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Polyethylene glycol (PEG-400) as an efficient and recyclable reaction medium for one-pot synthesis of thiazoles / selenazoles

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ABSTRACT

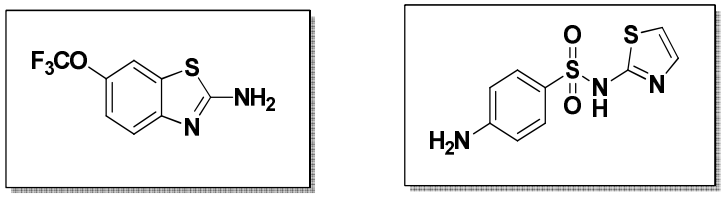
Polyethylene glycol (PEG-400) was found to be an efficient reaction medium for the one-pot synthesis of selenazoles/thiazoles from alkynes via the formation of 2,2-dibromo-1-phenylethanone is reported, in high yields under mild and catalyst free conditions.

Key words: Thiazole, selenazole, phenylacytelene, *N*-Bromo succinimide, catalyst free recyclable PEG-400

INTRODUCTION

In the past decades synthetic heterocyclic chemistry developed new drug scaffolds through iterative manipulation of functional groups. Among this, 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 [1] (Fig. 1). Thiazole derivatives have become increasingly important in the past few years because they have proven to be extremely useful intermediates for the preparation of new biological materials. The thiazole ring system is a useful structural motif found in numerous biologically active molecules [2]. This structure has found applications in drug development for the treatment of allergies [3] hypertension [4]. Schizophrenia [5], inflammation [6], bacterial [7] and HIV [8] infections. In addition in various pesticides possessing a thoazole nucleus is well known in agriculture. Large numbers of thiazole derivatives have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory [9], anti-tumour [10], anti-hyperlipidemic [11], anti-hypertensive [12] and several other biological properties [13]. Thus, the thiazole nucleus has been much studied in the field of organic and medicinal chemistry.

Selenazoles have been extensively studied as synthetic tools [14] as well as for their biological significance [15]. Among them, 1,3-selenazoles are of pharmacological relevance due to their antibiotic and cancerostatic activity [16] .Therefore, there is sustained interest in developing simple and efficient methods for the synthesis of selenazoles and thiazoles, which include both solid phase synthesis [17] and solution phase [18] synthesis. Narender et al., reported the synthesis of selenazoles/thiazoles by the condensation of Phenacyl bromides /tosylates with selenourea/thiourea/thiobenzamide by employing β-cyclodextrin as catalyst [19]. Recently Varma and co-workers synthesized diaryl thiazoles from various α-tosyloxy ketones in water [20]. 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 this context, PEG has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable. To the best of our knowledge, there are no reports for the synthesis of synthesis of selenazoles and thiazoles using PEG-400 as a reaction medium under catalyst-free conditions.



Riluzole (anticonvulsant) **Sulfathiazole (antibacterial)**

Figure 1. Some biologically active drugs with thiazoles/selenazoles skeleton

In our efforts toward the development of novel eco friendly method 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 PEG-400 (Schemes 1 and 2).

In recent years, the use of alternative solvents such as ionic liquids, polyethylene glycol and super critical fluids has gained importance as green reaction media in view of environmental perception [21, 22] .Though water is a safe alternative, it is not always possible to use water as a solvent due to hydrophobic nature of the reactants and the sensitivity of many catalysts to aqueous conditions [23]. In this context, PEG has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable.

MATERIALS AND METHODS

In our initial studies on the way to the development of this methodology, phenyl acetylene (1.0 mmol) was reacted with *N*-bromo Succinamide (1.0 mmol) and thiourea/selenourea (1.0 mmol). It was observed that the reaction proceeded efficiently when *N*-bromo Succinamide (1.5 mmol) was used, but the reaction proceeded 50% only. When the same reaction was attempted using 2 eqvts. of NBS, the reaction proceeded to completion within 8h and yielded the corresponding thiazole derivative in 85% yield (see Table 1). 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), which further reacted with thiourea/selenourea to afford the desired product. The scope of the reaction was expanded by reacting various substituted selenourea/thiourea derivatives with phenyl acetylene 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 as well as by direct comparison with authentic samples.

In general, the reaction proceeded smoothly with various substrates was very clean, and a series of selenozole derivatives were obtained in high yields (Table 1). The yields of aromatic α-bromoketones (phenacyl bromides) were comparatively higher than the hetero aromatic α-bromo ketones (Table 1, entries 11 and 12). These reactions proceed smoothly without the formation of any by products or rearranged products. All of the products were characterized by ^{1}H NMR, IR, and mass spectrometry and compared with the reported data [24] .

General procedure: A mixture of phenylacetylene (1.0 mmol %) was added followed by NBS. After 10 min, thiourea (1.0 mmol) was taken in 5 mL polyethylene glycol-400. The resulting mixture was allowed to stir at 85 ^{0}C for 8h. After completion of the reaction as monitored by TLC. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was removed under reduced pressure, and the crude product was purified by Colum chromatography on silica gel using ethyl acetate: hexane mixture (3:7) as eluent to yield (208 mg 82%) in desired product.

The characteristic data of compounds are given below.

Compound (1, Table 2): *4-phenylthiazol-2-amine*: mp 130-132 ^{0}C. ^{1}H-NMR : ($CDCl_3$, 300 MHz): 7.69 (m, 2H), 7.36-7.24 (m, 3H), 6.63 (s, 1H) 5.40 (brs, 2H). ^{13}C ($CDCl_3$+DMSO-d_6, 75 MHz) : 167.9, 149.5, 127.9, 127.0, 125.4, 100.9. ESI-MS (*m/z*): 177(M+H)$^{+}$. Anal. calcd for: ($C_9H_8N_2S$) C, 61.34; H, 4.58; N, 15.90; S, 18.19%; found C, 61.25; H, 4.49; N, 15.85; S, 18.12%;

Compound (3, Table 2): *4-(p-tolyl)thiazol-2-amine*: mp 135-137 ^{0}C ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : 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%;

Compound (5, Table 2)*: 4-(4-fluorophenyl)thiazol-2-amine:* **S**olid, mp 113 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) 7.68 (m, 2H), 7.06 (m, 2H), 6.55 (m, 1H), 5.50 (brs, 2H);) ESI-MS (*m/z*): 195(M+H)$^+$. Anal. calcd for: ($C_9H_7FN_2S$) C, 55.65; H, 3.63; N, 14.42; S, 16.51 % ; found C, 55.56; H, 3.55; N, 14.33; S, 16.45 %;

Compound (6, Table2)*: N-(4-fluorophenyl)-4-phenylthiazol-2-amine*: **S**olid, mp 105-107 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : δ 7.77-7.75 (m, 2H), 7.34-7.25 (m, 6H), 7.00-6.94 (m, 2H), 6.72 (s, 1H); ^{13}C($CDCl_3$/DMSO-d_6, 200 MHz): δ: 162.5, 161.2, 158.5, 146.3, 134.5, 128.2, 123.5, 119.4, 118.6, 112.0, 111.7, 110.0, 100.0; ESI-MS (*m/z*): 271(M+H)$^+$. Anal. calcd for: ($C_{15}H_{11}FN_2S$) C, 66.65; H, 4.10; N, 10.36; S, 11.86 %; found C, 66.55; H, 4.07; N, 10.31; S, 11.82%.

Compound (7, Table 2)*: N-(3,4-difluorophenyl)-4-phenylthiazol-2-amine*: **S**olid, mp 103-105 ^{0}C. ^{1}H-NMR (DMSO-d_6, 300MHz) : 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($CDCl_3$/DMSO-d_6, 200 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 C, 62.35; H, 3.43; N, 9. 66; S, 11.06%.

Compound (8, Table 2)*: N-(4-chlorophenyl)-4-phenylthiazol-2-amine*: **S**olid, mp 128-130 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : δ 7.79-7.76 (m, 3H), 7.37-7.27 (m, 5H), 6.77 (s, 1H), 3.65 (s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ: 151.3, 139.0, 134.5, 129.3, 128.6, 128.0, 127.8, 126.2, 119.4, 101.7; ESI-MS (*m/z*): 287(M+H)$^+$. Anal. calcd for: ($C_{15}H_{11}ClN_2S$) C, 62.82; H, 3.87; N, 9.77; S, 11.18%; found C, 62.73; H, 3.89; N, 9.71; S, 11.12%.

Compound (9, Table2): *N-(2-chloro-6-methoxyphenyl)-4-phenylthiazol-2-amine*: **S**olid, mp 130-132 ^{0}C. ^{1}H-NMR ($CDCl_3$, 300MHz) : 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%.

Compound (10, Table 2): *4-((4-phenylthiazol-2-yl)amino)benzonitrile*: **S**olid, mp 165-167 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : δ (500 MHz): 7.78-7.76 (m, 2H), 7.60-7.58 (m, 1H), 7.52-7.50 (m, 1H), 7.46-7.37 (m, 4H), 7.32-7.29 (m, 1H), 7.24 (s, 1H), 6.87 (s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 75 MHz): δ; ESI-MS (*m/z*): 278(M+H)$^+$. Anal. calcd for: ($C_{16}H_{11}N_3S$) C, 69.29; H, 4.00; N, 15.15; S, 11.56 %; found C, 69.15; H, 3.96; N, 15.10; S, 11.49 %.

Compound (11, Table 2): *N-(4-fluorophenyl)-4-(m-tolyl) thiazol-2-amine*: **S**olid, mp 105-107 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : 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 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 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 % .

Compound (12, Table2): *N-(2,4-difluorophenyl)-4-(p-tolyl)thiazol-2-amine*: **S**olid, mp 108-110 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : δ 8.28-8.05 (m, 1H), 7.72 (d, 2H), 7.25-7.20 (m, 2H), 6.96-6.87 (m, 2H), 6.8 (s, 1H), 2.38 (s, 3H), 1.63 (brs, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 75 MHz): δ: 163.7, 152.2, 138.2, 129.7, 120.5, 120.4, 111.8, 104.6, 104.2, 103.9, 102.1, 21.6; ESI-MS (*m/z*): 303(M+H)$^+$. Anal. calcd for: ($C_{16}H_{12}F_2N_2S$) C, 63.56; H, 4.00; N, 9.27; S, 10.61 %; found C, 63.48; H, 3.98; N, 9.23; S, 10.58 %.

Compound (13, Table 2): *N-(3,4-difluorophenyl)-4-(4-fluorophenyl)thiazol-2-amine*: **S**olid, mp 98-101 ^{0}C. ^{1}H-NMR (DMSO-d_6, 300MHz) : 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; N, 9.15; S, 10.47 %; found C, 58.71; H, 2.88; N, 9.07; S, 10.38%.

Compound (1,Table 3): *(1, 4-phenyl-1,3-selenazol-2-amine*: **S**olid, mp 132 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : δ 7.55-7.32 (m, 4H), 7.85 (d, 2H, J=6.59 Hz), 5.69 (br, s, 2H); ^{13}C-NMR ($CDCl_3$/DMSO-d_6, 75MHz) δ 170.8, 153.3, 145.1, 129.8, 127.5, 110.7, 13.9, 13.1. ESI-MS (*m/z*): 225(M+H)$^+$. Anal. calcd for ($C_9H_8N_2Se$) C, 48.44; H, 3.61; N, 12.55; C, 48.44; H, 3.61; N, 12.55 %; C, 48.34; H, 3.56; N, 12.51 %.

Compound (3, Table 3): *N,N-dimethyl-4-phenyl-1,3-selenazol-2-amine*: **S**olid, mp 112 ^{0}C ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : 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 %.

Compound (5,Table 3): *4-(4-fluorophenyl)-1,3-selenazol-2-amine*: **S**olid, mp 140-142 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 500MHz): δ 7.74-7.68 (m, 2H), 7.12-7.00 (m, 3H), 5.66 (br s, 2H); ESI-MS (*m/z*): 243$(M+H)^+$. Anal. calcd for ($C_9H_7FN_2Se$) C, 44.83; H, 2.93; F, 7.88; N, 11.62 %; found. C, 44.79; H, 2.85; N, 11.51 %.

Compound (6, Table 3): *N,N-dimethyl-4-(naphthalen-2-yl)-1,3-selenazol-2-amine:* **S**olid, mp 118-120 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : 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 %.

Compound(9, Table 3): *N,N-dimethyl-4-(pyridin-3-yl)-1,3-selenazol-2-amine*: **S**olid, mp 125 ^{0}C. ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : δ 8.54-8.52 (m, 1H), 8.05-7.96 (m, 2H), 7.71-7.66 (m, 1H), 7.16-7.11 (m, 1H), 3.17 (s, 6H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ ; ESI-MS (*m/z*): 254$(M+H)^+$. Anal. calcd for ($C_{10}H_{11}N_3Se$) C, 47.63; H, 4.40; N, 16.66 %; found. C, 47.51; H, 4.33; N, 16. 59 %.

Compound (10,Table 3): *4-(2-(dimethylamino)-1,3-selenazol-4-yl)benzonitrile*: **S**olid, mp 132 ^{0}C ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 300MHz) : δ: 7.94-7.91 (m, 2H), 7.62-7.59 (m, 2H), 7.38 (s, 1H), 3.17 (s, 6H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz): ESI-MS (*m/z*): 278 $(M+H)^+$. Anal. calcd for ($C_{12}H_{11}N_3Se$) C, 52.18; H, 4.01; N, 15.21 %; found. C, 52.09; H, 3.95; N, 15. 16 %.

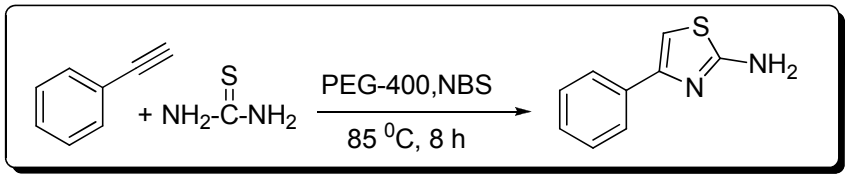
RESULTS AND DISCUSSION

In the first trail, the reaction was carried out between phenyl acetylene followed by NBS as model substrates in presence of PEG-400 under neat conditions. It was found that the reaction proceeds in PEG-400 at 60 ^{0}C giving 50% yield. With this result in hand, we started standardization of the reaction conditions by performing the reaction in different solvents at varied temperatures as illustrated in Table 1. PEG-400/ 85 ^{0}C / 8h were proved to be optimum conditions for this reaction with best yields among the tested conditions. At room temperatures the reaction did not takes place in any of the solvents tested including PEG-400.

Table 1. Effect of Solvent

Solvent	Temperature	Yield
DCM	Reflux	30
Methanol	Reflux	25
Water	80	0
Acetonitrile	80	0
PEG-400	85	90
PEG-400	60	50
PEG-400	RT	0

Scheme 1. Synthesis of selenazoles in presence of PEG-400



Scheme 2. Synthesis of thiazoles in presence of PEG-400

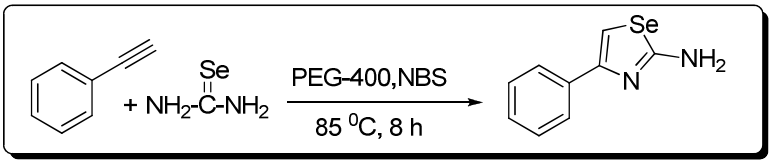
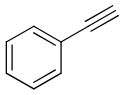
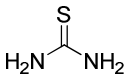
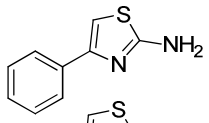
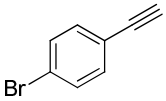
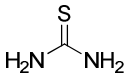
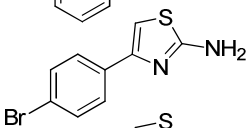
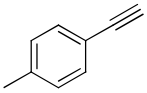
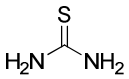
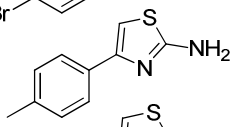
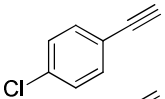
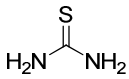
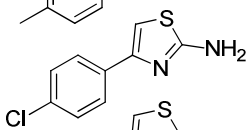
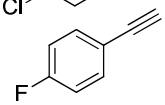
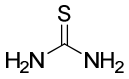
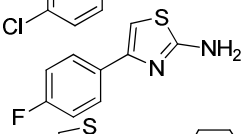
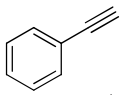
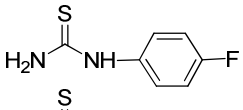
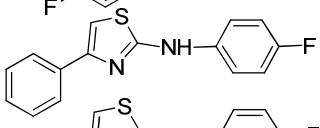
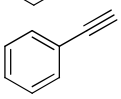
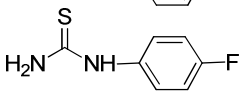
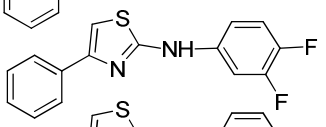
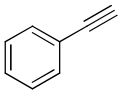
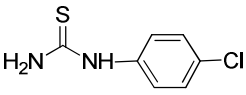
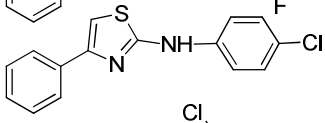
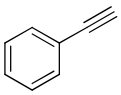
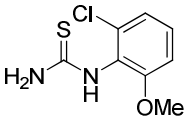
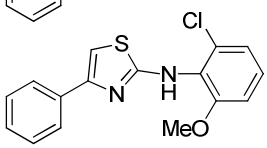
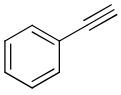
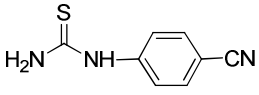
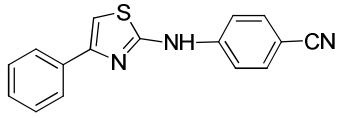
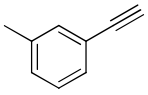
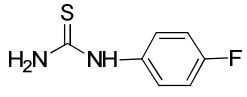
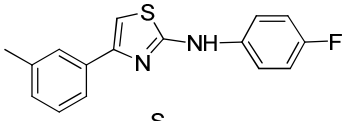
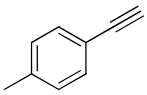
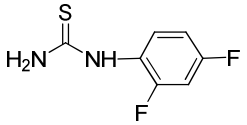
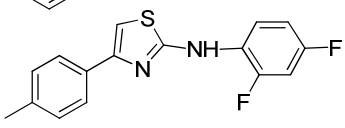
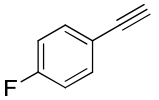
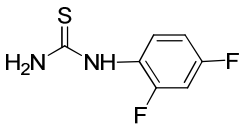
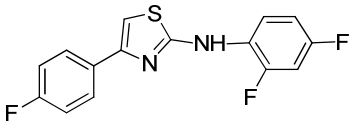
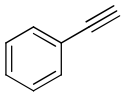
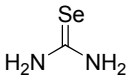
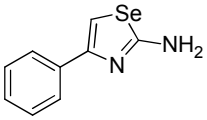
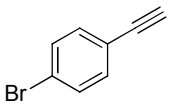
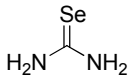
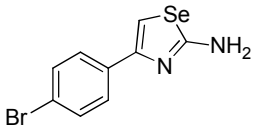
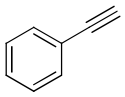
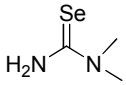
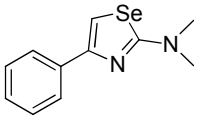
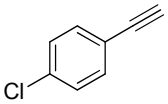
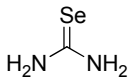
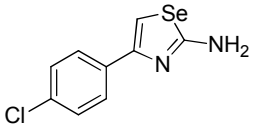
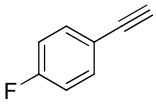
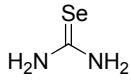
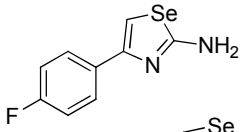
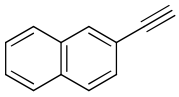
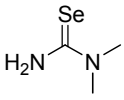
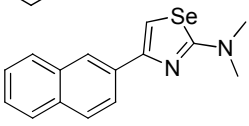
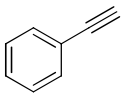
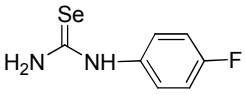
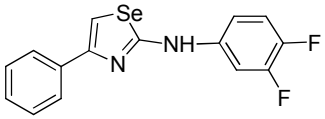
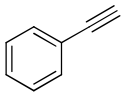
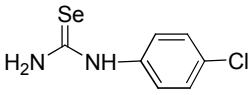
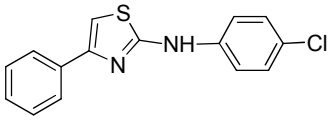
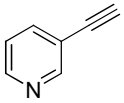
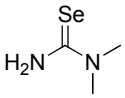
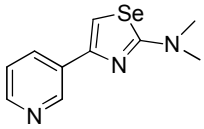
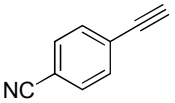
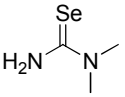
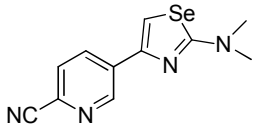


Table 2, PEG-400 mediated synthesis of thiazoles

Entry	Phenylacetylene	Thiourea	Product	Time (h)	Yield (%)
1				6.0	75
2				7.0	70
3				5.0	80
4				4.0	75
5				3.0	70
6				5.0	65
7				7.0	70
8				6.0	65
9				6.0	60
10				5.0	55
11				6.0	65
12				5.0	60
13				6.0	65

[a] *Reaction conditions: phenylacetylene, (1.0mmol), NBS (2.0mmol), thiourea (1.0 mmol) and PEG-400(5 mL);* [b] *Isolated yields.*

Table 3, PEG-400 mediated synthesis of selenozoles

Entry	Phenylacetylene	Selenourea	Product	Time (h)	Yield (%)
1				6.0	75
2				7.0	70
3				5.0	80
4				4.0	75
5				3.0	70
6				5.0	65
7				7.0	70
8				6.0	65
9				6.0	60
10				5.0	55

[a] *Reaction conditions: phenyl acetylene (1.0mmol), NBS (2.0 mmol), selenourea (1.0 mmol) and PEG-400 (5 Ml) at 85 ^{0}C; [a] Isolated yields.*

CONCLUSION

In conclusion, we have developed, an efficient approach for the synthesis of substituted thiazoles/selenazoles under mild conditions in encouraging yields using PEG-400 without any need of any additive or acid catalyst. The mild reaction conditions, inexpensive reaction medium, operational simplicity, and high yields are advantages of the protocol.

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