = 657.8–741.0 ppm). The 2,4-diaryl-1,3-selenazoles bearing three electron-withdrawing groups (Cl and NO_2) on two peripheral phenyl rings in **2h** and **2i** show much higher chemical shifts than the others with electron-releasing groups or less electron-withdrawing groups on two peripheral phenyl rings. 1,3-Selenazoles **2l–q** having one peripheral naphthalene ring show significantly bigger chemical shifts than 1,3-selenazoles **2a–g** bearing two peripheral phenyl rings, further confirming that the naphthalene ring can act somehow as an electron-withdrawing functional group in the molecule.

Crystals of selenoamides **1f**,**h**,**i** and 2,4-diaryl-1,3-selenazoles **2b–g**,**m–p**[36] suitable for X-ray crystallographic analysis were obtained by the diffusion of hexane into a dichloromethane solution of the compound at room temperature in each case. The structures have a single molecule of the compound in the asymmetric unit, except for **1f** and **1h** in which the asymmetric unit contains two independent molecules. Crystal data and structure refinement for compounds **1f**,**h**,**i** and **2b–g**,**m–p** are summarized in Tables **S1–S3** and selected bond lengths and angles are listed in Tables **S4–S6** of the Supporting Information.

The structures of **1f** and **1i** both crystallize in the space group *P*-1, whereas **1h** crystallizes in the *C*2/*c* space group. In **1f**, **1h**, and **1i** the bond lengths of the C=Se double bond range from 1.833(4)–1.843(6) Å and the C–N bond lengths are in the range from 1.304(6)–1.310(7) Å and are comparable to the literature values for the typical C=Se double bond distances [1.81(5)–1.856(4) Å] and C–N distances [1.270(7)–1.324(8) Å] in primary selenoamides.[28,31] The selenoamide functionalities are not particularly coplanar with the aryl backbone, with the dihedral angles between the Se(1)–C(1)–N(1) mean plane and the aryl mean plane being 29.33(38.41), 25.31(20.41), and 60.80°, respectively. The biggest angle is observed in **1i**, suggesting the biggest spatial crowding effect from the naphthalene ring plane with the selenium atom avoiding any *peri* interaction (Figure 1).

Surprisingly, N–H···Se hydrogen bonding was not observed in **1f**,**h**,**i** unlike previous reports for similar selenoamides.[28,37] However, there is the strong N–H···O hydrogen-bond interaction occurring in **1f**. The O atom from the *para* position CH_3O group on the phenyl ring acts as hydrogen-bond acceptors towards the N–H groups of a neighboring molecule giving rise of a 'zigzag chain' polymeric architecture as shown in Figure 2. The N–H···OCH_3 and N···O–CH_3 distances are 2.20 [2.12] Å and 2.986(6) [2.969(6)] Å, respectively, obviously, these values are strong enough to challenge the classic intrabackone N–H···O=C hydrogen bonds in the amide groups and carbamate group [in which the N–H···O=C and N···O=C lengths are 2.218 and 2.97 Å in amide group, and the N–H···O=C and N···O=C lengths are 3.141 and 3.58 Å in the carbamate group].[38] Furthermore, the N–H···O at 48.27 [161.28]° angles in **1f** are wider than that in the amide group (the angle N–H···O 141°) and that in the carbamate group (the angle N–H···O 79°).[38] The results can confirm that the N–H···O–CH_3 hydrogen bonding in **1f** appears to be significantly stronger than the N–H···Se hydrogen bonding [N–H···Se distances ranging from 2.48(9)–2.90(14) Å and Se···N lengths ranging from 3.403(3)–3.580(11) Å, with the angle N–H···Se ranging from 115(1)–174(5)°] in the selenoamide groups,[28,37] and the N–H···S hydrogen bonding [N–H···S distances ranging from 2.55–2.78 Å and S···N lengths ranging from 3.394(18)–3.605(3) Å, with the N–H···S angles ranging from 158.0–173.0°] in the thioamide groups.[39,40]

The supramolecular assembly in **1f**, **1h**, and **1i** making up the form of three-dimensional networks were built by the slightly different hydrogen bonding and other intermolecular interactions. The multisheeted supramolecular assembly in **1f** is formed by the strong intermolecular N–H···O hydrogen bonds in conjunction with a series of weak O–C–H···O/N/Se, C–H···O intermolecular interac-

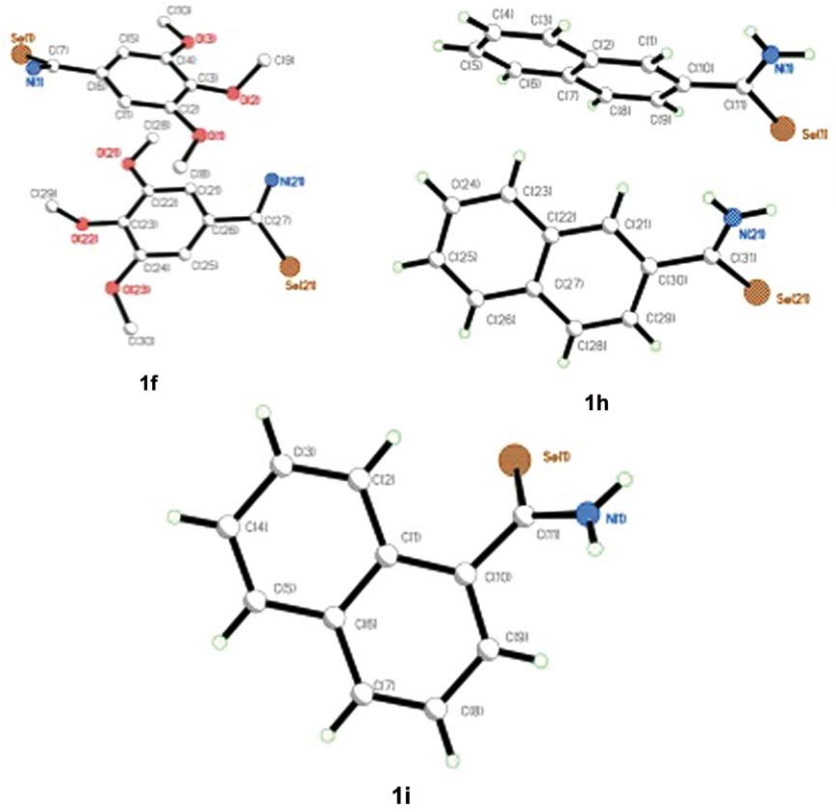


Figure 1 Single-crystal X-ray structures of **1f**, **1h**, and **1i**

tions and π–π stacking interaction (Figure S1 of the Supporting Information). However, details of packing motif reveal that intermolecular interactions in **1h** and **1i** are somehow different from **1i**: the neat-crossed-layer framework in **1h** and the multistaged network in **1i** are formed by a combination of N–H···Se, C–H···Se, and C–H···N intermolecular interactions, and π–π stacking interaction, the latter involves π-systems such as phenyl rings and naphthalene rings (Figures S2 and S3 of the Supporting Information). In the π–π stacking interactions in **1f**, two adjoining parking aryl rings have a dihedral angle of 25.78°, contributed from strong N–H···O hydrogen bonds and weak N–H···Se, C–H···Se, and C–H···N intermolecular interactions. Whilst, there are two sets of π–π stacking interactions in the supramolecular assembly of **1h** with a dihedral angle of 57.49°, for each set of π–π stacking interaction, the naphthalene rings of the molecules at (x, y, z) and (x + 1, y + 1 z + 1), which are completely parallel, have an interplanar spacing of 3.643 Å, falling within the conventional range [3.6197(19)–3.670(4) Å] for π-interactions.[41] However, the π–π stacking interactions in **1i** are strictly parallel with the naphthalene rings of the molecules at (x, y, z) and (x + 1, y + 1, z + 1) having an interplanar spacing of 3.788 Å, which is slightly longer than that in the structure of **1h**. Furthermore, all selenium atoms keep close contacts with pairs between neighboring stacks in solid structure of **1h**. As a result, a zigzag arrangement of the selenium atoms occurs with the intermolecular Se···Se distances d_1 and d_2 are respective 3.915 and 4.181 Å, the values are very closer than the van der Waals distance between two selenium centers (4.0 Å).[42] The short Se···Se contact is believed to play an important role for the packing in the solid state.[43]

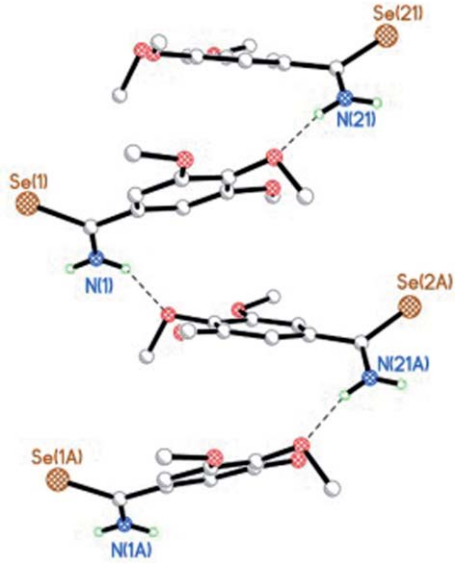


Figure 2 X-ray crystal structure of **1f** showing 'zigzag chain' polymeric network built up with 'head to tail' linked by the strong N–H···O hydrogen bonding

On the molecular level (Figure 3), the newly formed five-membered N(1)–C(2)–Se(3)–C(4)–C(5) rings in structures **2b**–**g** and **2m**–**p** possess similar near-planar conformation with Se atom deviating from 0.000–0.012 Å, respectively, from the selenazole mean planes. There are some differences in the dihedral angles between peripheral ring planes and the selenazole ring mean planes ranging from 1.02–20.38°, with the exceptions of the structures **2n** and **2p**, where the dihedral angles are 42.82° and 37.89°, respectively. Due to the rotational symmetry, this leads to the planes of their phenyl rings being inclined from respective 5.46–49.66° with respect to each other. The C–Se bond distances in **2b**–**g** and **2m**–**p** vary from 1.803(13)–1.909(3) Å, covering the range of C–Se bond lengths ob-

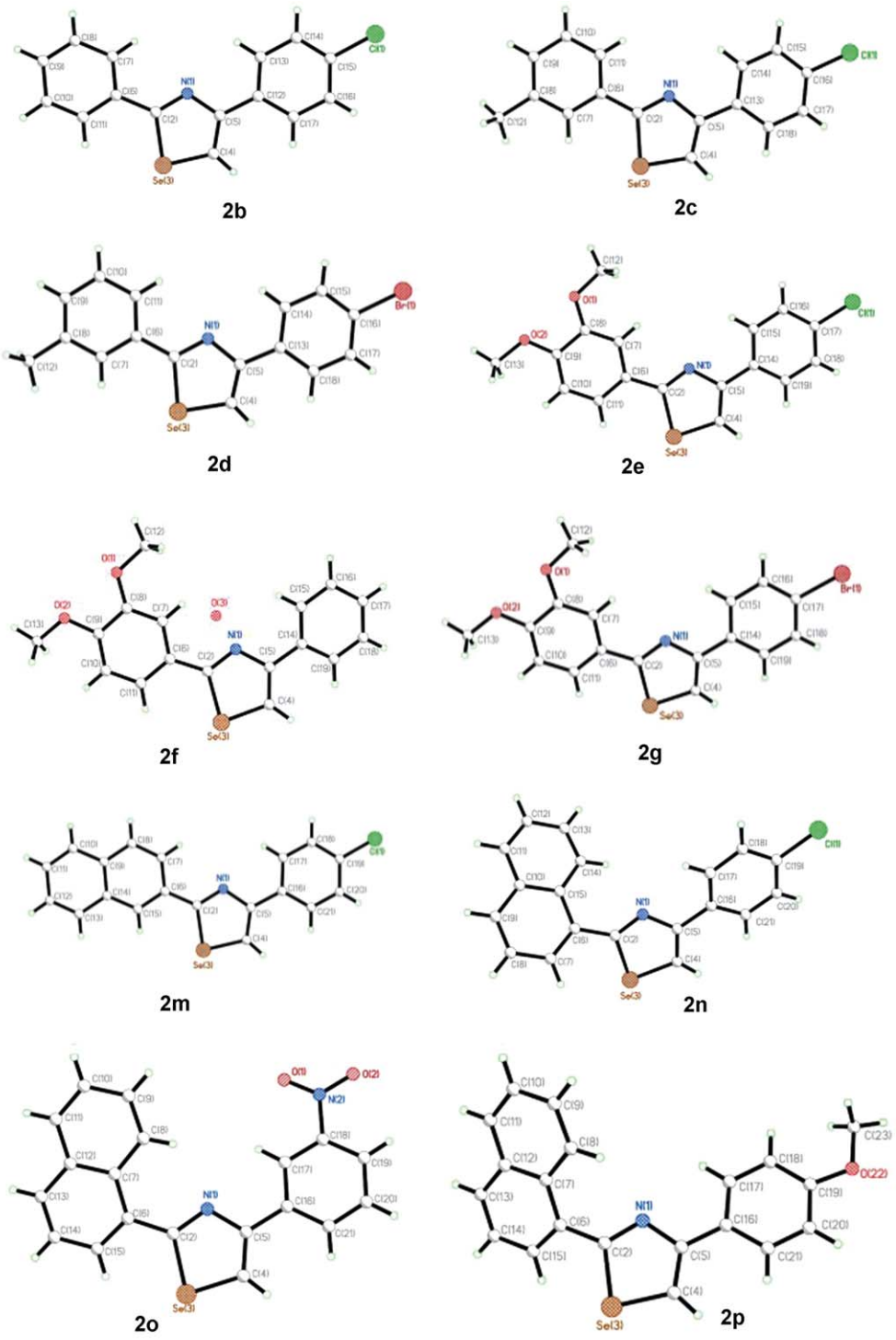


Figure 3 Single-crystal X-ray structures of **2b**–**g** and **2m**–**p**

served in the five-membered ring 1,3,4-selenadiazoles [1.87–1.89 Å][37,41,44,45] and in 2,5-diarylselenophenes (ca. 1.86–1.89 Å),[46] and are marginally shorter than that would be expected from the typical C–Se single-bond lengths [ca. 1.92–1.94 Å].[47–49] Both C=N double-bond distances [1.285(14)–1.309(11) Å] and C–N single-bond distances [1.377(13)–1.403(11) Å] in these structures are comparable with those in the reported 1,3-selenazoles [1.268(11) Å for C=N bond and 1.384(11) Å for C–N bond],[11] which are significantly shorter than the usual C–N single-bond length of 1.47 Å,[50–52] indicating clearly that some degree of delocalization occurring in these newly formed selenazole rings. The C–Se–C angles in structures **2b**–**g** and **2m**–**p** differing from 84.24(15)–85.3(4)° are considerately wider than that in the reported similar structure [83.3(5)°],[11] and that in 1,3,4-selenadiazoles [81.9(4)–82.7(2)°],[37,41,44,45] and significantly smaller than that in the 2,5-diarylselenophenes [87.8(8)°],[46] indicating the size order for the C–Se–C angles in the five-membered ring systems being: 1,3,4-selenadiazoles < 1,3-selenazoles < 2,5-diarylselenophenes.

Despite the similarities between compounds **2b**–**g** and **2m**–**p** in terms of their chemical constitution and their overall molecular shape, the intramolecular or intermolecular interaction are somehow different for all these compounds to form supramolecular aggregation arrangements (Figures S4–S13 of the Supporting Information). The aggregation in **2c**, **2d**, and **2m** is dominated by C–H···X (X = Cl, Br) intermolecular interactions, C–H···Se intermolecular interactions, C–H···N intermolecular interactions, and π–π stacking interactions that lead to the formation of multistaged or multisheeted network structures; whilst the structure of the structure of **2b** contains C–H···Cl intermolecular interactions, C–H···Se intermolecular interactions, and C–···N intermolecular interactions leading to the formation of a disordered multistaged aggregate, but the π–π stacking interactions are absent. Interestingly, the supramolecular structure of **2n** consists of a combination of C–H···N intermolecular interactions, C–H···Cl intermolecular interactions and π–π stacking interactions to build-up a multilayered supramolecular assembly, however, the C–H···Se intermolecular interaction being absent. On the other hand, in compounds **2e** and **2g**, there is a combination of multi C–H···O intermolecular interactions, multi C–H···N intermolecular interactions, the multi C–H···X (X = Cl, Br) intermolecular interactions, C–H···Se intermolecular interactions, and π–π stacking interactions present, in which involve the aryl ring H atoms, azole ring H atoms, OCH_3 group H atoms, and the N, O, X (Cl, Br) atoms. The similar supramolecular assembly as **2e** and **2g** was observed in compound **2f** apart from the multi C–H···X (X = Cl, Br) intermolecular interactions being absent. Surprisingly, the C–H···N intramolecular interactions are dominated in compounds **2o** and **2p** in conjunction with a combination of C–H···N intermolecular interactions, the multiple C–H···O intermolecular interactions, the multiple C–H···Se intermolecular interactions, and π–π stacking interactions, in which also involve the aryl ring H atoms, azole ring H atoms, and the N, O, Se atoms in **2o** (Figure S12) and the aryl ring H atoms, azole ring H atoms, OCH_3 group H atoms, and the N, O, Se atoms in **2p** (Figure S13). In addition, the weak intermolecular Se···Se close contacts between neighboring stacks with linear arrangement of the selenium atoms were observed, the Se···Se distances d_1 within a stack are respective 4.235, 4.417, and 3.937 Å, the values are very approximate to the van der Waals distance between two selenium centers (4.0 Å)[42] in the structures of **2f**, **2g**, and **2m** leading to their structural conformation somewhat different from each other.

In summary, Woollins' reagent reacts with one equivalent of arylnitrile, followed by water to give a series of primary arylselenoamides **1a**–**i** in good to excellent yields. The cyclization of primary arylselenoamides with α-halo ketones delivered a variety of new 2,4-diaryl-1,3-selenazoles **2a**–**q** in excellent yields. Thirteen single-crystal structures were studied to reveal that three X-ray single-crystal structures of selenoamides **1f**, **1h**, and **1i** have very close structural similarities along with similar intermolecular interactions, such as the strong N-H···O hydrogen bonding and the weak N–H···Se, C–H···O/N/Se intermolecular interactions, and π–π stacking interactions; 1,3-selenazoles **2b**–**g** and **2m**–**p** possess rather similar molecular conformations and intermolecular interactions such as the newly formed five-membered N(1)–C(2)–Se(3)–C(4)–C(5) rings being near planar with the weak C–H···O/N/Se/Br/Cl intermolecular interactions and π–π stacking interactions. Furthermore, the C–H···N intramolecular interaction was found in two cases of 2,4-diaryl-1,3-selenazoles; the close contacts between Se atoms of neighboring stacks in structures of **1h**, **2f**, **2g**, and **2m** were also observed. These intermolecular interactions, close contacts, and π–π stacking interactions play a major role in stabilizing the crossed-layer supramolecular assemblies in the solid state.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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