

## Synthesis and Selenation of Tandem Multicomponent Condensation Adducts

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**Abstract:** A number of four-component condensation adducts, which were readily obtained from one-pot reaction of aryl carboxylic acids, arylaldehydes, arylamines and *c*-hexylisocyanide, were treated with two equivalents of Woollins' reagent leading to the formation of a series of novel selenoamides with one or two C=Se groups, or heterocyclic compounds such as 1,3-selenazole and 1,3-selenazolidin-5-one.

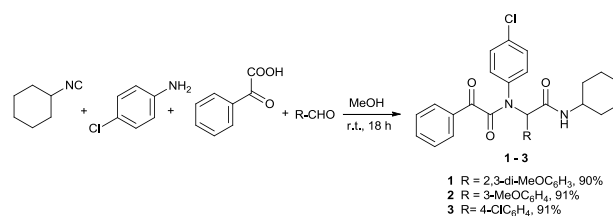
**Key words:** *One-pot reaction* / *Multicomponent condensation adducts* / *Woollins' reagent* / *Selenoamides* / *Selenium-nitrogen heterocycles*

The multicomponent reaction has been applied successfully for the synthesis of different kind of scaffolds and even for efficient construction of even simple heterocycles,<sup>1-7</sup> a number of substituents can be varied over a broad range, multicomponent reactions often access products of one specific scaffold, limiting the overall chemical diversity. To overcome this shortage, multicomponent reactions were combined with other types of reaction afterwards such as Diels-Alder reactions,<sup>8-12</sup> click chemistry,<sup>13</sup> cyclization strategies<sup>14</sup> and other approaches<sup>15-19</sup> to generate structural diversity and a high degree of complexity in a minimal number of reaction steps. To our knowledge, however, there is no protocol for the synthesis of chalcogenated amides in such condensation adducts so far. Thus, the development of an efficient approach for the synthesis of chalcogenated adducts remains a challenge.

2,4-Bis(phenyl)-1,3-diselenadiphosphethane-2,4-diselenide [ $\{\text{PhP}(\text{Se})(\mu\text{-Se})\}_2$ ] (Woollins' reagent), a selenium counterpart of the well-known Lawesson's reagent, has been well documented as an efficient phosphorus-selenium building block or selenation reagent in organic synthetic chemistry in recent years.<sup>20</sup> The reaction of Woollins' reagent with a variety of organic substrates exhibits a diverse spectrum ranging from simple oxygen-selenium exchange to the formation of complex phosphorus-selenium small- and macro-heterocycles as well as the surprising phosphorus-selenium-free products.<sup>21-33</sup> In light of our continuing interest in the application of Woollins' reagent in organic synthesis, herein, we report the synthesis of a series of new adducts *via* tandem four-component condensation, and their corresponding selenation derivatives.

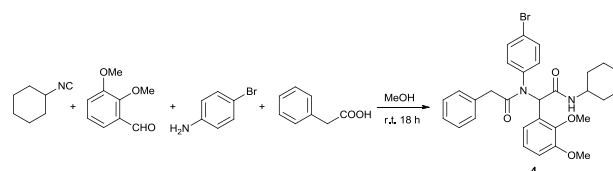
It has been well known that a highly flexible multicomponent reaction between aldehydes, amines, carbonyl compounds, and isocyanides to form *N*-aryl amines.<sup>34,35</sup> While searching for new acidic substituents in the Ugi reaction, we thought that a suitable electron-withdrawing group on a carbonyl group could trigger both the imine activation and the irreversible rearrangement in the key step of the reaction.

Indeed, we found that phenylglyoxylic acid reacting with an equivalent of cyclohexyl isocyanide, *p*-chloroaniline and substituted benzaldehydes such as 2,3-dimethoxybenzaldehyde or 3-methoxybenzaldehyde or 4-chlorobenzaldehyde is a very straightforward and efficient four-component reaction. This reaction proceeded smoothly at room temperature in methanol medium within 18 hours to provide the desired *N*-aryl amines **1** – **3** in excellent yields (Scheme 1).<sup>36</sup>

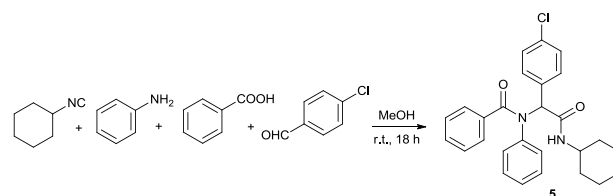


**Scheme 1** Formation of four-component condensation adducts **1** – **3**

The high yield, simple reaction protocol, and originality of this tandem process prompted us to explore the reaction more widely with a variety of substrates. Phenylacetic acid and benzoic acid are proved to be good substrates for this process and reacted with various amines, isocyanides and arylaldehydes. The reaction of phenylacetic acid with one equivalent of cyclohexylisocyanide, 2,3-dimethoxybenzaldehyde and 4-bromoaniline gave rise to the expected adduct **4** in 99% yield under these conditions as shown in Scheme 2. Meanwhile, benzoic acid reacted with equal-molar amount of cyclohexylisocyanide, 4-chlorobenzaldehyde and aniline also leading to the corresponding adduct **5** in 99% yield (Scheme 3). These results showed that benzoic acid is more reactive than phenylacetic acid contributing to the desired products in high yields.

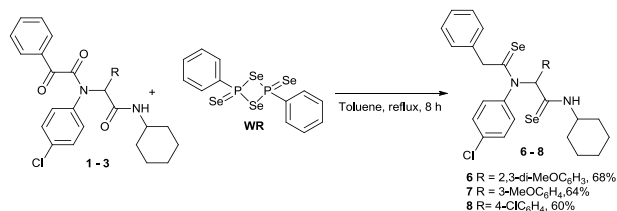


**Scheme 2** Formation of four-component condensation adduct **4**



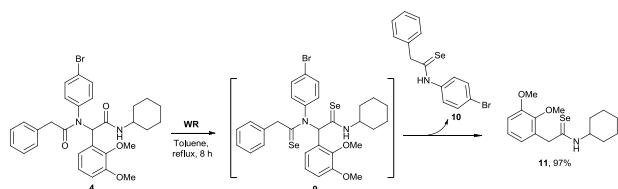
**Scheme 3** Formation of four-component condensation adduct **5**

The selenation reactions with Woollins' reagent (**WR**) were carried out with condensation adducts giving diverse outcomes. Woollins' reagent was obtained by means of the literature method.<sup>20</sup> Treating **1** – **3** with two equivalents of Woollins' reagent in refluxing toluene delivered, upon work up in air, the corresponding selenoamides **6**, **7** and **8** containing two C=Se double bond groups in 68%, 64% and 60% yields, respectively, rather than three C=Se double bond groups as shown in Scheme 4.<sup>37</sup> It is worth noting that one C=O group conjoined phenyl ring from starting materials **1** – **3** was reduced by Woollins' reagent into CH<sub>2</sub> group, at the same time as the other two amide C=O groups were converted successfully by Woollins' reagent into the corresponding C=Se groups leading to selenoamides **6** – **8**. We assume that the five-membered cyclisation ring products were not obtained because of steric hindrance of the two big substituent groups in the bridge N-CH chain between the two C=Se groups, and even prolonged reaction time did not lead to the formation of five-membered ring products.



**Scheme 4** Selenation of the adducts **1** – **3** into the selenoamides **6** – **8**

Performing the reaction of amide **4** with two equimolar amounts of Woollins' reagent under the same conditions we found that the expected selenoamide **9** was not formed but selenoamide **11** with one C=Se group was obtained as depicted in Scheme 5. We speculate that amide **4** was originally transformed into selenoamide **9**, the latter intermediate then decomposed further into two small pieces: selenoamides **10** and **11**, each bearing one single C=Se group and both are thus more stable than the expected intermediate **9**. Indeed, compound **10** was identified in the reaction mixture by <sup>77</sup>Se NMR at  $\delta_{\text{Se}}$  701.8 ppm accompanied by  $\delta_{\text{Se}}$  541.8 ppm for compound **11**. Unfortunately, compound **10** was not obtained from flash chromatography for full characterization.



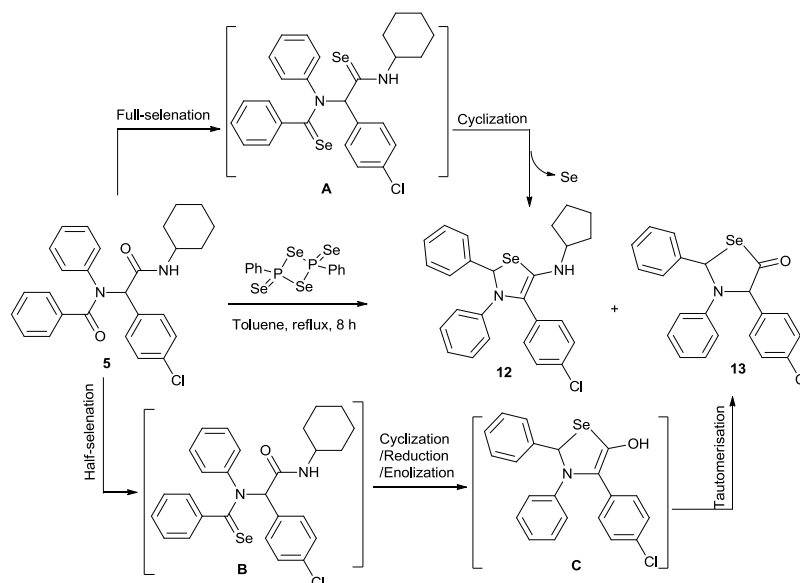
**Scheme 5** Selenation of the adducts **4** into the selenamide **11**

Surprisingly, the reaction of amide **5** with two equivalents of Woollins' reagent afforded two products: a five-membered ring 1,3-selenazole **12** and a five-membered ring 1,3-selenazolidin-5-one **13** in 32% and 24% isolated yields, respectively (Scheme 6). We propose that 1,3-selenazole **12** might derive from an unstable fully selenated intermediate **A** by the cyclization, meanwhile 1,3-selenazolidin-5-one **13** comes from the unstable

half selenated intermediate **B**, followed by a cyclization, a reduction and an enolization into intermediate **C** and finally tautomerization leading to **13**. We recognize that this mechanism is speculative but note that similar analogous sulfur products have been documented in the reaction of di-amides with Lawesson's reagent.<sup>38-40</sup>

All new compounds **1** – **8**, **11** and **13** were fully characterized by multi-nuclear (<sup>1</sup>H, <sup>13</sup>C, <sup>77</sup>Se) NMR spectroscopy, IR spectroscopy and mass spectroscopy. All compounds showed the anticipated [M]<sup>+</sup> or [M+H]<sup>+</sup> peak in their mass spectra and satisfactory accurate mass measurement. The <sup>13</sup>C chemical shifts in compounds **1** – **5** in the range 167.6 – 190.6 ppm are typical for C=O double bonds in amides. The <sup>13</sup>C chemical shifts for C=Se in compounds **6** being at  $\delta_{\text{C}}$  = 204.4 and 202.8 ppm, **7** at  $\delta_{\text{C}}$  = 202.6 and 201.5 ppm, and **8** at  $\delta_{\text{C}}$  = 198.8 and 198.3 ppm are considerably lower than that in the five- or six-membered heterocyclic compounds containing C=Se double bonds ( $\delta_{\text{C}}$  = 287 – 294 ppm)<sup>41</sup> and are marginally lower than that in the reported selenoamides ( $\delta_{\text{C}}$  = 203 – 218 ppm).<sup>41-44</sup> Meanwhile, in compound **11**, the <sup>13</sup>C chemical shift for C=Se is 204.4 ppm, falling within the range are typical for selenoamides.<sup>41,42</sup> The <sup>77</sup>Se chemical shifts for C=Se groups **6** – **8** and **11** range from  $\delta_{\text{Se}}$  = 540.1 to 546.9 ppm and are significantly lower than that in primary aryl substituted selenoamides (average value *ca.* 631 ppm)<sup>43</sup> and in methyl dimethyldiselenocarbamate ( $\delta_{\text{Se}}$  = 602 ppm),<sup>44</sup> however, these values are drastically shifted to high-field, compared to that in the six-membered systems such as 1-thia-3,3,5,5-tetramethyl-4-cyclohexanselenone ( $\delta_{\text{Se}}$  = 2131 ppm) and selenofenchone ( $\delta_{\text{Se}}$  = 1613 ppm).<sup>45</sup> With respect to heterocycles **12** and **13**, the <sup>13</sup>C chemical shifts for the C=O in **13** being at  $\delta_{\text{C}}$  = 198.4 ppm falls with the range of 160-220 ppm for carbonyl carbon atoms. In **12** the <sup>77</sup>Se NMR spectrum displays a singlet signal at  $\delta_{\text{Se}}$  = 707.9 ppm, comparable to related selenium-nitrogen heterocyclic compounds.<sup>46</sup>

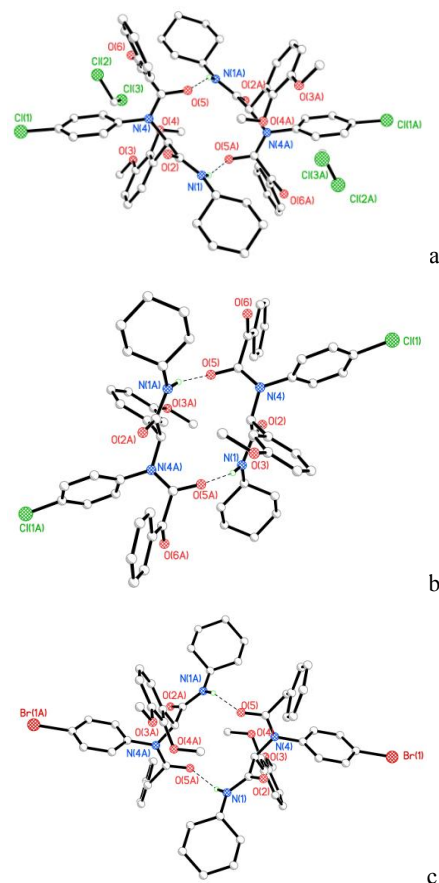
Recrystallization by diffusion of hexane into dichloromethane solutions in air at room temperature gave crystals of **1**, **2**, **4**, **6**, **11** and **13** suitable for X-ray diffraction studies as shown in Figures 1 - 2 and Figures S1 – S6, with structural data given in Tables S1 and S2. Compounds **1** and **2** crystallize in the triclinic space group *P*-1, meanwhile, compound **4** in the monoclinic space group *P*2<sub>1</sub>/*c*. It is noted that compound **1** was found to be co-crystallized with one molecule of dichloromethane. The structural conformations of **1**, **2** and **4** are arranged with the three phenyl rings being inclined to one another at 55.64°, 71.98° and 53.26° in **1**; 63.35°, 64.75° and 61.90° in **2**, and 85.7°, 43.8° and 52.2° in **4**. The distances of C(2)-N(1) and C(5)-N(4) in **1** (1.329(4) Å and 1.339(4) Å), in **2** (1.346(5) Å and 1.342(4) Å) and in **4** (1.346(7) Å and 1.365(7) Å) are quite similar to each other, indicating some multiple bond character present due to the effect of the adjacent C=O double bond.



**Scheme 6** Selenation of the adducts **5** into the heterocycles **12** and **13**

The X-ray analysis reveals that the two amide groups within all three diamides **1**, **2** and **4** adopt an antiparallel conformation relative to the quaternary carbon and there is no intramolecular hydrogen bonding.<sup>47</sup> However, there are very similar intermolecular hydrogen bond interaction between the amide hydrogen atoms of one molecule and the oxygen atom of the amide group of another molecule leading to the formation of a faked dimeric ‘fourteen-membered ring’ conformations in **1**, **2** and **4** as shown in Figure 1. The N-H...O lengths range from 2.106 to 2.164 Å and N...O distances range from 2.937(7) to 3.058(4) Å, accompanied by the N-H...O angles of 157.15°, 154.68° and 157.23° close to a typical N-H...O=C interaction.<sup>48</sup>

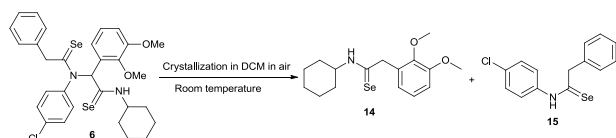
Based on the results of X-ray analysis, the two amide groups within all three diamides **1**, **2** and **4** adopt an antiparallel conformation relative to quaternary carbon and there is no intramolecular hydrogen bonding.<sup>47</sup> However, there are very similar intermolecular hydrogen bond interaction between the proton of amide group of one molecule and the O atom of amide group of other molecule leading to the formation of a robust three-dimension ‘fourteen-membered ring’ framework, held in place by the basic dimer unit in structures of **1**, **2** and **4** as shown in Figure 1. The N-H...O lengths ranging from 2.106 to 2.163 Å and N...O distances ranging from 2.937 to 3.068 Å, accompanied by the N-H...O angle holding respective 157.15°, 154.68° and 157.23° are nearly falling within a typical N-H...O=C interaction of good geometry.<sup>48</sup>



**Figure 1** Molecular structures of **1** (a), **2** (b) and **4** (c) show the intermolecular N-H...O hydrogen bonds to form fourteen-membered rings.

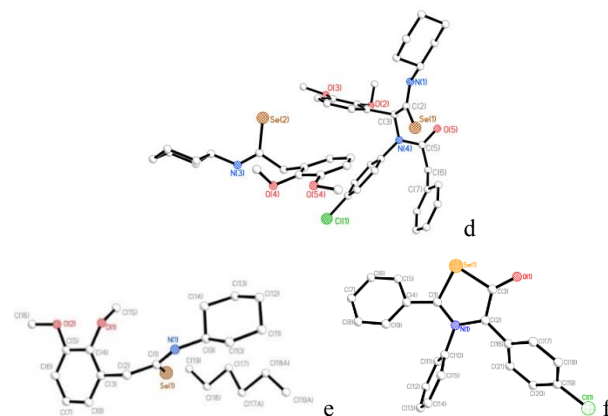
Interestingly, **6** co-crystallizes in the triclinic space group *P*-1 with two different molecules (namely, the selenoamide **14** and the solvated dichloromethane) in the unit cell (Figure 2). Selenoamide **14** is apparent one of two decomposed fragments **14** and **15** from the selenoamide **6** during the crystallization process as depicted in Scheme 7. Indeed, we did not find any

trace of compounds **14** and **15** in either the crude reaction mixture or the original compound **6** by multi-NMR spectra. Furthermore, this co-crystallization prevented characterization of compounds **14** and **15** by multi-NMR and mass spectroscopy. In **6**, the selenium atom is almost co-planar with a phenyl ring plane (C3-C4-C5-C6-C7-C8). Whilst, the C1-N1-Se1 unit in **14** is coplanar with C32, the dihedral angle between the phenyl ring plane and the C31-Se2-N3 mean plane is 85.3° as a consequence of the strong steric effect imposed by the two *ortho*- and *meso*- methoxyl groups. Notably, the C=Se double bond and C-N single bond lengths in the amide functional groups are 1.814(8) and 1.826(10) Å, and 1.329(12) and 1.296(11) Å for molecules **14** and **6**, respectively, comparable to the values in the known selenoamides [1.81(5) – 1.856(4) Å for C=Se double bonds and 1.270(7) – 1.324(8) Å for C-N single bonds].<sup>42,49</sup> Interestingly, intramolecular N-H⋯O hydrogen bonding was observed in **6** and **14** to form faked seven-membered ring conformations. The N-H⋯O distances (2.09 and 2.15 Å), and N⋯O distances (2.920 and 3.031 Å) and the N-H⋯O angles (157.46 and 175.19°) are comparable to those in molecules **1**, **2** and **4**.



**Scheme 7** Decomposed products **14** and **15** of the selenamide **6** during crystallization process

Compound **11** co-crystallizes in the triclinic space group *P*-1 with another solvated molecule of *n*-hexane in the unit cell as depicted in Figure S5. The C=Se double bond and C-N single bond distances [1.829(9) and 1.319(9) Å, respectively] are in good agreement with the literature values for the normal C=Se double bond distances [1.81(5) to 1.856(4) Å] and C-N distances [1.270(7) to 1.324(8) Å] in primary selenoamides.<sup>42,49</sup> The selenoamide functionality is not particularly coplanar with either the peripheral aryl backbone or cyclohexane ring, with the dihedral angles between the Se(1)-C(1)-N(1) mean plane and the aryl plane/the cyclohexane mean plane being 88.84 and 66.91°, respectively, whilst two peripheral aryl plane and cyclohexane mean plane declines up to 32.15° each other. Interestingly, the typical N-H⋯Se hydrogen bonding was not observed as previous reports on the similar selenoamides,<sup>40,41</sup> however, there is a strong N-H⋯O hydrogen bond interaction in the structure of **11**. The O atoms on the *ortho*-position CH<sub>3</sub>O group in the phenyl ring act as hydrogen bond acceptors towards the N-H groups of a neighbouring molecule leading to the ‘fourteen-membered ring heterocyclic’ architecture as shown in Figure 4. The N-H⋯O and N⋯O distances are 2.12 Å and 2.992(10) Å, respectively, accompanied by an N-H⋯O angle of 171.9°.



**Figure 2** Molecular structures of **6** co-crystallized with **14** (d), **11** (e) and **13** (f) (Hydrogen atoms at carbon atoms omitted for clarity).

Compound **13** crystallizes in the monoclinic space group *P*2<sub>1</sub>/*c* (Figure S6). Surprisingly, we have found no published X-ray crystal structure data on this newly formed Se-C-N-C-C ring backbone. The five-membered Se1-C1-N1-C2-C3 ring is almost perfectly planar, the O atom being 0.007 Å out of the plane. The three phenyl rings attaching to the five-membered ring orientate differently each other. The dihedral angles between the five-membered ring plane and three phenyl rings are 35.90, 68.91 and 38.71°, respectively. Furthermore, due to the rotational symmetry, this leads to the planes of their phenyl rings being inclined by 57.60, 68.96 and 71.47° with respect to each other. Two different C-Se distances [1.849(3) and 1.946(3) Å] show one C-Se bond having somewhat double bond character, which is close to the values found in selenadiazoles<sup>23,29,50</sup> and the other C-Se bond reveals its typical single bond nature (*ca.* 1.94 Å). The two C-N bonds [1.341(3) and 1.403(3) Å] also demonstrate multiple/single bond distances.

In summary, a series of new adducts were prepared by using multicomponent condensation reaction from readily available substrates. The newly formed adducts were reacted with Woollins’ reagent giving rise to a variety of novel selenoamides and selenium-nitrogen heterocyclic compounds in good yields. All new products were fully characterized by multi-NMR and mass spectroscopy and six representative X-ray structures were elucidated successfully. The solid state structures of adducts **1**, **2** and **4** display intermolecular N-H⋯O hydrogen bonds leading to dimeric fourteen-membered ring architectures. The structure of selenoamide **6** co-crystallizes with one of its two decomposed products. Surprisingly, typical N-H⋯Se hydrogen bonding in the structure of selenoamide **11** was not observed as previous reports on the similar selenoamides, instead, there is the strong intermolecular N-H⋯O hydrogen bond interaction present. The newly formed five-membered ring Se-C-N-C-C(=O) in heterocyclic compound **13** is almost perfectly planar. The synthesis and X-ray single crystal structures of a series of new selenoamides and 1,3-selenazolic compounds provide a valuable addition to the library of selenium-containing heteroatom compounds known.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

X-ray data for compounds **1**, **2**, **4**, **6**, **11** and **13** CCDC 1017055-1017060 can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) or from the Cambridge Crystallographic Data centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax (+44) 1223-336-033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk).

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- Preparation of N-(4-Chlorophenyl)-N-(1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-2-oxo-2-phenylacetamide (3). General procedure:** A mixture of cyclohexylisocyanide (1.100 g, 10.0 mmol) and 4-chlorobenzaldehyde (1.362 g, 10.0 mmol) and 4-chloroaniline (1.276 g, 10 mmol) and phenylglyoxylic acid (1.406 g, 10.0 mmol) in 20 mL of dry CH<sub>3</sub>OH was stirred at room temperature for 18 h. The mixture was then concentrated on ca. 5 mL and purified by silica gel column (eluted by 1 : 9 ethyl acetate / dichloromethane) to give 4.60 g of the titled compound as a white solid in 91% yield. M.p. 196-198°C. Selected IR (KBr, cm<sup>-1</sup>): 1686(s), 1660(s), 1536(s), 1490(s), 1337(m), 1227(s), 1094(s), 1015(s), 807(m), 693(s), 583(m), 563(m), 433(m). <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, δ), 7.94 (d, J(H,H) = 7.2 Hz, 2H, Ar-H), 7.60 (d, J(H,H) = 7.2 Hz, 2H, Ar-H), 7.49-7.44 (m, 3H, Ar-H), 7.21 (d, J(H,H) = 7.2 Hz, 2H, Ar-H), 7.10 (d, J(H,H) = 7.2 Hz, 2H, Ar-H), 6.98 (d, J(H,H) = 7.2 Hz, 2H, Ar-H), 6.16 (s, 1H, CH), 5.60 (d, J(H,H) = 7.7 Hz, 1H, NH), 3.88-3.81 (m, 1H, cyclohexyl-H), 1.98-1.01 (m, 11H, cyclohexyl-H) ppm. <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, δ), 190.4 (C=O), 167.7 (C=O), 167.3 (C=O), 135.3, 135.0, 134.7, 133.1, 132.9, 132.1, 131.8, 129.7, 129.0, 128.9, 128.8, 64.0, 49.3, 32.8, 25.5, 24.9 ppm. MS (CI<sup>+</sup>, m/z), 509

[M+H]<sup>+</sup>. Accurate mass measurement [CI<sup>+</sup>, m/z]: 509.1386 [M+H]<sup>+</sup>, calculated mass for C<sub>28</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>: 509.1393.

(37) **Preparation of N-(4-Chlorophenyl)-N-(2-(cyclohexylamino)-1-(2,3-dimethoxyphenyl)-2-selenoethyl)-2-phenylethaneselenoamide (6).**

**General procedure:** A mixture of N-(4-Chlorophenyl)-N-(2-(cyclohexylamino)-1-(2,3-dimethoxyphenyl)-2-oxoethyl)-2-oxo-2-phenylacetamide (0.534 g, 1.0 mmol) and Woollins' reagent (1.07 g, 2.0 mmol) in 20 mL of dry toluene was refluxed for 8 h. A brown suspension was formed. Upon cooling to room temperature, the mixture was filtered to remove insoluble solid and the filtrate was dried in vacuum. Then, the residue was dissolved in ca. 1 mL of dichloromethane and was purified by silica gel column (eluted by 1 : 5 ethyl acetate / dichloromethane) to give 0.440 g as a pale yellow solid in 68% yield. M.p. >210°C (Dec.). Selected IR (KBr, cm<sup>-1</sup>): 1649(s), 1647(s), 1587(m), 1536(m), 1483(vs), 1451(s), 1430(s), 1273(s), 1223(m), 1168(m), 1088(s), 1003(s), 749(s), 706(s). <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, δ), 8.87 (d, J(H,H) = 8.5 Hz, 1H, Ar-H), 7.98-6.21 (m, 11H, Ar-H), 6.21 (s, 1H, CH), 5.70 (d, J(H,H) = 8.0 Hz, 1H, NH), 3.84 (s, 3H, OCH<sub>3</sub>), 3.81-3.79 (m, 1H, cyclohexyl-H), 3.76 (s, 3H, OCH<sub>3</sub>), 3.40 (s, 2H, CH<sub>2</sub>), 2.08-0.85 (m, 10H, cyclohexyl-H) ppm. <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, δ), 204.4 (C=Se), 202.8 (C=Se), 152.6, 148.2, 140.7, 131.0, 129.3, 129.2, 128.5, 128.4, 128.1, 126.9, 124.5, 123.6, 122.6, 113.5, 74.0, 66.9, 55.8, 53.5, 36.8, 25.4, 24.4 ppm. <sup>77</sup>Se NMR (CD<sub>2</sub>Cl<sub>2</sub>, δ), 546.0 and 542.5 ppm. MS (CI<sup>+</sup>, m/z), 649 [M+H]<sup>+</sup>. Accurate mass measurement [CI<sup>+</sup>, m/z]: 649.0629 [M+H]<sup>+</sup>, calculated mass for C<sub>30</sub>H<sub>33</sub>ClN<sub>2</sub>O<sub>2</sub>Se<sub>2</sub>H: 649.0635.

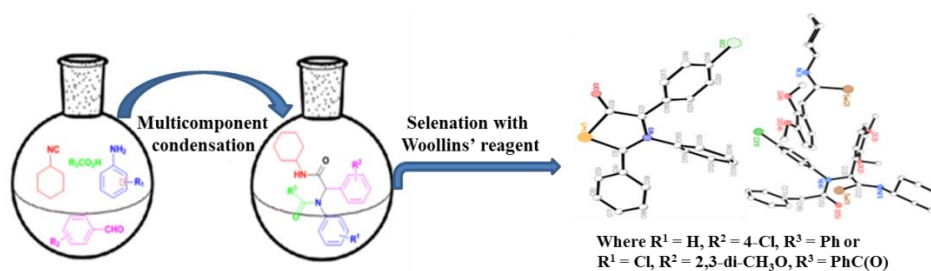
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## Graphical abstract

**Synthesis and Selenation of Tandem Multicomponent Condensation Adducts**

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Novel selenium compounds were obtained through four-component-one-pot condensation followed by selenation with Woollins' reagent.