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An Eco-friendly, Hantzsch-Based, Solvent-Free Approach to 2-Aminothiazoles and 2-Aminoselenazoles

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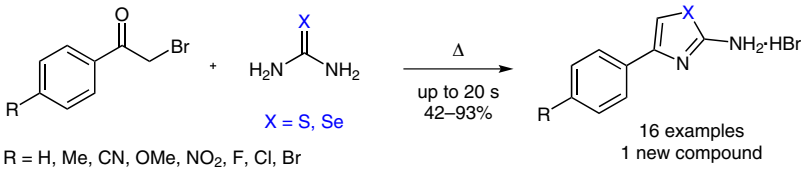

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Abstract We report a simple, fast, and eco-friendly solvent-free protocol for the synthesis of 2-aminothiazoles and 2-amino-1,3-selenazoles (16 examples) through Hantzsch condensation without the use of a catalyst. It is noteworthy that this type of procedure is unprecedented for the synthesis of 1,3-selenazoles. Reactions proceed to completion in a few seconds and products are obtained in moderate to excellent yields after easy workup. Moreover, the synthesis of 4-(2-amino-1,3-selenazol-4-yl)benzonitrile hydrobromide is reported for the first time.

Key words thiazoles, 1,3-selenazoles, synthesis, solvent-free, heterocycles

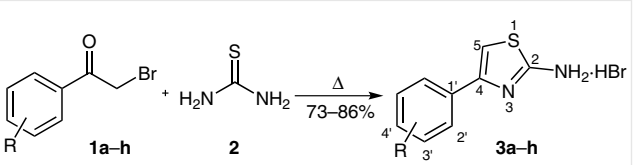
The 2-aminothiazole and 2-amino-1,3-selenazole ring systems have received much attention from medicinal chemists worldwide because of their wide range of biological activity, such as antimicrobial, anti-HIV, antioxidant, anticancer, among others.[1,2] In view of the importance of these heterocyclic cores, many synthetic methodologies have been reported in the literature.[2,3] Despite this, the Hantzsch condensation (1887)[4] of α-halocarbonyl compounds with thioureas or selenoureas remains a prominent method for the synthesis of these compounds.[1]

In the last few years, many novel protocols that improve Hantzsch's original procedure have been reported. In 2008, for example, Potewar and co-workers described the synthesis of 2-aminothiazole derivatives in water for 1–2 hours.[5] In 2006, the supramolecular synthesis of 2-amino-1,3-selenazoles from selenourea in water using β-cyclodextrin as a catalyst was described.[6] Other noteworthy procedures include solid-supported synthesis,[7] the use of ionic liquids[8,9] or catalysts such as ammonium molybdophosphate,[10] and reactions carried under microwave irradiation.[11]

We recognize the potential of these methodologies, however they have drawbacks, such as longer reaction times, the use of toxic organic solvents, ionic liquids, or catalysts, tedious workup, and harsh reaction conditions.[5–11]

Therefore, the development of improved economic and environmentally friendly procedures that can eliminate or reduce the use of volatile organic solvents without imposing longer reaction times is not only desirable, but it has also become crucial to organic synthesis. In this context, we report a rapid, efficient solvent-free protocol for the synthesis of 2-aminothiazoles and 2-amino-1,3-selenazoles through Hantzsch cyclization from thiourea and selenourea.

The multicomponent, solvent-free, one-pot synthesis of various thiazole derivatives at room temperature was previously described by Dawane and Konda.[12] Initially, we examined their protocol for the synthesis of 2-aminothiazole building blocks. Unfortunately, in this case, the reaction proceeded very slowly at room temperature with undesirable yields. However, to our surprise the reaction appeared to occur instantly with release of hydrogen bromide when the temperature was raised to the melting point of the 2-bromoacetophenone **1**. In order to investigate the optimal conditions for this reaction, 2-bromoacetophenone (**1g**) was added to a 5-mL round-bottom flask and heated to its melting point (48–51 °C); powdered thiourea (**2**) was then added directly to the flask. As expected, the results confirmed our initial observation as we witnessed the instant release of HBr and the reaction proceeded to completion in a few seconds (Scheme 1). TLC analysis showed that complete conversion of 2-bromoacetophenone (**1g**) into the corresponding 2-aminothiazole (**3g**) was not achieved when an equimolar amount of thiourea (**2**) was used. We then raised the quantity of thiourea to 1.2, 1.5 and 2 equiv-



Scheme 1 Solvent-free synthesis of 2-aminothiazoles **3a–h**

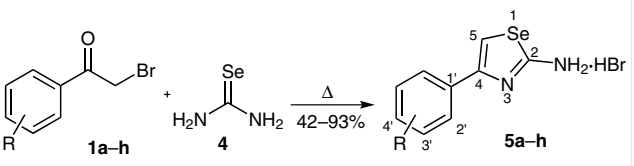
alents, establishing the former as the best proportion in this case. The optimal condition for each substituent is described in Table 1.

Table 1 Reaction Conditions, Yields, and Melting Points Obtained for Thiazoles **3a–h**

R	2-Aminothiazole	Proportion (**1**/**2**)	Time	Yield (%)	Mp (°C)
4-OMe	**3a**	2:1	instant	83	229–231
4-F	**3b**	1.2:1	10 s	73	236–238
4-Me	**3c**	2:1	20 s	80	286–287
4-NO_2	**3d**	2:1	instant	86	235–238
4-Cl	**3e**	2:1	15 s	79	236–239
4-Br	**3f**	2:1	instant	85	225–227
H	**3g**	1.2:1	10 s	77	220–222
4-CN	**3h**	2:1	instant	69	222–224

Purification was carried out by the addition of water to the powdered solid. Pure products were obtained in the form of insoluble salts in high yields after filtration (70–98%). Furthermore, excess reagent can be easily recovered from the water after evaporation. It is noteworthy that this reaction also proved to be efficient on a gram scale (5–10 mmol).

To our knowledge, there are no solvent-free methods for the synthesis of 2-amino-1,3-selenazoles available in the literature. Due to the increasing importance of this core in medicinal chemistry, we examined the scope of our protocol by reacting 2-bromoacetophenones **1a–h** with selenourea (**4**) in order to obtain the corresponding 1,3-selenazole building blocks **5**. It is noteworthy that product **5h** has not been previously reported in the literature. Complete reaction was observed when two equivalents of selenourea (**4**) were used for all products, except for compounds **5e**,**f**,**h**. However, raising the quantity of selenourea (**4**) to 2.5 equivalents did not improve the efficiency in these cases and equivalent yields were obtained. Therefore, two equivalents of selenourea (**4**) were optimal for this reaction. All reactions proceeded to completion instantly (Scheme 2).



Scheme 2 Solvent-free synthesis of 2-amino-1,3-selenazoles **5a–h**

Excess reagent was removed by washing the powdered solid with water, except for compounds **5e**,**f**,**h** in which total conversion of 2-bromoacetophenone **1e**,**f**,**h** into the desired product was not observed. In these cases, the substances were also washed with ethanol (1 mL). All products were obtained in the form of an insoluble salt, as expected, in moderate to excellent yields (Table 2).

Table 2 Yields and Melting Points Obtained for Selenazoles **5a–h**

R	2-Aminoselenazole	Yield[a] (%)	Mp (°C)
4-OMe	**5a**	78	230–232
4-F	**5b**	76	236–238
4-Me	**5c**	80	286–288
4-NO_2	**5d**	93	235–238
4-Cl	**5e**	60	237–240
4-Br	**5f**	42	225–226
H	**5g**	93	220–222
4-CN	**5h**	58	221–223

[a] Using a 1:2 ratio of **1**/**4** in all cases.

In summary, we have developed a fast and reproducible protocol for the synthesis of various 2-aminothiazoles and 2-amino-1,3-selenazoles through Hantzsch cyclization from thiourea and selenourea. It is noteworthy that in the synthesis of 1,3-selenazoles, solvent-free procedures without the use of a catalyst are unprecedented. All products were obtained in moderate to excellent yields and no hazardous waste was generated, making this procedure interesting for green chemistry approaches. Product **5h** has not been previously reported in the literature.

All reagents were used as obtained from commercial suppliers without further purification. Melting points were determined on a Buchi Melting Point B-545 and are uncorrected. ^{1}H NMR spectra were recorded using a Bruker DRX 400 spectrometer (^{1}H at 400 MHz) in MeOD or acetone-d_6 with TMS as internal standard. MS analyses were performed on MS micromass ZMD using electrospray ionization; samples were introduced by the standard direct insertion probe method. HRMS analysis was performed on a Bruker TOF compact using electrospray ionization.

2-Aminothiazoles 3a–h; General Procedure

The 2-bromoacetophenone **1a–h** (199–278 mg, 1 mmol) was heated to its melting point in a 5-mL round-bottom flask. Powdered thiourea (**2**, 91.2–152 mg, 1.2–2 mmol; see Table 1) was then added to the flask, and reaction proceeded to completion after a few seconds to

give the desired thiazoles. Powdered solid was washed with water (5–10 mL) and filtered. Excess thiourea was recovered from water after evaporation.

4-(4-Methoxyphenyl)thiazol-2-amine Hydrobromide (3a)

[CAS Reg. No. 111317-60-3]

Beige solid; yield: 171 mg (83%); mp 229–231 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.80–7.76 (m, 2 H, Ph), 6.93–6.89 (m, 2 H, Ph), 6.76 (s, 1 H, H5), 6.35 (br s, 2 H, NH_2), 3.80 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ = 169.7 (C2), 160.9 (C4′), 152.5 (C4), 130.1 (Ph), 128.8 (Ph), 115.4 (C3′), 101.2 (C5), 56.4 (OCH_3)

MS (ESI): m/z = 206.9 ([M]$^+$, 100%).

4-(4-Fluorophenyl)thiazol-2-amine Hydrobromide (3b)

[CAS Reg. No. 1147205-03-5]

White solid; yield: 142 mg (73%); mp 236–238 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.92–7.86 (m, 2 H, Ph), 7.15–7.08 (m, 2 H, Ph), 6.91 (s, 1 H, H5), 6.43 (br s, 2 H, NH_2).

^{13}C NMR (100 MHz, acetone-d_6): δ = 169.1 (C2), 163.0 (d, J = 242.8 Hz, C4′), 150.6 (C4), 132.8 (d, J = 3.1 Hz, C1′), 128.5 (d, J = 7.9 Hz, C2′), 115.9 (d, J = 21 Hz, C3′), 102.6 (d, J = 1.1 Hz, C5).

MS (ESI): m/z = 194.9 ([M]$^+$, 100%).

4-(p-Tolyl)thiazol-2-amine Hydrobromide (3c)

[CAS Reg. No. 24966-91-4]

Pale yellow solid; yield: 152 mg (80%); mp 286–287 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.77–7.71 (m, 2 H, Ph), 7.16 (d, J = 7.9 Hz, 2 H, Ph), 6.85 (s, 1 H, H5), 6.38 (br s, 2 H, NH_2), 2.32 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.1 (C2), 139.1 (C4), 139.0 (Ph), 129.5 (Ph), 125.9 (Ph), 125.6 (Ph), 101.8 (C5), 20.7 (CH_3).

MS (ESI): m/z = 190.9 ([M]$^+$, 100%).

4-(4-Nitrophenyl)thiazol-2-amine Hydrobromide (3d)

[CAS Reg. No. 69018-01-5]

Yellow solid; yield: 190 mg (86%); mp 235–238 °C (Lit.[13] 251–256).

^{1}H NMR (400 MHz, MeOD): δ = 8.32 (d, J = 8.9 Hz, 2 H, H3′), 7.95 (d, J = 8.9 Hz, 2 H, H2′), 7.30 (s, 1 H, H5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.54 (C2), 147.46 (C4), 145.92 (C4′), 140.61 (C1′), 126.19 (Ph), 123.83 (Ph), 106.46 (C5).

MS (ESI): m/z = 221.9 ([M]$^+$, 100%).

4-(4-Chlorophenyl)thiazol-2-amine Hydrobromide (3e)

[CAS Reg. No. 69018-04-8]

Pale yellow solid; yield: 166 mg (79%); mp 236–239 °C.

^{1}H NMR (400 MHz, MeOD): δ = 7.66 (d, J = 8.6 Hz, 2 H, Ph), 7.53 (d, J = 8.6 Hz, 2 H, Ph), 7.13 (s, 1 H, H5).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.0 (C2), 133.7 (C4), 129.6 (Ph), 128.9 (Ph), 128.2 (Ph), 127.5 (Ph), 103.5 (C5).

MS (ESI): m/z = 210.9 ([M]$^+$, 100%), 211.8 ([M + 1]$^+$, 33%).

4-(4-Bromophenyl)thiazol-2-amine Hydrobromide (3f)

[CAS Reg. No. 42056-64-4]

White solid; yield: 218 mg (85%); mp 225–227 °C (Lit.[14] 239–242).

^{1}H NMR (400 MHz, MeOD): δ = 7.71–7.65 (m, 2 H, Ph), 7.61–7.56 (m, 2 H, Ph), 7.13 (s, 1 H, H5).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.27 (C2), 148.58 (C4), 134.05 (Ph), 131.27 (Ph), 127.48 (Ph), 120.01 (Ph), 102.32 (C5).

MS (ESI): m/z = 256.8 ([M]$^+$, 100%), 254.9 ([M + 2]$^+$, 98%).

4-Phenylthiazol-2-amine Hydrobromide (3g)

[CAS Reg. No. 34161-31-4]

White solid; yield: 137 mg (77%); mp 220–222 °C (Lit.[14] 181–183).

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.86 (d, J = 7.2 Hz, 2 H, Ph), 7.35 (dd, J = 7.6, 7.6 Hz, 2 H, Ph), 7.25 (t, J = 7.3 Hz, 1 H, H4′), 6.93 (s, 1 H, H5), 6.41 (br s, 2 H, NH_2).

^{13}C NMR (100 MHz, acetone-d_6): δ = 169.0 (C2), 151.7 (C4), 136.2 (Ph), 129.2 (Ph), 128.0 (Ph), 126.6 (Ph), 102.4 (C5).

MS (ESI): m/z = 177.0 ([M + H]$^+$, 100%).

4-(2-Aminothiazol-4-yl)benzonitrile Hydrobromide (3h)

[Amine CAS Reg. No. 436151-85-8]

Salmon solid; yield: 139 mg (69%); mp 222–224 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.05 (d, J = 8.5 Hz, 2 H, Ph), 7.75 (d, J = 8.6 Hz, 2 H, Ph), 7.24 (s, 1 H, H5), 6.56 (br s, 2 H, NH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.4 (C2), 148.1 (C4), 138.9 (C1′), 132.4 (Ph), 126.0 (Ph), 119.0 (CN), 109.2 (C4′), 105.4 (C5).

MS (ESI): m/z = 202.0 ([M + H]$^+$, 100%)

2-Amino-1,3-selenazoles 5a–h; General Procedure

The 2-bromoacetophenone **1a**–**h** (223–302 mg, 1 mmol) was heated to its melting point in a 5-mL round-bottom flask. Powdered selenourea (**4**, 246 mg, 2 mmol) was then added to the flask, and reaction proceeded to completion instantly to give the desired selenazole. Solids were powdered, washed with water (5–10 mL) and filtered. Products **5e**, **5f**, and **5h**, were also washed with EtOH (1 mL). Excess selenourea was recovered from water after evaporation.

4-(4-Methoxyphenyl)-1,3-selenazol-2-amine Hydrobromide (5a)

[Amine CAS Reg. No. 930300-93-9]

Salmon solid; yield: 197 mg (78%); mp 230–232 °C.

^{1}H NMR (400 MHz, MeOD): δ = 7.56 (d, J = 8.9 Hz, 2 H, Ph), 7.22 (s, 1 H, H5), 7.04 (d, J = 8.9 Hz, 2 H, Ph), 3.85 (s, 3 H, OCH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.7 (C2), 160.4 (C4′), 138.5 (C4), 127.81 (Ph), 122.7 (Ph), 114.9 (C3′), 104.7 (C5), 55.8 (OCH_3)

MS (ESI): m/z = 254.9 ([M + H]$^+$, 100%).

4-(4-Fluorophenyl)-1,3-selenazol-2-amine Hydrobromide (5b)

[Amine CAS Reg. No. 904929-70-0]

Pale yellow solid; yield: 183 mg (76%); mp 236–238 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.92–7.86 (m, 2 H, Ph), 7.42 (s, 1 H, H5), 7.09 (t, J = 8.9 Hz, 2 H, Ph), 6.71 (br s, 2 H, NH_2).

^{13}C NMR (100 MHz, acetone-d_6): δ = 171.5 (C2), 162.2 (d, J = 244.0 Hz, C4′), 150.1 (C4), 132.7 (d, J = 3.0 Hz, C1′), 127.7 (d, J = 8.0 Hz, C2′), 114.6 (d, J = 22 Hz, C3′), 105.0 (d, J = 2.0 Hz, C5).

MS (ESI): m/z = 243.0 ([M + H]$^+$, 100%).

4-(*p*-Tolyl)-1,3-selenazol-2-amine Hydrobromide (5c)

[Amine CAS Reg. No. 537692-29-8]

Brown solid; yield: 190 mg (80%); mp 286–288 °C.

^{1}H NMR (400 MHz, MeOD): δ = 7.51 (*J* = 8.2 Hz, 2 H, Ph), 7.32–7.30 (m, 3 H), 2.39 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.1 (C2), 150.7 (C4), 136.0 (Ph), 133.1 (Ph), 128.9 (Ph), 125.7 (Ph), 104.8 (C5), 20.7 (CH_3).

MS (ESI): *m*/*z* = 238.9 ([M + H]$^+$, 100%).

4-(4-Nitrophenyl)-1,3-selenazol-2-amine Hydrobromide (5d)

[Amine CAS Reg. No. 537692-30-1]

Yellow solid; yield: 250 mg (93%); mp 235–238 °C.

^{1}H NMR (400 MHz, MeOD): δ = 8.36 (d, *J* = 8.9 Hz, 2 H, H3′), 7.89 (d, *J* = 8.9 Hz, 2 H, H2′), 7.70 (s, 1 H, H5).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.2 (C2), 147.6 (C4), 145.8 (C4′), 141.0 (C1′), 126.6 (Ph), 123.9 (Ph), 111.4 (C5).

MS (ESI): *m*/*z* = 269.9 ([M + H]$^+$, 100%).

4-(4-Chlorophenyl)-1,3-selenazol-2-amine Hydrobromide (5e)

[Amine CAS Reg. No. 537692-27-6]

Salmon solid; yield: 154 mg (60%); mp 237–240 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.88 (s, 2 H, Ph), 7.51 (s, 1 H, H5), 7.36 (d, *J* = 8.6 Hz, 2 H, Ph), 6.73 (br s, 2 H, NH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.0 (C2), 149.9 (C4), 135.0 (Ph), 131.7 (Ph), 128.8 (Ph), 128.0 (Ph), 107.1 (C5).

MS (ESI): *m*/*z* = 258.8 ([M + H]$^+$, 100%).

4-(4-Bromophenyl)-1,3-selenazol-2-amine Hydrobromide (5f)

[Amine CAS Reg. No. 537692-28-7]

Pale brown solid; yield: 97 mg (42%); mp 225–226 °C.

^{1}H NMR (400 MHz, MeOD): δ = 7.67 (d, *J* = 8.6 Hz, 2 H, Ph), 7.56 (d, *J* = 8.6 Hz, 2 H, Ph), 7.44 (s, 1 H, H5).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.1 (C2), 137.9 (C4), 131.9 (Ph), 129.2 (Ph), 127.9 (Ph), 122.2 (Ph), 107.5 (C5).

MS (ESI): *m*/*z* = 232.8 ([M + H]$^+$, 100%).

4-Phenyl-1,3-selenazol-2-amine Hydrobromide (5g)

[CAS Reg. No. 156137-79-0]

Salmon solid; yield: 208 mg (93%); mp 220–222 °C.

^{1}H NMR (400 MHz, MeOD): δ = 7.63 (dd, *J* = 7.8, 1.8 Hz, 2 H, Ph), 7.51–7.47 (m, 3 H, Ph), 7.39 (s, 1 H, H5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.4 (C2), 149.4 (C4), 134.5 (C1′), 131.2 (Ph), 128.3 (Ph), 127.5 (Ph), 106.6 (C5).

MS (ESI): *m*/*z* = 224.0 ([M + H]$^+$, 100%).

4-(2-Amino-1,3-selenazol-4-yl)benzonitrile Hydrobromide (5h)

Salmon solid; yield: 144 mg (58%); mp 221–223 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.05 (d, *J* = 8.5 Hz, 2 H, Ph), 7.77 (s, 1 H, H5), 7.73 (d, *J* = 8.6 Hz, 2 H, Ph), 6.83 (br s, 2 H, NH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.1 (C2), 149.5 (C4), 140.2 (C1′), 132.9 (Ph), 126.9 (Ph), 119.5 (CN), 110.7 (C4′), 109.3 (C5).

MS (ESI): *m*/*z* = 247.9 ([M – H]$^-$, 100%).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_7N_3Se$: 249.9878; found: 249.9880.

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