Tetrahedron Letters 53 (2012) 3835–3838

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A tandem one-pot aqueous phase synthesis of thiazoles/selenazoles

B. Madhav, S. Narayana Murthy, B.S.P. Anil Kumar, K. Ramesh, Y.V.D. Nageswar *

Natural Product Chemistry, Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 5 March 2012
Revised 19 April 2012
Accepted 21 April 2012
Available online 11 May 2012

Keywords:
Thiazole
Selenazole
Phenylacetylenes
N-Bromo succinimide
Water

ABSTRACT

The first ever tandem one-pot synthetic protocol for the synthesis of thiazoles/selenazoles from alkynes via the formation of 2,2-dibromo-1-phenylethanone is reported. The reaction is catalyzed by β-cyclodextrin in aqueous medium and resulted in good yields.

Thiazoles, selenazoles are the principal core structures present in a variety of natural products and have acquired significance due to a wide variety of medicinal and biological properties associated with them (Fig. 1).[1] Selenazoles have been extensively described as synthetic tools,[2] as well as for their biological significance.[3] 1,3-Selenazoles act as antibiotic and cancerostatic[4] (Fig. 1). 2-Amino-1,3-selenazoles are known for their superoxide anion-scavenging activity.[5]

Thiazole skeleton has been associated with numerous biologically active molecules,[6] and its derivatives are useful in the treatment of hypertension,[7] schizophrenia,[8] inflammation,[9] allergies,[10] bacterial,[11] and HIV[12] infections. In particular, aminothiazoles act as ligands of estrogen receptors[13] as well as a novel class of adenosine receptor antagonists[14] whereas other analogs are used as fungicides, inhibiting in vivo growth of Xanthomonas and as an ingredient of herbicides and anthelmintic drugs.[15]

A few reports have appeared on the synthesis of selenazoles and thiazoles, which include both solid phase synthesis[16] and solution phase[17] synthesis. Narender et al., reported the synthesis of selenazoles/thiazoles by the condensation of phenacylbromides/tosylates with selenourea/thiourea/thiobenzamide by employing β-cyclodextrin as catalyst.[18] Recently Varma and co-workers synthesized diaryl thiazoles from various α-tosyloxy ketones in water.[19] Several protocols are also described using promoters or catalysts in different organic solvents for the synthesis of thiazoles and selenazoles. However, development of novel environmentally benign approaches for the synthesis of selenazoles/thiazoles, is highly desirable.

In continuation of our efforts toward the development of novel ecofriendly methodologies[20] which include the synthesis of heterocyclic compounds, we report herein, a mild and efficient one-pot protocol for the synthesis of substituted thiazole/selenazole derivatives, for the first time by a three-component reaction, involving phenyl acetylene, *N*-bromo succinimide and thiourea/selenourea in aqueous medium (Schemes 1 and 2). To the best of our knowledge there are no reports on the synthesis of thiazoles/selenazoles from phenylacetylenes. Developing new synthetic approaches in aqueous phase has gained prominence in organic synthesis, as it overcomes the harmful effects of organic solvents and reduces the environmental pollution. Water is also economically viable, nontoxic, and the most readily available reaction medium, making it an environmentally acceptable solvent for the design and development of green chemistry protocols.

Initialy, phenyl acetylene (1.0 mmol) was reacted with *N*-bromo succinimide (1.0 mmol) and thiourea (1.0 mmol) in the presence of

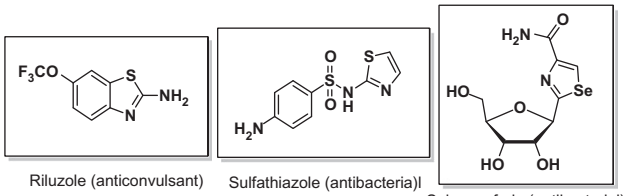
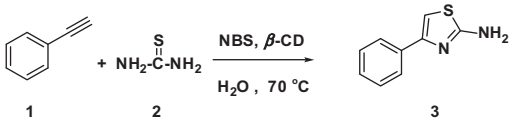


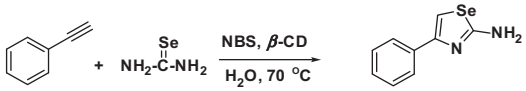
Figure 1. Biologically active thiazoles/selenazoles.

* Corresponding author. Fax: +91 40 27160512.
E-mail address: dryvdnageswar@gmail.com (Y.V.D. Nageswar).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.04.097



Scheme 1. Synthesis of selenazoles catalyzed by β-CD in aqueous medium.



Scheme 2. Synthesis of thiazoles catalyzed by β-CD in aqueous medium.

Table 1
Optimization of NBS equiv in the reaction[a]

Entry	NBS	Time (h)	*T* (°C)	Yield[b] (%)
1	0	12	90	—
2	1	12	90	35
3	1.5	10	90	45
4	2	4	70	72

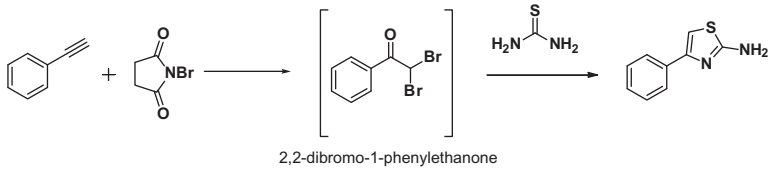
[a] Reaction conditions: phenyl acetylene (1.0 mmol), NBS, thiourea (1.0 mmol), water (10 mL).
[b] Isolated yield.

β-CD, resulting in lower yields of the desired product. It was observed that the reaction proceeded efficiently when (2.0 equiv) of *N*-bromo succinimide was used. In the absence of *N*-bromo succinimide, it was observed that the reaction did not proceed and starting materials were recovered (Table 1).

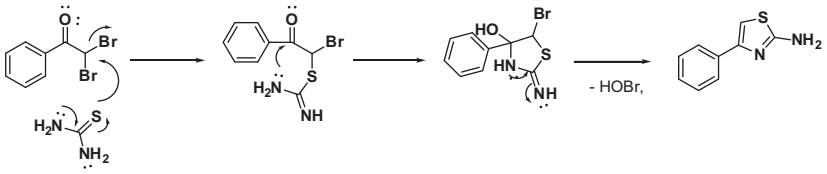
In the absence of β-CD, the product was obtained in 45% yield. While evaluating the efficiency of the catalytic system, 10 mol % of the catalyst loading was observed to be optimal for the reaction to proceed. Furthermore when the same reaction was carried out in the presence of NIS the corresponding product was produced in lower yields.

It was observed that the reaction proceeded through the in situ formation of 2,2-dibromo-1-phenylethanone, from *N*-bromo succinimide (2.0 equiv) and phenylacetylene (1.0 equiv) (Scheme 3), which further reacted with thiourea/selenourea to afford the desired product (Scheme 4).[22]

The scope of the reaction was expanded by reacting various substituted selenourea/thiourea derivatives with phenylacetylene substrates. In these reactions, substituents on the selenourea/thiourea did not have significant effect on the product yields. Similar trends were also observed in the case of phenylacetylenes. Several examples illustrating this simple and practical methodology are summarized in Table 2. All the products were characterized by ^{1}H, ^{13}C NMR and mass spectra[23] as well as by comparison with the known compounds.[21]



Scheme 3. Domino synthesis of thiazole via the in situ formation of 2,2-dibromo-1-phenylethanone.



Scheme 4. Possible reaction pathway for the synthesis of thiazole compounds.

Table 2
β-CD mediated synthesis of thiazoles[a]

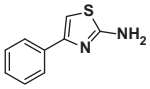
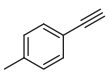
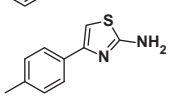
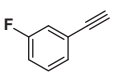
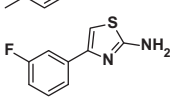
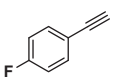
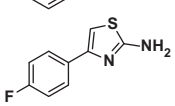
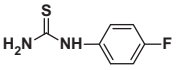
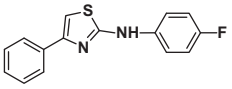
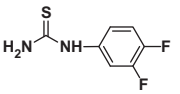
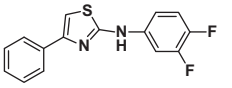
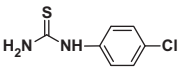
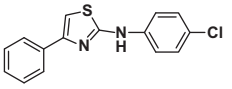
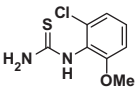
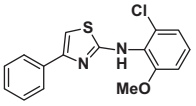
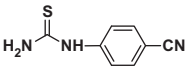
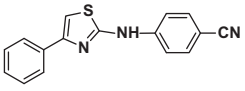
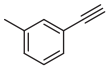
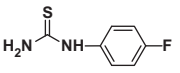
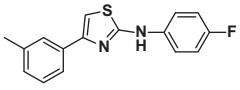
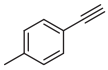
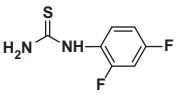
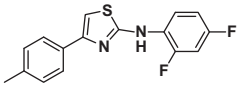
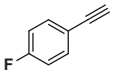
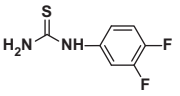
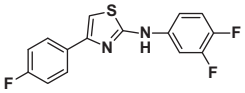
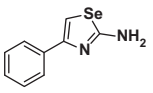
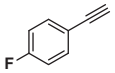
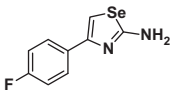
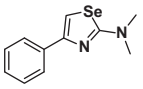
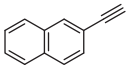
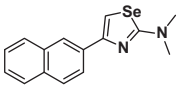
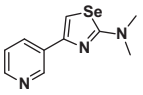
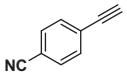
Entry	Phenylacetylene	Thiourea	Product	Yield[b] (%)
1				72
2				73
3				70
4				70

Table 2 (*continued*)

Entry	Phenylacetylene	Thiourea	Product	Yield[b] (%)
5				62
6				68
7				68
8				64
9				60
10				67
11				66
12				68

[a] Reaction conditions: phenylacetylene (1.0 mmol), NBS (2.0 mmol), thiourea (1.0 mmol) and catalyst (10 mol %) at 70 °C.
[b] Isolated yields.

Table 3
β-CD mediated synthesis of Selenazoles[a]

Entry	Phenylacetylene	Selenourea	Product	Yield[b] (%)
1				69
2				68
3				70
4				72
5				61
6				64

[a] Reaction conditions: phenylacetylene (1.0 mmol), NBS (2.0 mmol), selenourea (1.0 mmol) and β-CD (10 mol %) at 70 °C.
[b] Isolated yields.

Table 4
Recyclability of β-CD catalyst

Cycles	Yield (%)	Catalyst recovered (%)
Native	72	90
1	69	86
2	66	84
3	64	82

The recyclability of the β-CD catalyst was examined by using phenylacetylene (1.0 mmol), NBS (2.0 mmol) and thiourea (1.0 mmol) in H_2O (10 mL), as a model reaction.

In general, a model reaction was performed by the in situ formation of 1:1 β-CD complex with phenylacetylene (**1**) in water followed by the addition of NBS and thiourea (**2**) and stirred for 4 h at 70 °C to give the corresponding product (**3**) (Scheme 1). The substantial role of β-CD is illustrated by performing the reaction in water without using β-CD at 70 °C, where low yields were observed. NMR spectroscopy is one of the most important techniques used for characterization of inclusion complexes. The formation of inclusion complex results in the shift changes in the resonances of the host cyclodextrin as well as the guest protons. These changes were observed in the ^{1}H NMR spectra (D_2O) of β-CD, β-CD/phenylacetylene complex and freeze dried reaction mixture of β-CD/phenylacetylene complex with the thiourea at 1 h. Inclusion of the phenyl acetylene into β-CD from the secondary side of cyclodextrin was confirmed by an upfield shift of H_3 (0.03 ppm) and H_5 (0.05 ppm) protons of cyclodextrin in the β-CD/phenyl acetylene complex as compared to β-CD. This clearly demonstrates that the phenylacetylene is elegantly set for the addition reaction, in the hydrophobic microenvironment of β-cyclodextrin cavity. The catalyst β-CD can be easily recovered and reused.

In conclusion, we have developed a convenient one-pot aqueous phase synthesis of substituted thiazoles/selenazoles under mild conditions in encouraging yields. This method has several advantages over the existing methods such as in situ formation

of 2,2-dibromo-1-phenylethanone, ability to proceed without acids/bases or additives, under milder environmental friendly conditions. This protocol will be an interesting addition to the green chemistry (see Table 4).

Acknowledgments

We thank the CSIR, New Delhi, India, for fellowships to B.M., S.N.M., B.S.P. and the UGC for a fellowship to K.R.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.097.

References and notes

1. De Souza, M. V. N. *J. Sulfur Chem.* **2005**, *26*, 429.
2. (a) Casar, Z.; Majcen-Le Marechal, A.; Lorey, D. *New J. Chem.* **2003**, *27*, 1622; (b) Koketsu, M.; Ishihara, H. *Curr. Org. Chem.* **2003**, *7*, 175; (c) Duddeck, H.; Bradenahl, R.; Stefaniak, L.; Jazwinski, J.; Kamienski, B. *Magn. Reson. Chem.* **2001**, *39*, 709; (d) Archer, S.; McGarry, R. *J. Heterocycl. Chem.* **1982**, *19*, 1245.
3. Koketsu, M.; Choi, S. Y.; Ishihara, H.; Lim, B. O.; Kim, H.; Kim, S. Y. *Chem. Pharm. Bull.* **2002**, *50*, 1594.
4. (a) Goldstein, B. M.; Kennedy, S. D.; Hennen, W. J. *J. Am. Chem. Soc.* **1990**, *112*, 8265. and references cited therein; (b) Shafiee, A.; Khashayarmanesh, Z.; Kamal, F. *J. Sci. Islam. Repub. Iran* **1990**, *1*, 11; (c) Shafiee, A.; Shafaati, A.; Khamench, B. H. *J. Heterocycl. Chem.* **1989**, *26*, 709.
5. Sekhiguchi, A.; Nishina, A.; Kimura, H.; Fukumoto, R.-H.; Koichi, K.; Ishihara, H.; Koketsu, M. *Chem. Pharm. Bull.* **2005**, *53*, 1439.
6. Lewis, J. R. *Nat. Prod. Rep.* **1999**, *16*, 389.
7. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C. J. C.; Doharty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Bately, B. L.; Painchand, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olzon, S. C. J. *J. Med. Chem.* **1992**, *35*, 2562.
8. Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem.* **1990**, *33*, 311.
9. (a) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719; (b) Clemence, F.; Marter, O. L.; Delevalle, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Deraedt, R. *J. Med. Chem.* **1988**, *31*, 1453.
10. Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158.
11. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601.
12. Bell, F. W.; Cantrell, A. S.; Hoberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, J.; Zhang, H.; Zhou, X.-X. *J. Med. Chem.* **1995**, *38*, 4929.
13. Fink, B. A.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. *Chem. Biol.* **1999**, *6*, 205.
14. Van Muijlwijk-Koezen, J. E.; Timmerman, H.; Vollinga, R. C.; Von Drabbe Kunzel, J. F.; De Groote, S.; Ijzerman, A. P. *J. Med. Chem.* **2001**, *44*, 749.
15. *Comprehensive Heterocyclic Chemistry I*; Metzger, J. V., Ed.; Pergamon Press, 1984; Vol. 6, p 328.
16. Kazzouli, S. E.; Raboin, S. B.; Mouadbib, A.; Guillaumet, G. *Tetrahedron Lett.* **2002**, *43*, 3193.
17. (a) Bailey, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Stephen, P. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409; (b) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *62*, 196; (c) Goff, D.; Fernandez, J. *Tetrahedron Lett.* **1999**, *40*, 423.
18. (a) Narender, M.; Somi Reddy, M.; Kumar, V. P.; Reddy, V. P.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2007**, *72*, 1849; (b) Narender, M.; Somi Reddy, M.; Sridhar, R.; Nageswar, Y. V. D.; Rao, K. R. *Tetrahedron Lett.* **2005**, *46*, 5953.
19. Dalip, K.; Kumar, N. M.; Patel, G.; Gupta, S.; Varma, R. S. *Tetrahedron Lett.* **2011**, *52*, 1983.
20. (a) Murthy, S. N.; Madhav, B.; Kumar, A. V.; Rao, K. R.; Nageswar, Y. V. D. *Helv. Chim. Acta* **2009**, *92*, 2118; (b) Murthy, S. N.; Madhav, B.; Kumar, A. V.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron* **2009**, *65*, 5251; (c) Madhav, B.; Murthy, S. N.; Reddy, V. P.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2009**, *50*, 6025; (d) Murthy, S. N.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 3649; (e) Shankar, J.; Karnakar, K.; Srinivas, B.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 3938; (f) Murthy, S. N.; Madhav, B.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 5252; (g) Ramesh, K.; Murthy, S. N.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 2362; (h) Ramesh, K.; Murthy, S. N.; Karnakar, K.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 3937; (i) Ramesh, K.; Murthy, S. N.; Karnakar, K.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 4734; (j) Anil Kumar, B. S. P.; Madhav, B.; Harsha Vardhan Reddy, K.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 2862.
21. (a) Paul, S.; Gupta, V.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 439; (b) Valeria, C.; Pierluca, G.; Adriano, S.; Barbara, F. *Adv. Synth. Catal.* **2005**, *347*, 1341; (c) Ye, C.; Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561.
22. *General procedure:* β-Cyclodextrin (10 mol %) was dissolved in water (15 ml) at 70 °C and phenylacetylene (1.0 mmol) was added followed by NBS. After 10 min, thiourea (1.0 mmol) was added to this reaction mixture and stirred at 70 °C until the reaction was complete (Table 1). The mixture was extracted with ethyl acetate, and the extract was filtered. The organic layer was washed with water and dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the resulting crude product was further purified by column chromatography using hexane and EtOAc as eluent to give the title compound. The aqueous layer was cooled to 5 °C to recover β-CD by filtration. This β-CD was recycled without any loss of activity.
23. *Data for representative examples: 4-(p-Tolyl)thiazol-2-amine* (Table 2, *entry 2*): Solid, mp 135–137 °C ^{1}H NMR ($CDCl_3$/DMSO-d_6, 300 MHz): δ 7.60–7.58 (m, 2H), 7.14-7.11 (m, 2H), 6.57 (s, 1H), 5.28 (br s, 2H), 2.35 (s, 3H); ($CDCl_3$/DMSO-d_6, 200 MHz): δ 131.2, 128.3, 126.6, 126.4, 126.0, 125.2, 123.6, 27.3; ESI-MS (*m*/*z*): 191(M+H)$^+$. Anal. Calcd for ($C_{10}H_{10}N_2S$): C, 63.13; H, 5.30; N, 14.72; S, 16.85. Found C, 63.01; H, 5.25; N, 14.65; S, 16.78.
N-(3,4-Difluorophenyl)-4-phenylthiazol-2-amine (Table 2, *entry 6*): Solid, mp 103–105 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.6 (s, 1H), 8.6 (m, 1H), 7.83 (m, 2H), 7.37 (m, 2H), 6.95–6.89 (m, 3H), 2.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 162.0, 161.6, 158.8, 146.5, 134.8, 128.6, 123.8, 119.7, 118.9, 112.3, 112.0, 110.3,100.3; ESI-MS (*m*/*z*): 289 (M+H)$^+$. Anal. Calcd for ($C_{15}H_{10}F_2N_2S$): C, 62.49; H, 3.50; N, 9.72; S, 11.12. Found 62.35; H, 3.43; N, 9.66; S, 11.06.
N-(2-Chloro-6-methoxyphenyl)-4-phenylthiazol-2-amine (Table 2, *entry 8*): Solid, mp 130–132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62–7.60 (m, 4H), 7.41–7.32 (m, 6H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ: 162.3, 145.3, 133.8, 128.7, 128.2, 127.8, 127.5, 125.6, 120.6, 116.0, 110.2, 101.8, 55.5; ESI-MS (*m*/*z*): 312(M+H)$^+$. Anal. Calcd for ($C_{16}H_{13}ClN_2OS$): C, 60.66; H, 4.14; N, 8.84; S, 10.12. Found C, 60.52; H, 4.09; N, 8.78; S, 10.09.
N-(4-Fluorophenyl)-4-(m-tolyl)thiazol-2-amine (Table 2, *entry 10*): Solid, mp 105–107 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.59–7.56 (m, 3H), 7.31–7.21 (m, 2H), 7.08–7.07 (m, 1H), 7.01–6.98 (m, 2H), 6.72 (s, 1H), 2.36 (s, 3H), 1.53 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ: 160.6, 150.8, 137.9, 136.2, 134.1, 128.5, 126.9, 123.3, 121.0, 116.2, 115.9, 101.0, 21.5; ESI-MS (*m*/*z*): 285(M+H)$^+$. Anal. Calcd for ($C_{16}H_{13}FN_2S$): C, 67.58; H, 4.61; N, 9.85; S, 11.28. Found C, 67.42; H, 4.49; N, 9.74; S, 11.19.
N-(3,4-Difluorophenyl)-4-(4-fluorophenyl)thiazol-2-amine (Table 2, *entry 12*): Solid, mp 98–101 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.57 (s, 1H), 8.57–8.51 (m, 1H), 7.68 (s, 1H), 7.60 (m, 1H), 7.52 (m, 1H), 7.36–7.31 (m, 1H), 6.96–6.86 (m, 3H); ESI-MS (*m*/*z*): 307(M+H)$^+$. Anal. Calcd for ($C_{15}H_9F_3N_2S$): C, 58.82; H, 2.96; F, 18.61; N, 9.15; S, 10.47. Found C, 58.71; H, 2.88; N, 9.07; S, 10.38.
N,N-Dimethyl-4-phenyl-1,3-selenazol-2-amine(Table 3, *entry 3*): Solid, mp 112 °C ^{1}H NMR ($CDCl_3$/DMSO-d_6, 300 MHz): δ 7.83–7.80 (m, 2H), 7.34–7.19 (m, 4H), 3.16 (s, 6H). ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ 128.9, 128.7, 127.3, 127.1, 126.9, 126.8, 105.2, 41.1; ESI-MS (*m*/*z*): 253(M+H)$^+$. Anal. Calcd for ($C_{11}H_{12}N_2Se$): C, 52.60; H, 4.82; N, 11.15. Found C, 52.50; H, 4.77; N, 11.12.
N,N-Dimethyl-4-(naphthalen-2-yl)-1,3-selenazol-2-amine (Table 3, *entry 4*): Solid, mp 118–120 °C. ^{1}H NMR ($CDCl_3$/DMSO-d_6, 300 MHz): δ 7.03–7.00 (m, 2H), 6.72–6.67 (m, 4H), 6.55–6.38 (m, 2H), 2.32 (s, 6H). ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ: 128.4, 127.9, 127.8, 127.3, 126.4, 105.1, 41.0; ESI-MS (*m*/*z*):30 (M+H)$^+$. Anal. Calcd for ($C_{15}H_{14}N_2Se$): C, 59.81; H, 4.68; N, 9.30. Found C, 59.70; H, 4.59; N, 9. 23.