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An efficient one-pot synthesis of 2,5-disubstituted-1,3,4-thiadiazoles from aldehydes and hydrazides using Lawesson's reagent

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This article dedicated to Professor George A. Kraus, in honor of his distinguished career in synthetic organic chemistry

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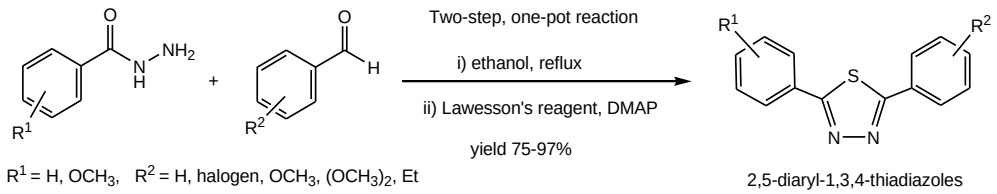
Abstract

Five-membered heterocyclic-ring systems, such as thiadiazoles, remain an important and prevalent scaffold in the development of novel leads in medicinal chemistry for a variety of therapeutic targets. A two-step, one-pot synthesis of 2,5-disubstituted-1,3,4-thiadiazole derivatives from aryl hydrazides and aryl aldehydes using Lawesson's reagent is described, yielding 2,5-disubstituted-1,3,4-thiadiazoles in moderate-to-high yields. Based on preliminary biological experiments, some of the newly synthesized thiadiazoles show antioxidant activity.



Keywords: 1,3,4-Thiadiazole, Lawesson's reagent, *N*-acylhydrazone, *N*-aroylhydrazone, dimethylaminopyridine

Introduction

Heterocyclic compounds are defined, according to IUPAC (International Union of Pure and Applied Chemistry), as cyclic compounds including at least two different atoms such as oxygen, sulfur or nitrogen in the ring. These compounds are important due to their wide range of biological activities. For example, the antiviral Sovaldi (Gilead Sciences), the antipsychotic Abilify (Otsuka), and the anti-inflammatory Nexium are among the most popular and widely used drugs worldwide.[1]

Among the heterocyclic compounds, 1,3,4-thiadiazole has attracted special interest in recent years in various areas, including pharmaceutical, agricultural, and materials chemistries. 1,3,4-Thiadiazole is a weak base due to the inductive effect of the sulfur in the ring, and possesses a relatively high aromaticity.[2,3,4] In addition, the ring is electron deficient due to the electron-withdrawing effects of the nitrogen atoms.[2] For these reasons, In the pharmaceutical field, 1,3,4-thiadiazole derivatives are known to exhibit diverse biological activities, such as antimicrobial[5], antiviral[6], anticonvulsant[7], antifungal,[8-10] antitubercular,[11-13] anticancer,[14] and immunomodulatory[15] activities. Some examples of commercially-available drugs containing the 1,3,4-thiadiazole ring are Megazol, Acetazolamide (Diamox), Furidiazine, and Desaglybuzole, shown in Figure 1.[16,17]

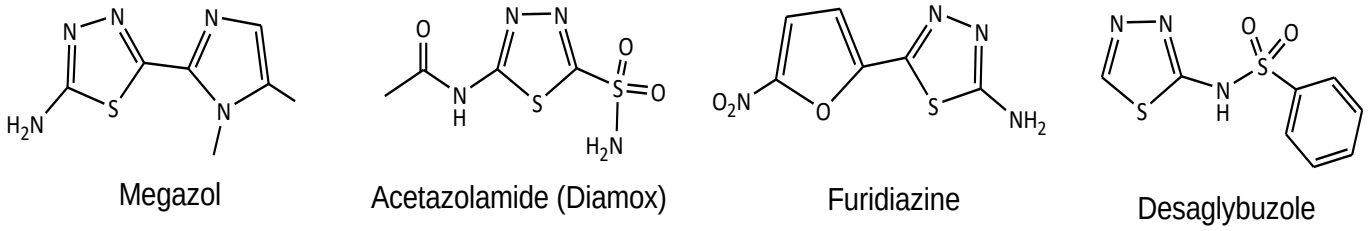
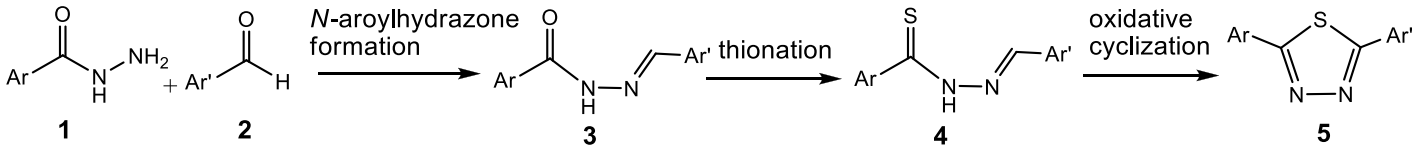


Figure 1. Commercially available 1,3,4-thiadiazole drugs

Synthetic methods to produce 1,3,4-thiadiazoles have been developed and studied over many decades due to the interest following the discovery of their diverse pharmacological and physiological activities. Well-known synthetic methods for 1,3,4-thiadiazoles include starting materials such as *N,N'*-diacylhydrazines,[18,19] thiosemicarbazides[20] or thiohydrazides,[21,22] as well as the transformation of 1,3,4-oxadiazoles.[23] Most existing synthetic methods, however, require harsh conditions, multi-step procedures, and scarce starting materials or experience difficulty in forming non-symmetric 1,3,4-thiadiazoles. Therefore, it is still necessary to develop a more efficient synthetic method to produce 1,3,4-thiadiazoles. We, herein, report a highly efficient, two-step, one-pot synthetic method for 2,5-disubstituted-1,3,4-thiadiazoles from aldehydes and hydrazides in good-to-excellent yields using a sequence of *N*-aroylhydrazone formation, thionation, cyclization and oxidation.

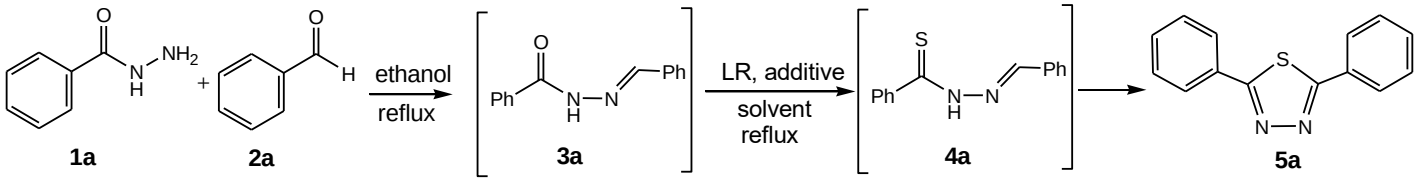
Results and Discussion

Originally, we thought that the synthesis of 1,3,4-thiadazole (**5**) could be brought about in a three-step reaction sequence. In Scheme 1, we illustrate the formation of the aroylhydrazone (**3**) from the corresponding hydrazide (**1**) and aldehyde (**2**), followed by thionation of **3** with Lawesson's reagent (**LR**)[24-26] to give a thiohydrazide intermediate (**4**). Oxidative cyclization of **4** using an oxidant such as I_2, [bis(trifluoro-acetoxy)iodobenzene] (PIFA) or $FeCl_3$ yields the disubstituted-1,3,4-thiadiazole (**5**).



Scheme 1: 1,3,4-thiadiazoles from aryl aldehydes and hydrazides in a three-step sequence

When compound **3** was treated with **LR**, however, the disubstituted-1,3,4-thiadiazole (**5**) was formed directly without oxidant, and with separation of the thiohydrazide (**4**). Therefore, we studied a two-step, one-pot synthesis of 2,5-diphenyl-1,3,4-thiadiazole (**5a**) from benzoylhydrazide (**1a**) and benzaldehyde (**2a**) without isolation of the *N*-benzoylhydrazone (**3a**) (Scheme 2). After refluxing for 2 hours, the ethanol was evaporated *in vacuo*. To the reaction mixture of crude **3a** (0.1 M) in solvent, **LR** was added, followed by addition of a base. In other trials, we omitted addition of the base. The resulting mixture was refluxed for 10 hours.



Scheme 2. Two-step, one-pot synthesis of 2,5-diphenyl-1,3,4-thiadiazole (**5a**) from benzoylhydrazide (**1a**) and benzaldehyde (**2a**) without separation of the *N*-benzoylhydrazone (**3a**) using **LR**

To determine the optimal procedure with solvents, thionating agents or additives, this one-pot reaction was investigated under several conditions (Table 1).

Table 1. Optimization of the synthesis of 2,5-diphenyl-1,3,4-thiadiazole (**5a**) from benzoylhydrazide (**1a**) and benzaldehyde (**2a**)[a]

Entry	Thionating reagent [eq]	Solvent	Additive [eq]	Yield (%)[b]
1	LR [0.5]	Toluene	-	68
2	LR [0.8]	Toluene	-	79
3	LR [1.0]	Toluene	-	65
4	LR [0.8]	THF	-	60
5	LR [0.8]	Ethanol	-	-
6	LR [0.8]	Toluene	2,6-lutidine [1.2]	73
7	LR [0.8]	Toluene	DBU [1.2]	79
8	LR [0.8]	Toluene	Piperidine [1.2]	85
9	LR [0.8]	Toluene	Pyridine [1.2]	77
10	LR [0.8]	Toluene	DMAP [1.2]	**96**
11	LR [0.8]	Toluene	DMAP [1.0]	86
12	LR [0.8]	Toluene	DMAP [1.6]	70
13[c]	LR [0.8]	Toluene	DMAP [1.2]	70
14	P_4S_{10} [0.8]	Toluene	DMAP [1.2]	13

[a] The reaction was accomplished with a corresponding aldehyde and hydrazide in ethanol at room temperature. After refluxing for 2 hr, the ethanol was evaporated *in vacuo*. To a remaining crude **3a**, **LR** and solvent were added, followed by addition of a base. The resulting mixture was refluxed for 10 hr.

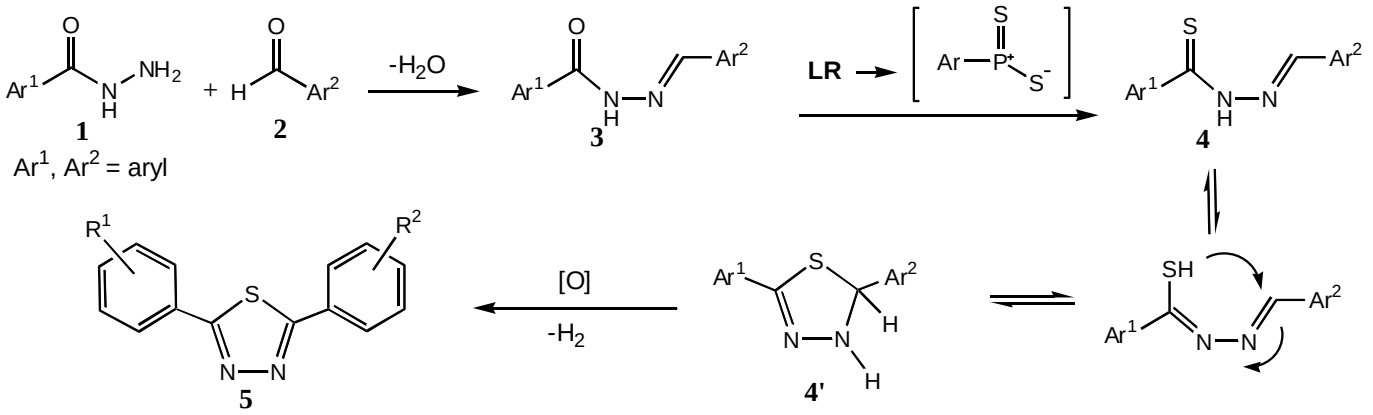
[b] Isolated yield.

[c] Two-pot synthesis including separation of **3a**.

Initially, the reaction was started with 0.5 equivalent of **LR**, since, stoichiometrically, one equivalent of **LR** produces two equivalents of dithiophosphine ylides to thionate a carbonyl group.[24-26] When 0.5 equivalent of **LR** was used, 2,5-diphenyl-1,3,4-thiadiazole (**5a**) was produced in 68% yield (Table 1, entry 1). The amount of **LR** was gradually increased to 0.8 or 1.0 equivalent (Table 1, entries 2-3). The highest yield (79%) was obtained using 0.8 equivalent of **LR** (Table 1, entry 2). When tetrahydrofuran (THF), which is more polar than toluene, was used, the yield was only 60%. No reaction occurred when ethanol was used (Table 1, entry 5). Next, the base-additive effect was investigated by adding various bases, while maintaining the amount of **LR** at 0.8 equivalent in refluxing toluene as described above. When using bases such as 2,6-lutidine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), piperidine, pyridine, and dimethylaminopyridine (DMAP), the number of byproducts were lower, and the yields were similar or higher than those in the trials omitting the bases. The highest yield (96%) was obtained when 1.2 equivalents of DMAP were used (Table 1, entry 10), and was superior compared to 1.0 equivalent or 1.6 equivalents of DMAP (Table 1, entries 11-12). On the other hand, the two-step synthesis involving separation of *N*-aroylhydrazone (**3**) showed a lower overall yield of 70% than the one-pot synthesis (Table 1, entry 13). Using another thionating reagent, P_4S_{10}, yielded only 13% of the desired product (Table 1, entry 14).

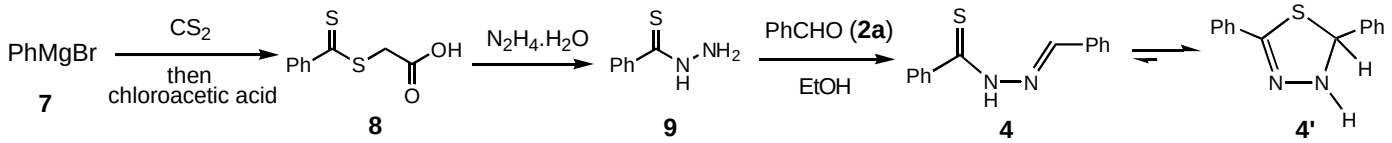
Based on the previous experimental results and the literature,[27] the mechanism of this reaction can be proposed as shown in Scheme 3. Following formation of the *N*-aroylhydrazone intermediate (**3**), it would react with **LR** to give the thiohydrazone (**4**). It is believed that dihydrothiadiazole (**4'**), which is the preferred

tautomeric form of the thiohydrazone (**4**), is readily oxidized to produce the disubstituted-1,3,4-thiadiazole (**5**).



Scheme 3. Proposed mechanism for formation of the 1,3,4-thiadiazoles.

To clarify the mechanism of this reaction, we needed to prove formation of intermediate **4** and/or **4'**. Therefore, we synthesized compounds **4** and **4'** by the known literature method.[27-29] After the reaction of the phenyl thiohydrazide (**9**) with benzaldehyde (**2a**), the ring tautomer dihydrothiadiazole (**4'**) was obtained, rather than the thiohydrazone (**4**) (Scheme 4). This was confirmed by analyzing ^{1}H and ^{13}C NMR spectra compared with the spectral data from a previous study.[29] During our one-pot reaction, a TLC spot of dihydrothiadiazole (**4'**) was also observed below the spot of 2,5-diphenyl-1,3,4-thiadiazole (**5a**). In addition, a small amount of **4'** was isolated and its structure confirmed. As a result, it is suggested that the dihydrothiadiazole intermediate (**4'**) **i**s directly formed from **3**, and immediately oxidized under the reaction conditions to produce 2,5-diphenyl-1,3,4-thiadiazole (**5a**).



Scheme 4. Results of literature method for synthesis of intermediates **4** and/or **4'**

As mentioned above, the use of a base is, presumably, to inhibit the reverse reaction of *N*-acylhydrazones (**3**) to aldehydes (**2**) and hydrazides (**1)**, and, thereby, improve the overall yield of the reaction. Also, according to the literature, pyridine has been reported to stabilize and activate the phosphine ylide by forming stable complexes with P_4S_{10}[30] and Woollins reagents (**WR**),[31] which has a structure similar to **LR**. **LR** is known to be in equilibrium with its dithiophosphine ylide in solution (Figure 2). This ylide is said to be the reactive intermediate in the thionation processes with **LR**.[24-26] Therefore, we hypothesized that DMAP would protect the inverse-hydrolysis reaction of *N*-acylhydrazone (**3**), stabilize and activate **LR** by forming a stable DMAP-dithiophosphine complex like pyridine.

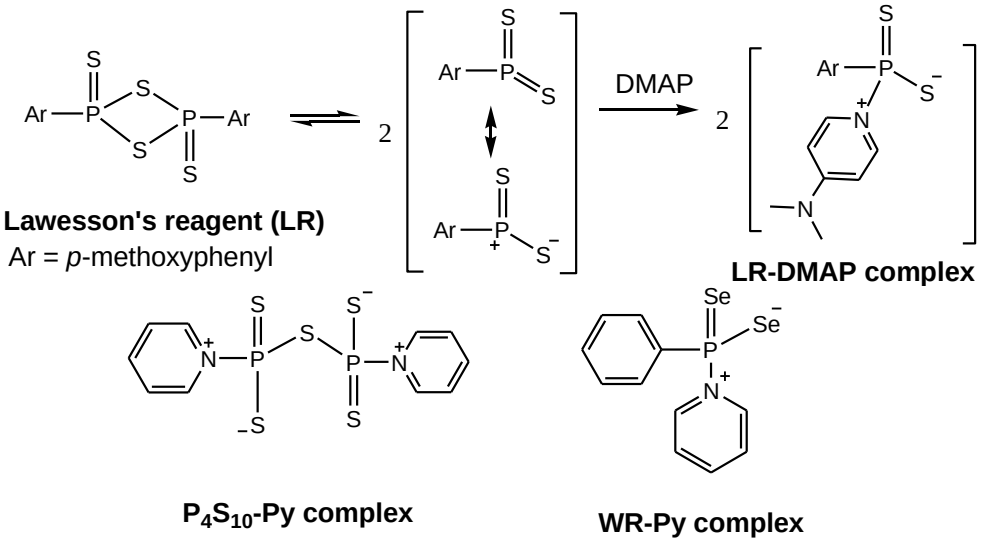
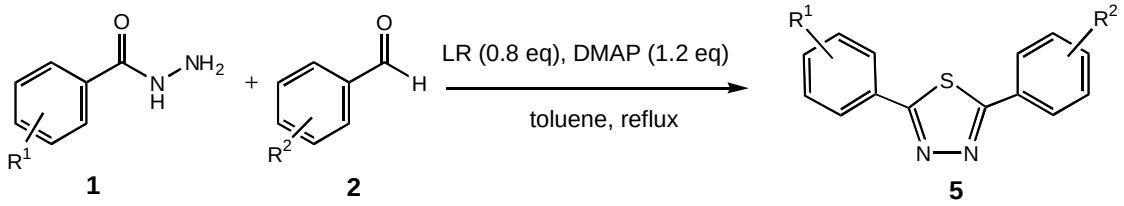


Figure 2. Proposed structures of DMAP-LR, P_4S_{10}-Py, and WR-Py complexes

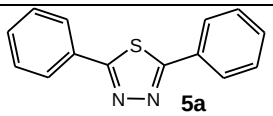
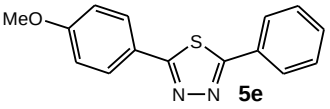
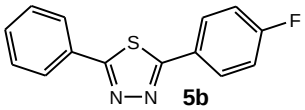
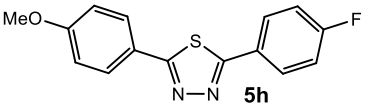
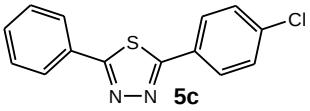
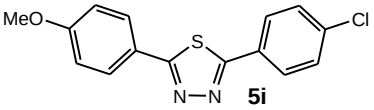
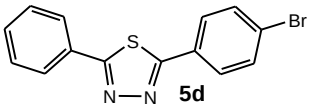
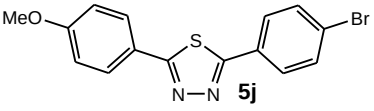
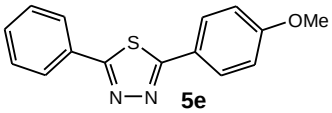
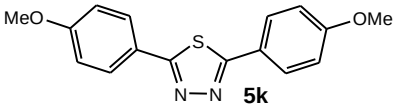
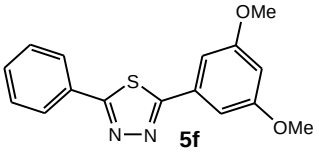
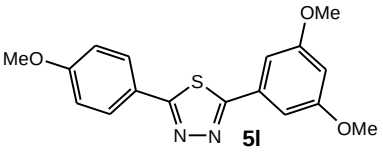
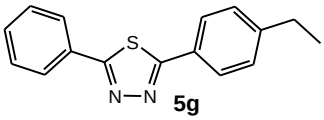
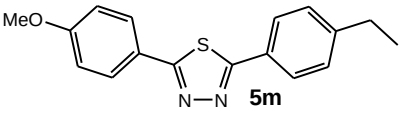
To extend the one-pot synthetic method to various 1,3,4-thiadiazoles (**5**), different combinations of aroylhydrazides (**1a-n**) and benzaldehydes (**2a-n**) were reacted under the same conditions as **5a**. First, the same amounts of aldehyde and hydrazide were reacted in refluxing ethanol for two hours. After the ethanol was evaporated, the remaining crude thiahydrazone (**3**) in the reaction vessel was reacted in toluene, refluxing with 0.8 equivalent of **LR** and 1.2 equivalents of DMAP for 12 hours as shown in Scheme 5.



Scheme 5. Synthesis of 2,5-diphenyl-1,3,4-thiadiazole derivatives (**5**). *Note:* Benzaldehyde (1.0 mmol) and benzoylhydrazide (1.0 mmol) were refluxed in ethanol for 2 hr, evaporated in vacuo, and then reacted with **LR** and DMAP in refluxing toluene.

A series of 2,5-disubstituted-1,3,4-thiadiazoles (**5a-m**) were prepared in moderate-to-high yields (75% to 97%) from hydrazides (**1a-n**) and aldehydes (**2a-n**), the results of which are summarized in Table 2.

Table 2: Results of reactions of hydrazides (**1**) and benzaldehydes (**2**) to yield 2,5-disubstituted-1,3,4-thiadiazole compounds (**5**)

Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
z	 **5a**	96	8	 **5e**	89
2	 **5b**	97	9	 **5h**	80
3	 **5c**	93	10	 **5i**	85
4	 **5d**	87	11	 **5j**	84
5	 **5e**	93	12	 **5k**	78
6	 **5f**	85	13	 **5l**	75
7	 **5g**	80	14	 **5m**	85

[a] Isolated yield by flash column chromatography.

In summary, a two-step, one-pot reaction was accomplished in refluxing ethanol using the same amounts of hydrazide **1** and aldehyde **2** without separating the hydrazine intermediate **3**, and in the absence of added oxidant.

Conclusions

In conclusion, we have developed a highly efficient, two-step, one-pot synthesis of 2,5-disubstituted-1,3,4-thiadiazoles in moderate-to-high yields from benzaldehydes and hydrazines using **LR** in the absence of an

additional oxidant. Based on the confirmation of the formation of thiadiazoline intermediate, a reaction mechanism has been proposed and the role of the base additives in this reaction has been suggested. According to preliminary biological experiments, some of the newly synthesized thiadiazoles show antioxidant activity. These results will be presented in a future study.

Experimental Section

General.

Melting points were determined using a Barnstead Electrothermal 9100 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL 300 MHz spectrometer and JEOL 75MHz spectrometer, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). The following abbreviations were used to explain the multiplicities: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, *br s* = broad singlet. High resolution mass spectrometry (HRMS) was performed using a JEOL JMS-700 M station mass spectrometer and electron impact ionization (EI-magnetic sector) mass spectrometer.

General procedure for synthesis of compounds 5a-5m

In a round bottom flask, corresponding aldehyde (**2**) (1.0 mmol) and hydrazide (**1**) (1.0 mmol) were added in ethanol (5.0 ml) at room temperature. The reaction mixture was refluxed for 2 hr. The ethanol was evaporated *in vacuo*. To the resulting crude product (**3**), Lawesson's reagent (0.8 mmol, 0.8 eq) and toluene (10 ml) were added, followed by 4-(dimethylamino)pyridine (1.2 mmol, 1.2 eq). The resulting mixture was refluxed for 10 to 15 hr until 2,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole was not detected by TLC. After evaporation of toluene, the residue was purified by flash-column chromatography.

2,5-Diphenyl-1,3,4-thiadiazole (**5a**)[32, 33] [CAS No. 1456-21-9]. White solid; Yield: 96%; mp 134-135 °C (Lit. 140 or 132 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47-7.56 (m, 4H), 7.98-8.07 (*m*, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 127.98, 129.23, 130.24, 131.15, 168.23 (thiadiazole C)

2-(4-Fluorophenyl)-5-phenyl-1,3,4-thiadiazole (**5b**)[33] [CAS No. 16020385-48-9]. White solid; Yield: 97%; mp 174-175 °C (Lit. 173 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.21 (*t*, *J* 8.5 Hz, 2 H), 7.48-7.55 (*m*, 3 H), 7.98-8.07 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 116.27, 116.56, 127.97, 129.25, 130.01, 131.23, 162.83, 166.17 (F-Phenyl-4-C), 166.99 (thiadiazole C), 168.28 (thiadiazole C)

2-(4-Chlorophenyl)-5-phenyl-1,3,4-thiadiazole (**5c**)[32] [CAS No. 17453-22-4]: White solid; Yield: 93%; mp 177-178 °C (Lit. 180 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.41-7.56 (*m*, 5 H), 7.89-8.06 (*m*, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 128.01, 128.71, 129.11, 129.28, 129.53, 130.05, 131.32, 137.28, 166.98 (thiadiazole C), 168.49 (thiadiazole C)

2-(4-Bromophenyl)-5-phenyl-1,3,4-thiadiazole (**5d**)[33] [CAS No. 17453-23-5]. White solid; Yield: 87%; mp 153-154 °C (Lit. 152 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.51-7.53 (*m*, 3 H), 7.65 (*d*, *J* 8.6 Hz, 2 H), 7.90 (*d*, *J* 8.6 Hz, 2 H), 8.02 (*dd*, *J* 6.6, 2.9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 125.77, 128.18, 129.31, 129.46, 130.20, 131.50, 132.66, 167.24 (thiadiazole C), 168.69 (thiadiazole C)

2-(4-Methoxyphenyl)-5-phenyl-1,3,4-thiadiazole (**5e**)[33] [CAS No. 1456-67-3]. White solid; Yield: 93% from phenylhydrazide and 4-methoxybenzaldehyde, 89% from 4-methoxybenzohydrazide and benzaldehyde; mp137-138 °C (Lit. 136 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.85 (*s*, 3 H), 6.96-7.05 (*m*, 2 H), 7.43-7.54 (*m*, 3 H), 7.91-8.05 (*m*, 4 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.60, 114.77, 123.13, 128.08, 129.37, 129.73, 130.58, 131.15, 162.22 (MeO-Phenyl-4-C), 167.62 (thiadiazole C), 168.19 (thiadiazole C)

2-(3,5-Dimethoxyphenyl)-5-phenyl-1,3,4-thiadiazole (**5f**). White solid; Yield: 85%; mp 144-145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.88 (*s*, 6 H), 6.60 (*t*, *J* 2.2 Hz, 1 H), 7.18 (*d*, *J* 2.2 Hz, 2 H), 7.47-7.55 (*m*, 3 H), 8.01 (*dd*, *J* 6.6, 2.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.73, 103.56, 106.02, 128.14, 129.39, 130.35, 131.36, 131.97, 161.42, 168.36 (thiadiazole C), 168.48 (thiadiazole C); HRMS (EI+): *m/z* Calcd. for $C_{16}H_{14}N_2O_2S^+$: 298.0776; found: 298.0764

2-(4-Ethylphenyl)-5-phenyl-1,3,4-thiadiazole (**5g**). White solid; Yield: 80%; mp 90-91 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.28 (*t*, *J* 7.6 Hz, 3 H), 2.72 (*q*, *J* 7.7 Hz, 2 H), 7.33 (*d*, *J* 8.3 Hz, 2 H), 7.44-7.57 (*m*, 3 H), 7.93 (*d*, *J* 8.3 Hz, 2 H), 7.97-8.06 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 15.18, 28.75, 127.74, 127.96, 128.02, 128.75, 129.21, 130.35, 131.05, 147.94, 167.84 (thiadiazole C), 168.38 (thiadiazole C) ; HRMS (EI+): *m/z* Calcd. for $C_{16}H_{14}N_2S^+$: 266.0878; found: 266.0872

2-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1,3,4-thiadiazole (**5h**). White solid; Yield: 80%; mp 160-161 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.89 (*s*, 3 H) 7.01 (*d*, *J* 9.0 Hz, 2 H), 7.19 (*t*, *J* 8.6 Hz, 2 H), 7.95 (*d*, *J* 8.8 Hz, 2 H), 8.00 (*dd*, *J* 8.8, 5.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.52, 114.72, 116.32, 116.62, 122.89, 126.77, 126.81, 129.64, 129.90, 130.02, 162.19, 162.84, 166.17, 166.30 (thiadiazole C), 168.18 (thiadiazole C); HRMS (EI+): *m/z* Calcd. For $C_{15}H_{11}FN_2OS^+$: 286.0576; Found: 286.0576

2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,3,4-thiadiazole (**5i**).[34] [CAS No. 17572-63-3]: White solid; Yield: 85%; mp190-191 °C (Lit. 186-187 °C]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.89 (*s*, 3 H) 7.01 (*d*, *J* 8.8 Hz, 2 H), 7.48 (*d*, *J* 8.6 Hz, 2 H), 7.95 (*dd*, *J* 8.8, 2.9 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.59, 114.80, 122.91, 129.04, 129.20, 129.64, 129.75, 137.22, 162.31, 166.33 (thiadiazole C), 168.43 (thiadiazole C)

2-(4-bromophenyl)-5-(4-methoxyphenyl)-1,3,4-thiadiazole (**5j**). White solid; Yield: 83% ; mp 215 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) 3.89 (*s*, 3 H) 7.01 (*d*, *J* 8.6 Hz, 2 H), 7.63 (*d*, *J* 8.4 Hz, 2 H), 7.88 (*d*, *J* 8.4 Hz, 2 H), 7.96 (*d*, *J* 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.59, 114.77, 122.85, 125.52, 129.36, 129.73, 132.59, 162.28, 166.41 (thiadiazole C), 168.45 (thiadiazole C); HRMS (EI+): m/z Calcd. For: $C_{15}H_{11}BrN_2OS^+$: 345.9775; Found: 345.9764

2,5-Bis-(4-methoxyphenyl)-1,3,4-thiadiazole (**5k**)[35] [CAS No. 17453-03-1]. White solid; Yield: 78%; mp 167-169 °C[Lit. 170-172 °C]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.88 (*s*, 6 H), 7.00 (*d*, *J* 8.8 Hz, 4 H), 7.94 (*d*, *J* 8.8 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.58, 114.72, 123.28, 129.61, 162.06, 167.40 (thiadiazole C)

2-(3,5-Dimethoxyphenyl)-5-(4-methoxyphenyl)-1,3,4-thiadiazole (**5l**). Light beige solid; Yield: 75%; mp 134-135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.88 (*s*, 6 H), 3.89 (*s*, 3 H), 6.59 (*t*, *J* 2.3 Hz, 1 H), 7.01 (*d*, *J* 8.8 Hz, 2 H), 7.16 (*d*, *J* 2.3 Hz, 2 H), 7.95 (*d*, *J* 8.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.57, 55.72, 103.42, 105.94, 114.74, 123.05, 129.69, 132.13, 161.41, 162.22, 167.56 (thiadiazole C), 168.25 (thiadiazole C); HRMS (EI+): *m/z* Calcd. for $C_{17}H_{16}N_2O_3S^+$: 328.0882; Found: 328.0869

2-(4-Ethylphenyl)-5-(4-methoxyphenyl)-1,3,4-thiadiazole (**5m**). White solid; Yield: 85%; mp 101-102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.28 (*t*, *J* 7.6 Hz, 3 H), 2.72 (*q*, *J* 7.5 Hz, 2 H), 3.89 (*s*, 3 H), 7.01 (*d*, *J* 9.0 Hz, 2 H), 7.32 (*d*, *J* 8.3 Hz, 2 H), 7.96 (*d*, *J* 9.0 Hz, 2 H), 7.92 (*d*, *J* 8.3 Hz, 2 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 15.35, 28.88, 55.56, 114.68, 123.16, 127.99, 128.07, 128.84, 129.63, 147.85, 162.06, 167.72 (thiadiazole C), 167.76 (thiadiazole C); HRMS (EI+): *m/z* Calcd. For $C_{17}H_{16}N_2OS^+$: 296.0983; Found: 296.1002

Procedure for synthesis of compound (8)[27,28]

In a round-bottom flask, following flame drying, 40 ml of 1M phenylmagnesium bromide (40 mmol) in THF was added. It was then cooled to 0 °C, and 2.42 ml of carbon disulfide (40 mmol) was slowly introduced dropwise. It was stirred at room temperature for 12 hr and then poured into 100 g of ice water and 3.78 g of chloroacetic acid (40 mmol). Anhydrous sodium carbonate 3.36g (20 mmol) was added and stirred for 24 hr at 90 °C. The liquid was adjusted to pH 2 with concentrated hydrochloric acid, and a red solid was obtained by recrystallization in a mixture of ethyl acetate and hexane.

2-(Phenylcarbonothionylthio)acetic acid (**8**) [CAS No. 942-91-6]. Yield: 72% ; mp 125-126 °C [Lit. 123-125 °C]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.28 (*s*, 2 H), 7.41 (*t*, *J* 7.7 Hz, 2 H), 7.57 (*t*, *J* 7.5 Hz, 1 H), 8.03 (*d*, *J* 7.9 Hz, 2 H), 10.52 (*br*. *s*., 1 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 38.76, 127.23, 128.69, 133.18, 144.20, 173.86, 225.89.

Procedure for synthesis of compound 9[28]

Compound **8** (2.0 g, 9.4 mmol) was dissolved in 1 M NaOH (10 mL, 1 eq) and H_2O (10 ml). Upon addition of hydrazine hydrate (1.7 g, 55%, 18.8 mmol), the orange color disappeared. After consumption of the starting material, the reaction mixture was acidified to pH 5-6 with dilute HCl (aq) and stirred for 1 hr while cooling in an ice bath. A white solid was filtered and recrystallized from water to produce benzothiohydrazide (**9**) as white crystals.

Benzothiohydrazide (**9**) [CAS No. 20605-40-7]. White solid; Yield: 60%; mp 80-82 °C[Lit. 78-80 °C]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.25 (*br*. *s*., 1 H), 7.37-7.46 (*m*, 3 H), 7.70 (*d*, *J* 7.0 Hz, 2 H), 12.13 (*br*. *s*., 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 127.82, 129.63, 129.69, 131.64, 167.97.

Procedure for synthesis of compound (4')[29]

In a round-bottom flask, benzaldehyde (0.5 mmol) and **9** (0.5 mmol) were added in ethanol (5 ml) for 2 hr at room temperature. After the reaction was complete, the ethanol was evaporated under vacuum, and the product was obtained by recrystallization in a mixture of ethyl acetate and hexane.

2,5-Diphenyl-2,3-dihydro-1,3,4-thiadiazole (**4'**) [CAS No. 82243-06-9]. Yield: 92%; mp 78-79 °C[Lit. 76-78 °C]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.36 (*s*, 1 H, C-5 H), 7.29-7.42 (*m*, 6 H), 7.43-7.53 (*m*, 2 H), 7.61-7.75 (*m*, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 74.72 (C-5), 126.65, 127.21, 128.69, 129.12, 129.25, 129.81, 131.37, 140.93, 146.65.

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