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# Regioselective One-pot Three Component Synthesis of Chiral 2-Iminoselenazolines by Sonication

Wong-Jin Chang[1], Manohar V. Kulkarni[1] and Chung-Ming Sun*[1,2]

[1]*Department of Applied Chemistry, National Chiao-Tung University, Hsinchu 300, Taiwan, R.O.C.* [2]*Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, 100, Shih-Chuan 1st Road, Kaohsiung, 80708, Taiwan, ROC*

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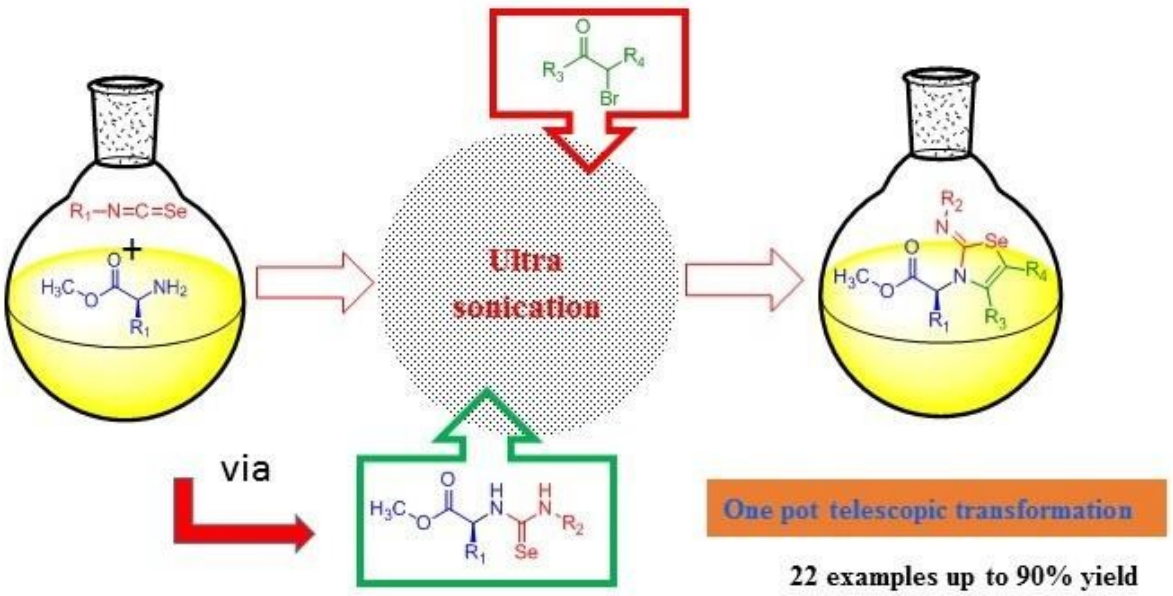


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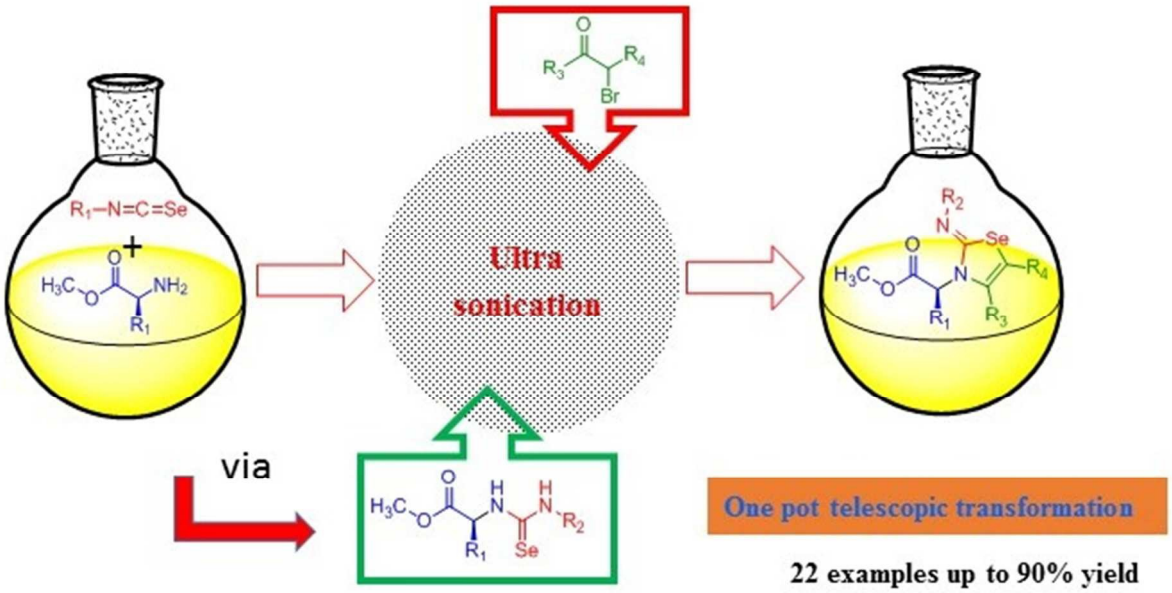
## Graphical Abstract




## Abstract

A one-pot multi-component reaction of selenourea which is *in situ* generated from *L*-amino esters and isoselenocyanate reacted with α-bromoketone under ultrasonication. Selenourea and α-bromoketone formed 2-imino selenazoles by *Hantzsch* selenazole-type reaction. The steric effect of α-substituted bromoketone



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on the rate of tandem reaction was studied to understand the reaction mechanism by isolation of key reaction intermediate, 2-iminoselenol.

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## Introduction

Functionalized organoselenium compounds serve as useful synthetic reagents and exhibit a wide range of biological properties such as antitumor, antimicrobial and antioxidant activities.[1] Synthesis of isosteric selenium analogs of biologically active sulphur compounds has often resulted in molecules with higher potency than their parent counterpart.[1d, 2] For example, imidazolene-2-selone as the inhibitor of thyroid peroxidase (TPO) displayed higher antioxidant activity than that of thione analogs.[3] There are few representatives of bioactive organoselenium compounds, such as imidazoline 2-selone and selenouracil are potent inhibitiors of LPO-catalyzed oxidation for anti-thyroid.[4-5] Selenazofurin is the blocker of IMP dehydrogenase and 2-acylamido selenazoles display anti SOC channel activity (Figure 1).[6-7] Other structure such as selenocysteine is employed in the synthesis of artificial proteins to probe the function of target selenoprotein in human body.[8] This motivated us to study the synthesis of structurally related 2-iminoselenazolines which may provide new pharmaceutical profiles. Some publications report to use thiourea and α-bromoketone to synthesize 2-

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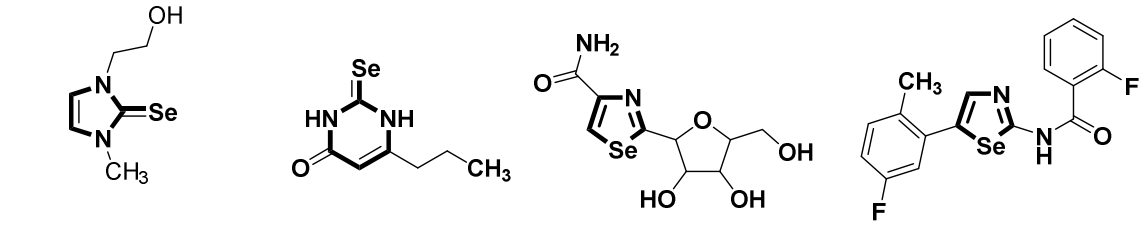
iminthiazoles.[9] In addition, the synthesis of 2-imino selenazoles is rarely studied, and only few methods for the synthesis of selenium-nitrogen heterocycles were reported.[10] The reactions of N-containing nucleophiles such as *β*-haloamines and propargyl amines with aryl or alkyl isoselenocyanates were utilized for the synthesis of 1,3-selenazolidin-2-imines.[11] Other reported synthesis of pure chiral selenazolidines was employed reaction of chiral isoselenocyanates in aqueous ammonia.[12] Reaction of readily available enantiopure α-aminoacids/esters is relatively unexplored for such transformations. Therefore, development an efficient method to synthesis 2-iminoselenazoline is of great interest to academia and pharmaceutical industry. Herein, we studied to incorporate selenium atom into the heterocyclic rings from aryl or alkyl isoselenocyanates to the synthesis the 2-iminoselenazoline by multicomponent coupling reactions.




Imidazoline 2-selone | Selenouracil | Selenazofurin | 2-Acylamido selenazoles

**Figure 1.** Structure related biologically active organoselenium compounds

Multicomponent reaction (MCR) is a powerful synthetic tool for the rapid and efficient construction of complicated molecular frameworks. Their flexibility to



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generate structural diversity and incorporation of molecular complexity in one-pot operation is well-recognized.[13] An essential rule to avoid isolation and purification of the intermediates in one pot reaction is a major factor to speed up synthesis of drug-like compounds.[14] MCRs are strategically amenable with modern synthetic tools such as microwave irradiation, ultrasonication, polymer and ionic liquid-supported synthesis. Combination to apply of these techniques is a driving force to discover new MCRs. Ultrasonication employs a non-electromagnetic radiation source of sound energy to induce chemical reactions by acoustic cavitations. Ultrasonication also accelerates chemical reactions by improvement of mixing reactants of mass and heat transfer in the reaction medium.[15] Ultrasound accelerated three component coupling synthesis of tetrahydropyrimidines,[16] phthalazinones,[17] spirooxindoles[18] and azoles[19] has been demonstrated their efficiency in multicomponent reactions.

In view of the power associated with ultrasonication and the biological importance of selenium analogs, we report a three component coupling reaction toward selenium-containing heterocycles. These telescoped reactions of *L*-amino esters, isoselenocyanates and α-substituted bromoketones for regioselective synthesis of enantiopure 2-iminoselenazolenes by ultrasonication were explored in one pot.

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## Result and Discussion

Initially, we tested the reactivity of *L*-aminoesters **2** with various aryl and alkyl-isoselenocyanates **1**, for the synthesis of selenium containing heterocycles from selenourea.[20] The required isoselenocyanates were synthesized using modified literature procedures from N-formylamines with various amines ($R_1NH_2$) in sonication. Continuously, N-formamide, triphosgene and triethylamine in dichloromethane were refluxed to generate intermediate isocyanide, which was further reacted with selenium powder to produce isoselenocyanates in one pot. (Scheme 1) The isolated yields were much higher than that of previous report by the application of sonication.[21] The structures of compound **1f** were confirmed by X-ray analysis (Figure 2).

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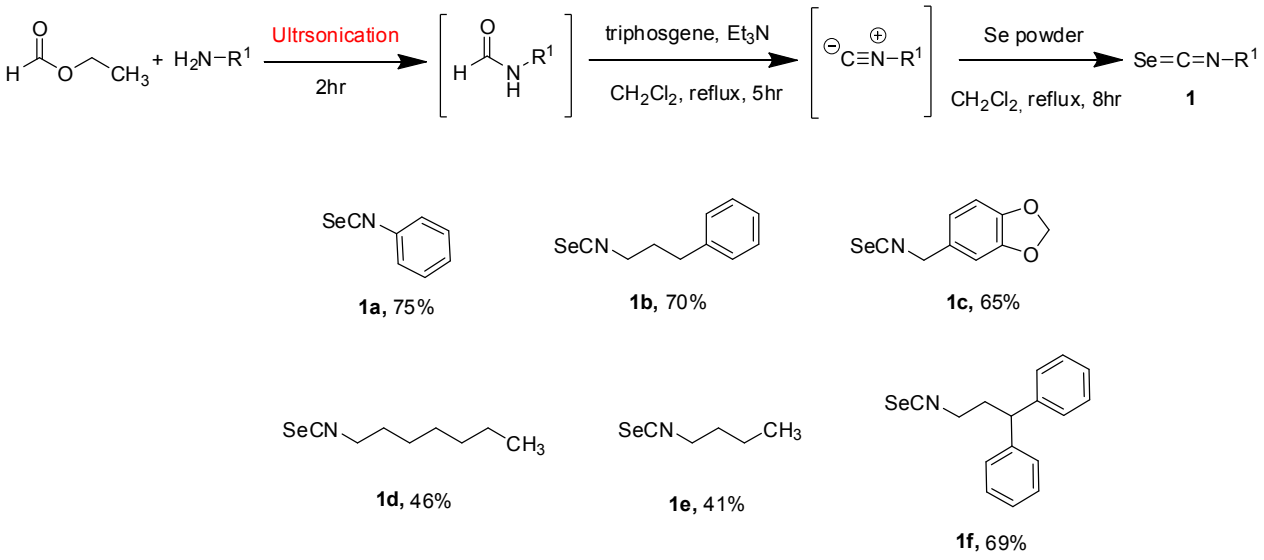


**Scheme 1.** Synthesis of isoselenocyanate **1** in one-pot

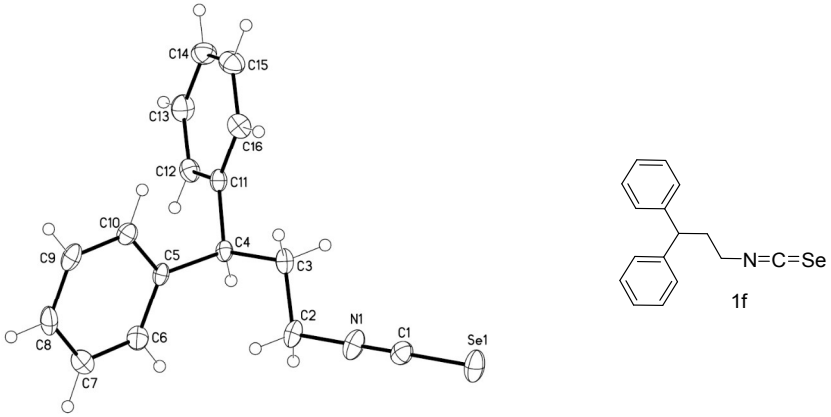


**Figure 2.** X-ray crystal structures of **1f**

With successful preparation of isoselenocyanates, we began to react *L*-phenylalanine methyl ester **2d** with phenyl selenoisocyanate **1d** to deliver



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intermediate selenourea **3d** within 30 min**.** Addition of phenacyl bromide to the above-mentioned reaction mixture led to the formation of 2-seleniimidazoles **5d** in 52 % yield. Base on this observation, we attempted to develop a one-pot procedure without prior isolation of selenourea **3**. The 2-seleniimidazoles **5d** was obtained in 72 % yield by one pot protocol which is higher than that of stepwise reaction (52 %). To explore the reaction conditions, a series of experiments to use *L*-amino acid methyl esters, isoslenocyanates, and α-bromoketones with variation of reaction parameters were performed (see SI). In order to accelerate the coupling reactions, we also applied microwave in the various solvents such as THF, acetonitrile, MeOH, DMF, and $H_2O$ for the same reaction stoichiometry. When the external base was added to the reaction mixture, intermolecular cyclization was performed first to deliver selenohydantoin which was not our desired selenourea **3**.

Although microwave irradiation increased the reaction yield and diminished the reaction time in some cases,[22] this harsh condition could cause decomposition and racemization of the temperature sensitive compounds such as chiral amino acids and carbonyl compounds…etc.[23] Moreover, selenourea is well-known air and light sensitive molecule, it is necessary to develop a mild reaction tool such as sonication to synthesize 2-iminoselenazolines.[24] We used ultrsonication to accelerate the reaction progress in various solvents such as THF,

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acetonitrile, MeOH, DMF, and $H_2O$. The compound **5a** was finally obtained in 80 % yield by sonication in acetonitrile.[25]

To ensure the stereochemistry of **5d** remains unaffected during these transformations, the other enantiomer **5d´** was synthesized from D-phenylalanine methyl ester. Chiral HPLC analysis of the products **5d** and **5d´** confirmed complete conservation of enantiomeric purity (see SI). As shown in Table1, we summarized this reaction with miscellaneous reagents and starting material. Treatment of α-aminoesters **2** with isoselenocyanates **1** under ultrasonication at room temperature to deliver corresponding selenourea **3** within 5 min in acetonitrile. The same reaction required 30 min reflux to reach completion. Further treatment of crude reaction mixture with various bromoketones **4a-l** led to the formation of 2-iminoselenazoles **5a-l** in 30 min by sonication (Table 1). This observation also contributes to study the ultrasonic effect and thermal refluxing condition on rates of reactions. For examples by the same stoichiometry, it took 3 hours to reflux in $CH_3CN$ to synthesize **5a**. The structure of compound **5f** was further confirmed by X-ray analysis (Figure 3).

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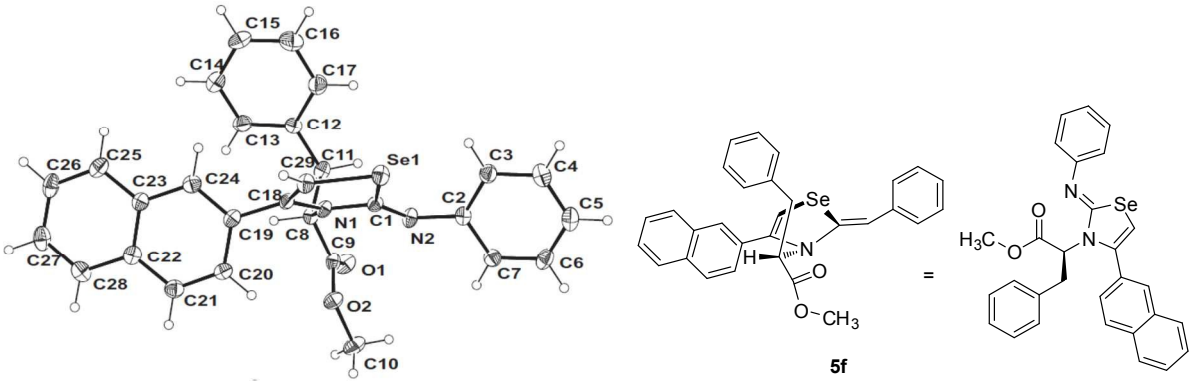
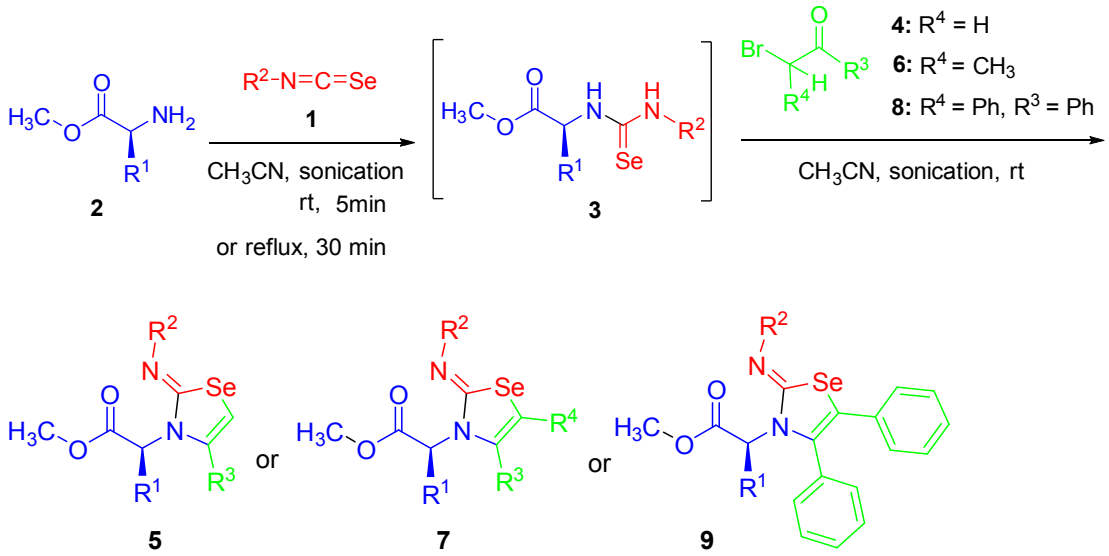



**Figure 3.** X-ray crystal structures of **5f**

**Table 1.** One pot, two step to synthesis of 2-iminoselenazole by α-bromoketone, isoselenocyanate, and *L*-aminoester

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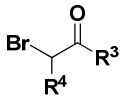
| Entry | $R^1$ | $R^2$-N=C=Se |  | Yield[d] |
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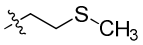
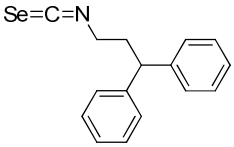
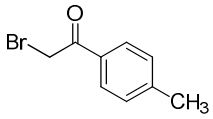
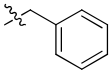
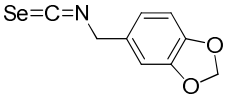
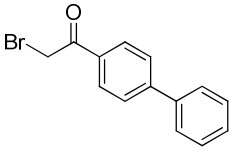
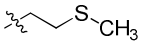
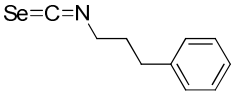
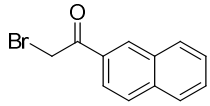
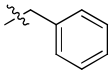
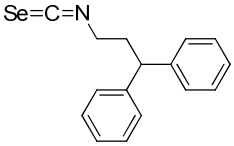
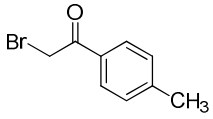
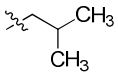
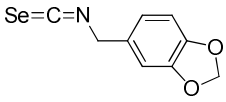
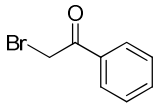
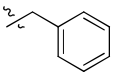
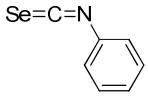
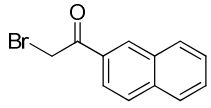
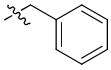
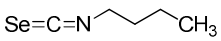
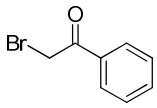
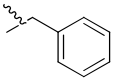
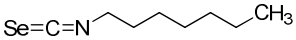
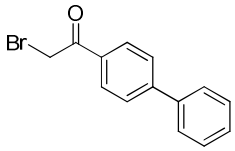
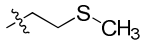
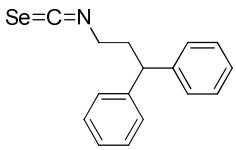
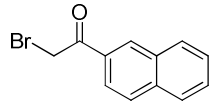
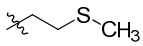
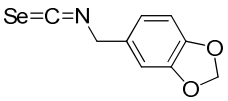
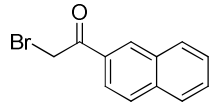
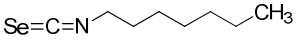
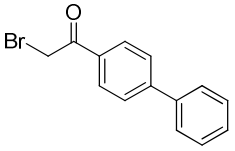
| 5a |  |  |  | 80% |
| 5b |  |  |  | 77% |
| 5c |  |  |  | 67% |
| 5d |  |  |  | 59% |
| 5e |  |  |  | 80% |
| 5f |  |  |  | 73% |
| 5g |  |  |  | 79% |
| 5h |  |  |  | 84% |
| 5i |  |  |  | 90% |
| 5j |  |  |  | 75% |
| 5k |  |  |  | 67% |



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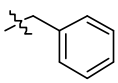
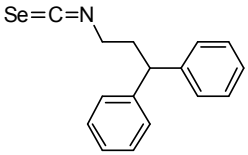
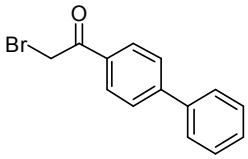
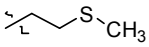
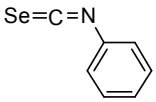
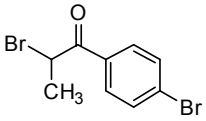
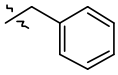
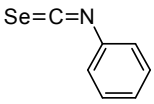
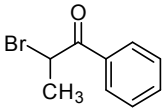
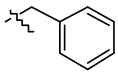
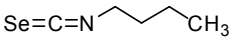
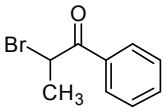
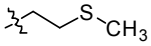
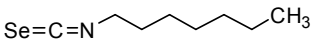
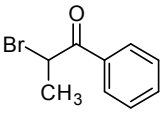
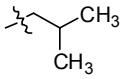
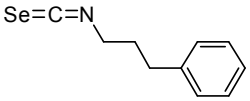
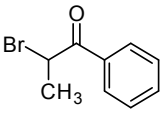
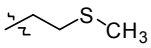
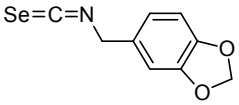
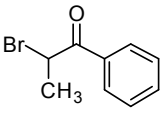
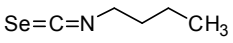
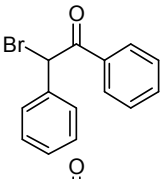
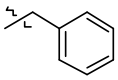
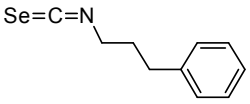
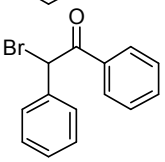
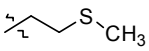
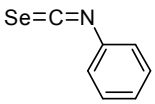
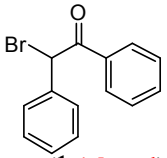
| 5l |  |  |  | 78% |
| 7a |  |  |  | 66% |
| 7b |  |  |  | 85% |
| 7c |  |  |  | 83% |
| 7d |  |  |  | 80% |
| 7e |  |  |  | 78% |
| 7f |  |  |  | 78% |
| 9a |  |  |  | 82% |
| 9b |  |  |  | 42% |
| 9c |  |  |  | 67% |

[a]Reaction Conditions : *L*-aminoesters (**2**, 1.0mmol), isoselenocyanate (**1**, 1.5mmol), α-bromoketone (**4**, 1.5mmol), MeCN (10ml), rt, step two 30min, total 35min.

[b]Reaction Conditions : *L*-aminoesters (**2**, 1.0mmol), isoselenocyanate (**1**, 1.5mmol), α-bromoketone (**6**, 1.5mmol), MeCN (10ml), rt, step two 90min, total 95min

[c]eaction Conditions : *L*-aminoesters (**2**, 1.0mmol), isoselenocyanate (**1**, 1.5mmol), α-bromoketone (**8**, 1.5mmole), MeCN (10ml), rt, step two 60min, total 65min

[d]Isolation yields

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Formation of selenazoles is favorable through Se-alkylation over N-alkylation followed by the regioselective cyclization to generate product **5**, according to a recent report regarding reaction of N, N′-biaryl selenourea with phenacyl bromide.[9a] Such a condensation of selenourea, with enolizable ketones and bromine is well-known as Hantzsch synthesis.[26] However, the interplay of ambident N *vs* Se nucleophilicity leading to ambiguous structural interpretation of imidazol-2-selenone or selenone-2-imine prompted us to study the reaction mechanism in more details.[27] We utilized condensation of selenourea with α-bromoketone to synthesize 2-iminoselenazolines in 90 min (Table 1, **7a~7f**). The structure of compound **7a** was confirmed by X-ray analysis (see SI). Secondary α-bromoketones are rarely used for Hantzsch selenazole type condensations due to their low reactivity. The α-substituted bromoketones required higher sonication time compared to that of unsubstituted bromoketones due to steric hindrance. We utilized this fact to study the reaction mechanism with possible isolation of reaction intermediates. The treatment of selenourea **3** with α-phenyl phenacyl bromide **8** under ultrasonication in acetonitrile for 40 min confirmed complete conversion into a new product, which is characterized to reveal the formation of 4, 5-diphenyl 2-imino 4-hydroxy 1, 3-selenazolidin **10** as possible reaction intermediate (Scheme 2). The structural characterization of **10** was also confirmed by X-ray crystallographic analysis (Figure 4). These similar results for the

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observations also made by Egan and Tadanier in Hantzsch thiazole synthesis.[25a] We synthesize a series of compounds **9a, 9b, 9c** to test the reactivity difference of $R_1$ and $R_2$ group with 2-bromo-1,2-diphenylethanone. The dehydrated 2-iminoselenazole **9** (Table 1, **9a~9c**) was eventually obtained by prolonged sonication for 60 min. Compound **9a** was less steric bulky to obtain higher yields, but compound **9b** with steric bulk groups $R_3$ and $R_1$ leads to less yield. Current studies have been restricted to benzoin condensation, ester hydrolysis, dichlorocyclopropanation and there are paucity of data to rationalize the steric effects in terms of the bulk of the two carbon electrophiles in such cyclization reactions.[28-30] Summarization the reaction time of selenourea with three kinds of α-bromoketone shows that the primary α-bromoketone was rapid (35 min), the 2-bromo-1,2-diphenylethanone was milder (65 min), and 2-bromopropiophenone was slower (95 min).

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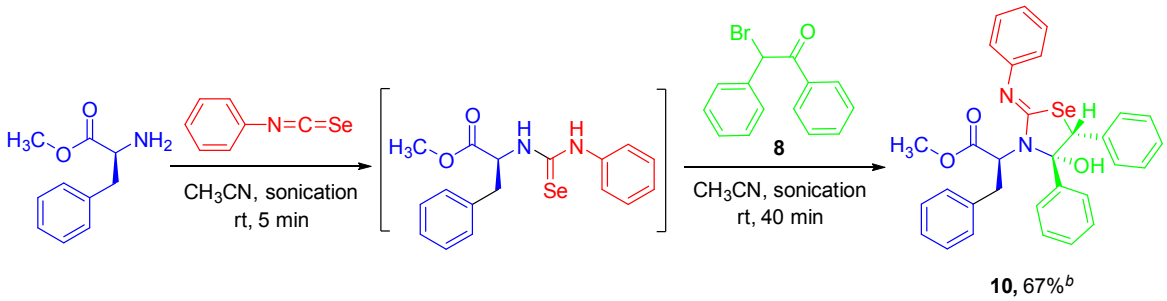
**Scheme 2.** One pot synthesis of 4, 5-diphenyl 2-imino -4-hydroxy 1, 3-selenazolidin **10**.

*a*




[a]Reaction Conditions : *L*-aminoesters (**2**, 1.0 mmol), isoselenocyanate (**1**, 1.5 mmol), 2-bromo-1,2-diphenylethanone (**8**, 1.5 mmol), $CH_3CN$ (10ml), rt, 45 min
[b]Isolated yields

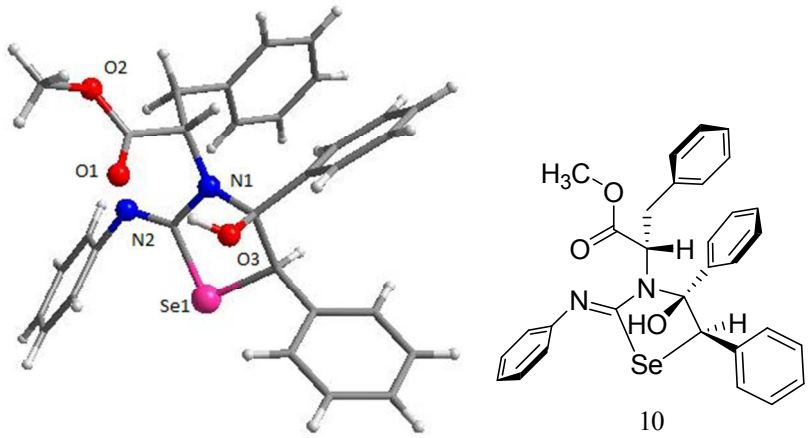



**Figure 4.** Structure of the 4-hydroxy-4,5-diphenyl-2-(phenylimino)-1,3-selenazolidin-3-yl)-3-phenylpropanoate **10**



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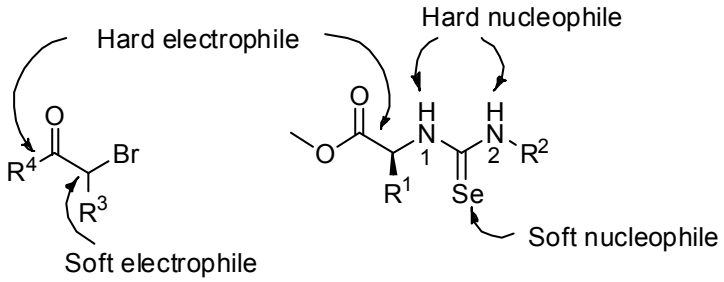
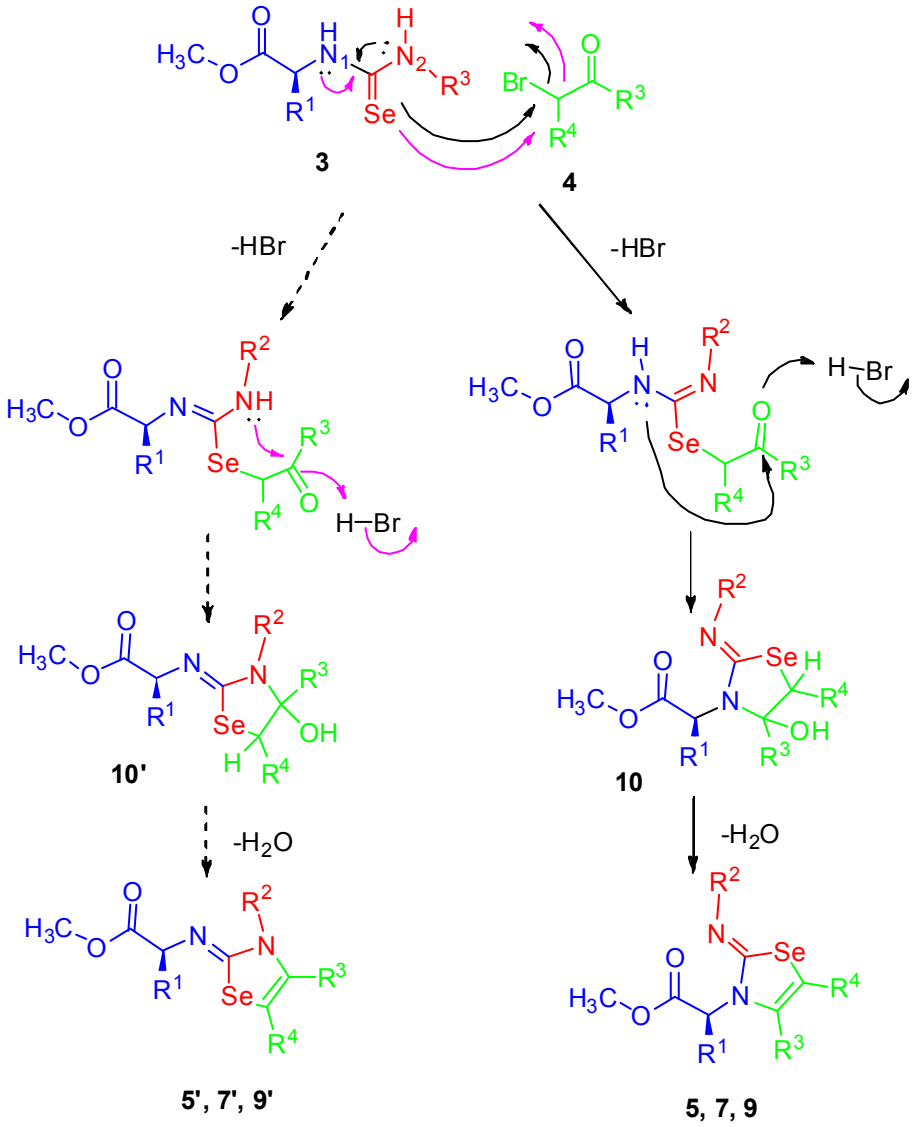



**Figure 5.** Various reactive sites in selenourea and α-bromoketone




**Scheme 3.** A plausible mechanism for the formation of 2-iminoselenazoles **5, 7, 9**



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Thus in presence of anhydrous acetonitrile, the selenourea reacts *via* soft nucleophile Se with soft electrophilic C-Br bond (Figure 5). The subsequent transformation involves loss of proton from $N_1$ and intramolecular nucleophilic attack of $N_2$ (hard nucleophile) on carbonyl group of ketone (hard electrophile) to deliver 2-iminoselenol **10** that on subsequent dehydration releases the observed product 2-iminothiozole **5, 7, 9** (Scheme 3). From our supposition, the $N_2$ was more reactive than $N_1$ because $N_1$ was near electron-withdrawing carbonyl group of amino ester to cause regioselectivity. Therefore, formation of the 2-iminoselenazoles **5, 7, 9** is due to preferential attack of selenium of its enhanced nucleophilicity and the driving force for the selective $N_1$ attack on the alkyl carbon to eliminate a stable hydrobromide salt. Furthermore, influence of steric factors on the reaction time has been effectively to characterize the intermediate 2-imino-5-selenol **10** which is undoubtedly confirmed that selenourea reacts *via* soft nucleophile (*i. e.* selenium atom).

In conclusion, we explored a regioselective synthesis of polysubstituted 2-iminoselenazoles by reaction of *in situ* generated selenoureas with α-bromoketones under environmentally benign ultrasonic activation at room temperature. We understand reaction mechanism through $N_1$ selenourea by reaction of soft nucleophile Se with soft electrophilic C-Br bond to form 2-iminoselenazoles. Intermediate of dihydro selenol in the construction of 2-imino selenazolines has

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been conclusively established in the seleno *Hantzsch* reaction. An efficient synthesis of enantiopure 2-iminoselenazoles from ready available building blocks may help to discover novel biological profiles of these skeletal diverse scaffolds.

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**Supporting Information:** Spectroscopic data of essential intermediates and final compounds as well as X-ray data of compounds **1f, 5f, 7a, 9b** are included in the Supporting Information.

## References

1. (a) Mukherjee, A. J.; Zade, S. S.; Singh, H. B.; Sunoj, R. B. *Chem. Rev.* **2010**, *110,* 4357. (b) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev*. **2004**, *104*, 655. (c) Mugesh, G.; Mont, W. W. D.; Sies, H. *Chem. Rev*. **2001**, *101*, 15. (d) Wirth, T. *Organoselenium Chemistry: Synthesis and Reactions*; WILEY-VCH, 2012, p361

RSC Advances Accepted Manuscript

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DOI: 10.1039/C5RA18763J

Published on 22 October 2015. Downloaded by UNIVERSITY OF NEBRASKA on 22/10/2015 16:30:02.

2. (a) Bhabak, K. P.; Mugesh, G. *Acc. Chem. Res*. **2010**, *43*, 1408. (b) Yoshimoto, N.; Itoh, T.; Inaba, Y.; Ishii, H.; Yamamoto, K. *J. Med. Chem.* **2013**, *56*, 7527. (c) Sasaki, N. T.; Inaba, Y.; Ishii, H.; Yamamoto, K. *J. Med. Chem.* **2012***, 55,* 7696.
3. Manna, D.; Roy, G.; Mugesh, G. *Acc. Chem. Res.*, **2013**, *46*, 2706.
4. Roy, G.; Jayaram, P. N.; Mugesh, G. *Chem.-Asian J.* **2013**, *8,* 1910.
5. Theo, J. V.; Kaptein, E.; Aboul-Enein, H. S. *Biochem. Biophys. Res. Commun.* **1992**, *189*, 1362.
6. Franchetti, P.; Cappellacci, L.; Sheikha, G. A.; Jayaram, H. N.; Gurudutt, V. V.; Sint, T.; Schneider, B. P.; Jones, W. D.; Goldstein, B. M.; Perra, G.; Montis, A. D.; Loi, A. G.; Colla, P. L.; Grifantini, M. *J. Med. Chem.* **1997**, *40*, 1731.
7. Cao, j.; Whitten, J. P.; Pei, Y.; Wang, Z.; Rogers, E.; Grey, J. US Patent 2012010071516, Mar 22, 2001.
8. (a) Aldaga, C.; Gromov, I. A.; García-Rubio, I.; Koenigc, K.; Schlichting, I.; Jauna, B.; Hilverta, D. *Proc. Natl. Acad. Sci.* **2009**, *106*, 5481. (b) Hazebrouck, S.; Camoin, L. Faltin, Z.; Strosberg, A. D.; Eshdat, Y. *J. Biol. Chem.* **2000**, *75*, 2871.
9. (a) Han, M.; Nam, K. D.; Shin, D.; Jeong, K.; Hahn, H. K. *J. Comb. Chem.* **2010**, *12*, 518. (b) Altintop, M. D.; Kaplancılı, Z. A.; Çiftçi, G. A.; Demirel, R. *Eur. J. Med. Chem.* **2014**, *74*, 264.

RSC Advances Accepted Manuscript

View Article Online
DOI: 10.1039/C5RA18763J

Published on 22 October 2015. Downloaded by UNIVERSITY OF NEBRASKA on 22/10/2015 16:30:02.

10. (a) Atanassov, P. K.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta.* **2010**, *93*, 395. (b) Sommen, G. L.; Linden, A.; Heimgartner, H. *Eur. J. Org. Chem.* **2005**, *14*, 3128.

11. (a) Ueda, S.; Terauchi, H.; Suzuki, K.; Watanabe, N. *Tetrahedron Lett.* **2005**, *46*, 233. (b) Xie, Y.; Liu, J.; Li, J. *Tetrahedron Lett.* **2011**, *52*, 932.

12. Ueda, S.; Terauchi, H.; Suzuki, K.; Yano, A.; Matsumoto, M.; Kubo, T.; Minato, H.; Arai, Y.; Tsuji, J.; Watanabe, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1361.

13. (a) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463-472. (b) Tourie, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109,* 4439. (c) Graaff, C. D.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41,* 3969. (d) Biggs-Houk, J. E.; Younai, A.; Shaw, J. T. *Curr. Opinion. Chem. Biol.* **2010**, *14,* 371.

14. Schreiber, S. L. *Nature,* **2009**, *457*, 153.

15. (a) Bravo, J. L.; Lopez, I.; Cintas, P.; Silvero, G. Arevalo, M. J. *Ultrason. Sonochem.* **2006**, *13*, 408. (b) Cravotto, G.; Cintas, P. *Chem. Soc. Rev.* **2006**, *35*, 180.

16. Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Chebanov, V. A. *J. Comb. Chem.* **2007**, *9,* 797.

17. Shukla, G.; Verma, R. K.; Verma, G. K.; Singh, M. S. *Tetrahedron Lett.* **2011**, *52*, 7195.

RSC Advances Accepted Manuscript

View Article Online
DOI: 10.1039/C5RA18763J

Published on 22 October 2015. Downloaded by UNIVERSITY OF NEBRASKA on 22/10/2015 16:30:02.

18. Dabiri, M.; Tisseh, Z. N.; Bahramenejad, M.; Bazgir, A. *Ultrason. Sonochem.* **2011**, *18*, 1153.

19. (a) Saleh, T. S.; Eldebss, T. M. A.; Albishri, H. M. *Ultrason. Sonochem.* **2012**, *19*, 49. (b) "Recent advances in the Ultrasound assisted synthesis of azoles" by Pizzuti, L.; Franco, M. S. F. A.; Flores, F. C.; Quina, F. H.; Pereira, C. M. P. in Green Chemistry-Environmentally Benign Approaches, Kidwai, Ed. Mishra, M.; N. K. ISBN 9535103349, 01, 81.

20. (a) Asanuma, Y.; Fujiwara, S.; Ike, T. S.; Kambe, N. *J. Org. Chem.* **2004**, *69*, 4845. (b) Koketsu, M.; Ishihara, H. *Curr. Org. Chem.* **2003**, , 175.

21. (a) López, Ó.; Maza, S.; Ulgar, V.; Maya, l.; Fernández-Bolaños, J. *Tetrahedron.* **2009**, *65*, 2556. (b) Galina, K.; Jaroslav, R.; Zdeňka, P.; Zdeněk, N.; Kateřina, V.; Alexandr, H. *Tetrahedron.* **2013**, 6*9*, 8798.

22. Kappe, C. O. *Angew. Chem.* Int. Ed. **2004**, *43*, 6250.

23. (a) *Dictionary of Organic Compounds*, 6th ed.; Chapman and Hall: New York, 1995; Vol. 6, p5646. (b) Narender, M.; Reddy, M. S.; Kumar, V. P.; Reddy, V. P.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2007**, *72,* 1849.

24. Zhang, Z.; Zha, Z.; Gan, C.; Pan, C.; Zhou, Y.; Wang, Z.; Zhou, M. M. *J. Org. Chem.* **2006**, *71*, 4339.

25. Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504.

RSC Advances Accepted Manuscript

View Article Online
DOI: 10.1039/C5RA18763J

26. (a) Egan, R. S.; Tadanier, J. *J. Org. Chem.* **1968**, *33*, 4422. (b) Qiao, Q; So, S. S.; Goodnow, R. A. *Org. Lett.* **2001**, *3*, 3655.

27. Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8,* 5397.

28. Tuulmets, A.; Hagu, H.; Salmar, S.; Cravotto, G.; Jarv, J. *J. Phys. Chem. B,* **2007**, *111,* 3133.

29. Salmar, S.; Cravotto, G.; Tuulmets, A.; Hagu, H. *J. Phys. Chem. B,* **2006**, *110*, 5817.

30. Wang, M. L.; Prasad, G. S. *Ultrasonics. Sonochem.* **2012**, *19*, 1139.

Published on 22 October 2015. Downloaded by UNIVERSITY OF NEBRASKA on 22/10/2015 16:30:02.

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