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Eco-efficient, regioselective and rapid access to 4,5-disubstituted 1,2,3-thiadiazoles *via* [3 + 2] cycloaddition of α-enolicdithioesters with tosyl azide under solvent-free conditions†

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An efficient, sustainable, and regioselective one-pot synthesis of hitherto unreported 4-aroyl/hetaroyl/alkanoyl-5-alkyl/allyl/benzylsulfanyl-1,2,3-thiadiazoles has been achieved by [3 + 2] cycloaddition of α-enolicdithioesters with tosyl azide through cascade 1–2 (S–N) and 3–4 (C–N) bond connections involving Wolff-type heterocyclization. Optimally, the reactions are very fast and completed within 2–15 minutes, when a mixture of α-enolicdithioester and tosyl azide was stirred at 0 °C in the presence of Et_3N under solvent-free conditions. Furthermore, no co-catalyst or activator is necessary. The eco-compatibility, mild conditions, excellent yields, easy purification, and avoidance of expensive/toxic reagents are advantages of this protocol to access this medicinally privileged substructure.

Introduction

Synthetic organic chemistry occupies a central role in every area of our increasingly technological society, retains its importance as it is an integral part of new drug discovery, and is the basis of the bulk of the chemical industry. Synthesis of heterocycles is key in organic synthesis, since heterocycles are indispensable materials in the functioning of any developed society.[1] Among the four isomeric forms of thiadiazoles, 1,2,3-thiadiazoles[2] are versatile privileged scaffolds present in many bioactive natural products and pharmaceuticals, and exhibit diverse applications in medicine[3] and agriculture.[4] Among the various pharmacological profiles of 1,2,3-thiadiazoles, their antibacterial,[5a,b] antiamoebic,[5c] anticancer,[5d] anti-HIV,[5e,f] antifungal,[6a–c] and antiviral[6d–f] properties seem to be the best documented. Additionally, 1,2,3-thiadiazoles are also useful intermediates to construct several important bioactive compounds such as thioacetanilides (as potent HIV-1 non-nucleoside reverse transcriptase inhibitors),[7a] acrylamide derivatives (antihepatitis B virus),[7b] benzylamides (inhibitors of non-regulated cell death),[7c] and 1,2,3-thiadiazole-containing pyrazolones as substituents (potent KDR/VEGFR-2 kinase inhibitors).[7d] Furthermore, 1,2,3-thiadiazoles undergo cleavage in the presence of strong base to form alkynethiolates,[8a] which were further utilized as synthons for the synthesis of dendrimers,[8b,c] tetrathiafulvalenes,[8d,e] 2-benzofuran thiolates,[8f] amides of 1-adamantylthioacetic acids,[8g] and 1,1-dialkylindolium-2-thiolates.[8h] Moreover, the properties of easy breakdown of the 1,2,3-thiadiazole ring through release of N_2 into low molecular weight compounds favor the use of its derivatives as eco-friendly pesticide candidates with low toxicity.[9] In addition, thiadiazole can act as the bio-isosteric replacement of the thiazole moiety, so it acts like third and fourth generation cephalosporins.

Among many strategies towards substituted 1,2,3-thiadiazoles,[10] cyclization of hydrazones with thionyl chloride (Hurd–Mori synthesis),[10a] cycloaddition of diazoalkanes onto a C=S bond (Pechmann synthesis),[10b,c] and heterocyclization of α-diazo thiocarbonyl compounds (Wolff synthesis)[10d] are the most favourite protocols. A number of interesting applications of the Hurd–Mori reaction[11] and the Wolff synthesis[12] are reported. Recently, Kumar *et al.*[13] have synthesized 1,2,3-thiadiazoles using ionic liquid-supported sulfonyl hydrazine. Although the reported methods are useful tools and serve the synthetic requirements, most of them suffer from significant limitations such as harsh reaction conditions, expensive

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†Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of all compounds. CCDC reference numbers 889622 (**3aa**) and 914821 (**3ad**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3gc37047j

catalysts/reagents, prolonged reaction times, multistep syntheses, and poor availability of starting materials. In view of these limitations, there is still a need for exploration of mild, efficient, rapid, and widely applicable eco-compatible routes for the synthesis of 1,2,3-thiadiazole derivatives owing to their great synthetic and medicinal relevance. In the present investigation, the application of Wolff synthesis has been adopted utilizing tosyl azide,[14a] which is a good substrate for the introduction of a diazo functional group. In most recent times, organic azides have become widely used in organic synthesis as valuable intermediates and building blocks,[14b,c] particularly in the synthesis of nitrogen-containing heterocycles, peptide chemistry, materials science, polymer chemistry, and drug discovery.[14d] Thus, organic azides have assumed an important position at the interface of chemistry, biology, medicine, and materials science.

Synthetic strategies regarding how to construct and cleave carbon–carbon (C–C) and carbon–heteroatom (C–X) bond(s) represent the central theme in organic synthesis, and are also cutting-edge methodology. The drive to environmentally sustainable or so-called 'green technologies' looks for alternative ways to reduce drastic prerequisites for reactions. Because of the increasing public concern for the harmful effects of organic solvents on the environment and the human body, solvent-free reactions[15] have aroused the attention of organic chemists due to their more efficient and less labour-intensive methodologies. So, it is now often claimed that 'the best solvent is no solvent'. Furthermore, solvent-free reactions offer several advantages such as faster reaction rates, reduced reaction time, less energy consumption, easy separation, and products with high yields and better purity. Due to the above considerations, in recent years it has become an important green protocol to perform reactions under solvent-free conditions.[15]

Results and discussion

Simple polyfunctional molecules are ideal starting materials in diversity-oriented synthesis, which aims at providing quick access to libraries of molecules. Synthons containing both electrophilic and nucleophilic sites have great potential in developing new reaction pathways. One such synthon is β-oxodithioester, a thio-analogue of the normal β-ketoester with general formula **1** (Fig. 1). Notably, its reactivity is far different from the normal β-ketoester due to the unique array of three nucleophilic (O, C and S) and two electrophilic (C=O and C=S) centres. Due to the presence of these active centres, enolic and dithioester moieties, the reactions of α-enolicdithioesters with various electrophilic and nucleophilic reagents have been exploited to construct five-/six-membered and fused heterocycles, depending on the reaction conditions, during the past few years.[16]

In continuation of our research interests regarding the synthetic utility of β-oxodithioesters,[17] and as a part of our ongoing programme aimed at exploring one-pot solvent-free synthetic protocols,[18] we report herein a simple, convenient, and solvent-free synthesis of 4,5-disubstituted 1,2,3-thiadiazoles involving Wolff-type heterocyclization from [3 + 2] atom fragments. As an interesting alternative, this two-component one-pot domino process led to the concomitant creation of two new bonds (C–N and S–N) and one ring. So far, to the best of our knowledge, this is first report on the use of α-enolicdithioesters and tosyl azide for the straightforward synthesis of 4,5-disubstituted 1,2,3-thiadiazoles.

α-Enolicdithioesters, pivotal three-carbon synthons, are not commercially accessible, and have been easily synthesized in good yields by stirring methyl ketones with (*S*,*S*)-dialkyltrithiocarbonate in the presence of NaH in DMF–hexane (1 : 4) mixture according to a reported procedure.[16d] Tosyl azide has been synthesized by the literature method.[14a] Thus, treatment of α-enolicdithioesters **1** with tosyl azide **2** in the presence of Et_3N (TEA) at 0 °C under solvent-free conditions resulted the corresponding 4,5-disubstituted-1,2,3-thiadiazoles **3** within 2–15 minutes in good to excellent yields with tosyl amide only as the waste, which was removed by simple washing (Scheme 1).

Initially, to optimize the reaction conditions for the synthesis of substituted 1,2,3-thiadiazoles, methyl 3-hydroxy-3-phenyl-prop-2-enedithioate **1a** and tosyl azide **2** were taken as model substrates. The effects of different bases, solvents, and temperatures were examined on the model reaction and the results are listed in Table 1. Generally, base plays an important role in the formation of 1,2,3-thiadiazoles. Obviously, without any base, the reaction did not take place in dichloromethane (DCM) as well as under solvent-free conditions at room temperature even after 24 h of stirring, and the starting materials remain entirely unconsumed (Table 1, entries 1 and 2). With this failure, we next carried out the above model reaction in the presence of Et_3N (1.0 equiv.) at room temperature under solvent-free conditions. Surprisingly, the reaction proceeded rapidly in exothermic fashion to give the corresponding

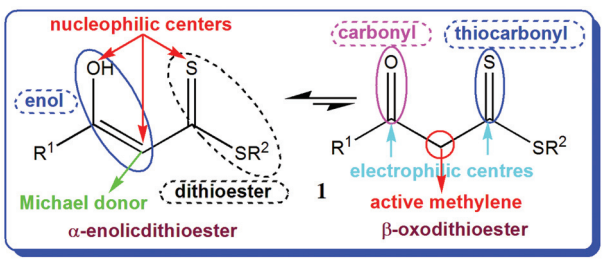
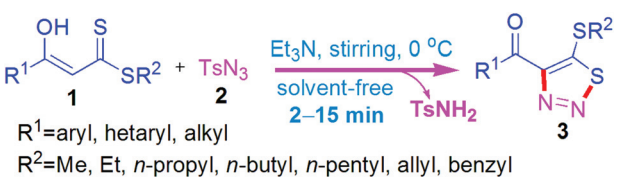
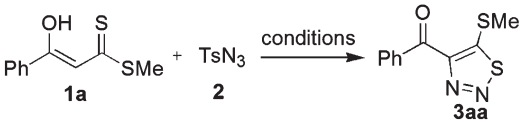


Fig. 1 Reactive sites of α-enolicdithioesters **1**.



Scheme 1 Synthesis of 4,5-disubstituted 1,2,3-thiadiazoles **3**.

Table 1 Optimization of reaction conditions for the synthesis of **3aa**[a]



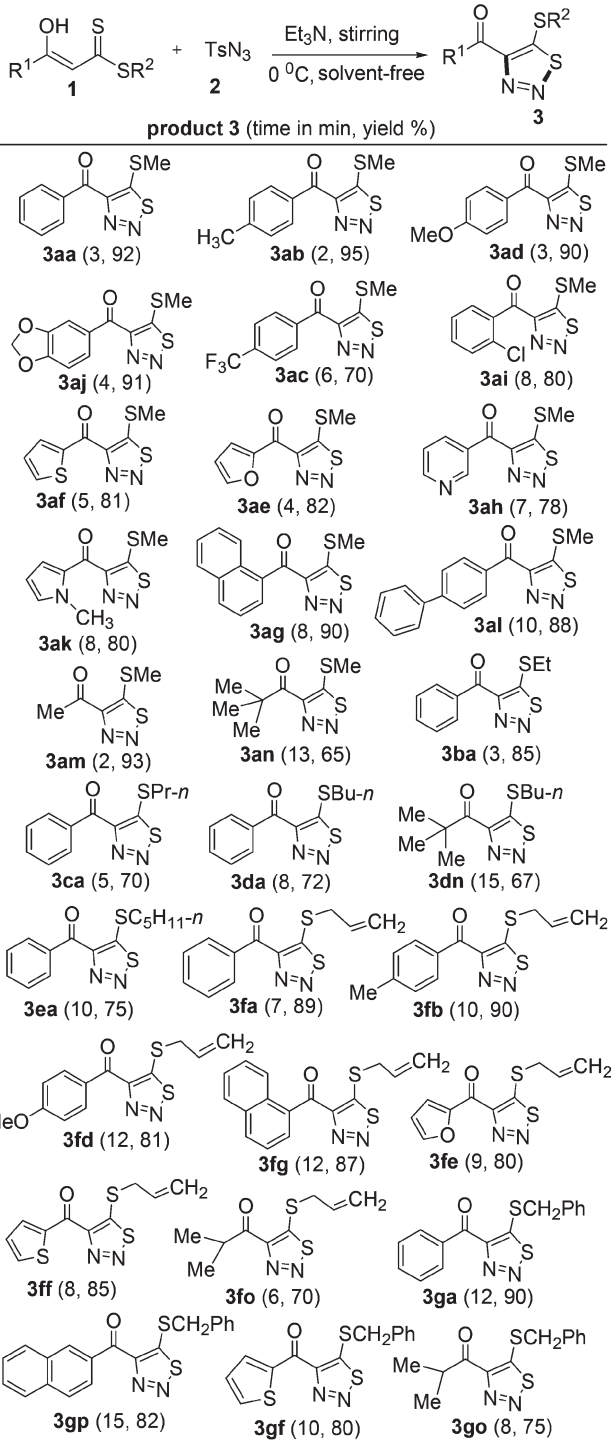
Entry	Base (equiv.)	Solvent	Temp. (°C)	Time	Yield[b] (%)
1	None	DCM	25	24 h	—[c]
2	None	None	25	24 h	—[c]
3	TEA (1.0)	None	25	2 min	55[d]
4	TEA (1.0)	None	15	2 min	68[d]
5	**TEA (1.0)**	**None**	**0**	**3 min**	**92**
6	DABCO (1.0)	None	0	10 min	81
7	DMAP (1.0)	None	0	8 min	80
8	DBU (1.0)	None	0	10 min	82
9	Pyrrolidine (1.0)	None	0	12 min	85
10	Piperidine (1.0)	None	0	10 min	82
11	DIPA (1.0)	None	0	10 min	84
12	Pyridine (1.0)	None	0	4 h	55
13	Bu^tOK (1.0)	None	0	15 min	75
14	K_2CO_3 (1.0)	None	0	20 min	78
15	NaOH (1.0)	None	0	15 min	70
16	TEA (1.0)	DCM	0	8 h	65
17	TEA (1.0)	CH_3CN	0	8 h	60
18	TEA (1.0)	DMF	0	8 h	65
19	TEA (1.0)	DMSO	0	6 h	69
20	TEA (1.0)	MeOH	0	6 h	70
21	TEA (1.0)	EtOH	0	7 h	70
22	TEA (1.0)	H_2O	0	30 min	80
23	TEA (1.0)	Toluene	0	9 h	40
24	TEA (0.5)	None	0	10 min	82
25	TEA (1.3)	None	0	3 min	88

[a] Reactions were carried out using **1a** (1.0 mmol) and **2** (1.0 mmol). [b] Isolated pure yield. [c] No reaction. [d] Highly exothermic reaction.

product **3aa** in 55% yield within 2 minutes (Table 1, entry 3). Since at room temperature, the reaction is highly exothermic, so we performed the reaction at lower temperatures (Table 1, entries 4 and 5). To our delight, the desired product **3aa** was obtained exclusively in 92% yield at 0 °C within 3 minutes (Table 1, bold entry 5).

Encouraged by the above results, other readily available organic bases such as DABCO, DMAP, DBU, pyrrolidine, piperidine, diisopropyl amine (DIPA), pyridine and Bu^tOK, and inorganic bases like K_2CO_3 and NaOH, were also examined separately at 0 °C under solvent-free conditions. All the above bases afforded the desired product in good yield. However, compared to Et_3N, they gave relatively lower yield in longer time (Table 1, entries 6–15). Triethylamine promoted this transformation more efficiently than other organic and inorganic bases. Next, the utility of different solvents such as DCM, CH_3CN, DMF, DMSO, MeOH, EtOH, H_2O, and toluene was also investigated, but no superior results were obtained (Table 1, entries 16–23). Finally, the amount of Et_3N was investigated, and the results showed that increasing or decreasing the amount of Et_3N resulted in slightly lower yields (Table 1, entries 24 and 25). Thus, the best reaction condition for the synthesis of **3aa** was found to be 1.0 equiv. of Et_3N at 0 °C under solvent-free conditions (entry 5, bold in Table 1).

Table 2 α-Enolicdithioesters scope for the synthesis of **3**



Experiments probing the scope and generality of this process under optimized conditions are summarized in Table 2. A broad spectrum of α-enolicdithioesters **1**, bearing R^1 as aryl, hetaryl, extended aromatics and alkyl groups, and R^2 as saturated and unsaturated alkyl groups, could be employed to afford thiadiazoles **3** in good to excellent yields. As can be seen from Table 2, all reactions proceeded very fast and

afforded the corresponding products **3** in high yields within 2–15 minutes.

To probe electronic and steric influences on the annulation strategy, a wide range of dithioesters derived from acetophenone containing both electron-donating and electron-withdrawing groups were employed. α-Enolicdithioesters bearing R^1 as aryl group with electron-donating substituents gave considerably higher yields than those with electron-withdrawing groups (Table 2, entries **3ab**, **3ad**, **3aj** *vs.* **3ac**). After successful utilization of aromatic dithioesters, we next extended our study to various heteroaromatic dithioesters obtained from 2/3-substituted heteroaromatic compounds such as 2-acetylthiophene, 2-acetylfuran, 3-acetylpyridine, and *N*-methyl-3-acetylpyrrole, which was also demonstrated to be effective substrates and afforded the desired compounds **3** in 78–85% yields (Table 2, entries **3af**, **3ae**, **3ah**, **3ak** and **3ff**). We were pleased to find that extended aromatics such as 1-naphthyl, 2-naphthyl, and biphenyl as R^1 substituents were also tolerated well resulting in high yields of the products **3** (Table 2, entries **3ag**, **3al**, **3fg** and **3gp**).

Notably, alkyl-substituted dithioesters derived from aliphatic ketones such as acetone and iso-propyl methyl ketone also went smoothly to give desired compounds **3** in good yields (Table 2, entries **3am**, **3fo** and **3go**). However, when the more bulky *tert*-butyl group was installed, the reaction became sluggish and yield decreased significantly, yet it remained good (≥65%, Table 2, entries **3an** and **3dn**). In order to extend the reaction scope further, we turned our attention to modification of the thioalkyl moiety R^2 at position 5 of thiadiazole ring. Therefore, we next tuned the dithioesters by introducing at R^2 different alkyl groups such as ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, allyl, and benzyl moieties. Gratifyingly, α-enolicdithioesters bearing the above alkyl groups at R^2 were also tolerated well and the desired thiadiazoles **3** were isolated in good yields (Table 2). Altering the methyl group at R^2 to an allyl group in α-enolicdithioesters resulted the desired 1,2,3-thiadiazoles **3** almost in comparable yields.

Noteworthy features of the conversion include the following: (1) elegant efficiency of the process has been demonstrated in bond formation (two new bonds created) and ring construction (one new ring); (2) the reaction proceeds through a three-step sequence, abstraction of enolic proton of α-enolicdithioester, nucleophilic attack of α-carbon of α-enolicdithioester on the sp-hybridized nitrogen of tosyl azide, and intramolecular S-cyclization; (3) the overall yields of this conversion are excellent; (4) the steric effect of *ortho*-substituent is minimal (Table 2, **3ai**); (5) electron-withdrawing group on the aromatic ring exhibit comparable reduced reactivity in the preparation of thiadiazloes (Table 2, **3ac**); (6) an electron-donating group gives a better result in the synthesis of thiadiazloes (Table 2, **3ab**, **3ad**, **3aj**); (7) the extended aromatic rings also afforded thiadiazloes in good yields (Table 2, **3ag**, **3al**, **3fg**, **3gp**).

The structures of all the newly synthesized 1,2,3-thiadiazole derivatives **3** were deduced by their satisfactory spectral (IR, ^{1}H, ^{13}C NMR, and mass) studies and explicitly established by

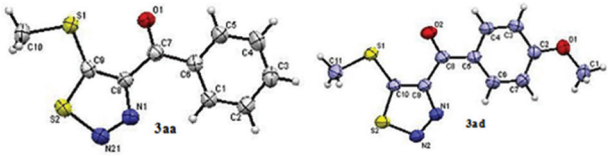
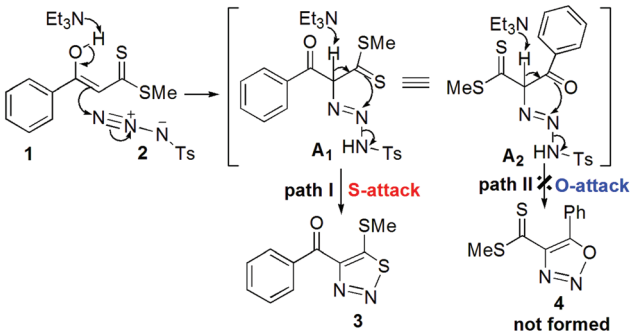


Fig. 2 ORTEP diagrams of **3aa** and **3ad**.



Scheme 2 Plausible mechanism for the formation of 1,2,3-thiadiazole **3**.

the single crystal X-ray diffraction analysis (see the ESI†)[19] of two representative compounds **3aa** and **3ad** (Fig. 2). The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values.

Taking into consideration the entire outcome, a plausible mechanistic pathway for the domino one-pot two-component heteroannulation is outlined in Scheme 2. The first step in the mechanism is believed to be the abstraction of enolic proton from α-enolicdithioesters **1** by Et_3N followed by nucleophilic attack of α-carbon on the sp-hybridized electrophilic nitrogen of tosylazide **2**, forming C–N bond to generate the intermediate $\mathbf{A_1}$, which is believed to be the key rate-determining step. The intermediate $\mathbf{A_1}$ is likely to cyclize *via* its two possible rotamers $\mathbf{A_1}$ and $\mathbf{A_2}$ through pathways **I** and **II** to furnish 1,2,3-thiadiazole **3** and 1,2,3-oxadiazole **4**, respectively, with the extrusion of *p*-tosyl amide. The intermediate $\mathbf{A_1}$ undergoes intramolecular cyclization by regioselective attack through sulfur *via* route **I** to give the desired 1,2,3-thiadiazole **3** exclusively in accordance with our previous results.[17d] The alternative intramolecular O-cyclization of $\mathbf{A_2}$ *via* route **II** could lead to 1,2,3-oxadiazole **4**, which was not observed even in trace amounts during our investigations, making the protocol highly selective.

Conclusions

In summary, we have developed an experimentally rapid, straightforward and regioselective protocol for the synthesis of 4,5-disubstituted 1,2,3-thiadiazoles by [3 + 2] cycloaddition of α-enolicdithioesters with tosyl azide in the presence of Et_3N at 0 °C under solvent-free conditions for the first time. Tosyl azide transfers the diazo-functional group to α-enolicdithioesters followed by Wolff cyclization to give the desired 1,2,3-

thiadiazoles. This transformation avoids the use of transition-metal catalyst and constructs two new bonds and one ring with both reactants efficiently being utilized. Importantly, the presence of keto- and alkylthio- groups at 4- and 5-positions of 1,2,3-thiadiazoles makes these compounds excellent entrants as precursors for further synthetic renovations to meet the need for diverse useful purposes. The removal of tosyl amide by simply washing makes the process very simple and no chromatographic separation is required except in the case of liquid products and compounds containing basic moieties. We hope this clean and green protocol may be of value for both synthetic and medicinal chemists for academic research and practical applications.

Experimental section

General information

The commercially available starting materials were used as received without further purification. α-Enolicdithioesters[16d] **1** and tosyl azide[14a] **2** were prepared by the reported procedures. Infrared (IR) spectra are recorded in KBr, and wavenumbers (ν) are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on NMR spectrometers operating at 300 and 75 MHz, respectively. Chemical shifts (δ) are given in parts per million (ppm) using the residue solvent peaks as reference relative to TMS. J values are given in Hz. Mass spectra were recorded using electrospray ionization (ESI) mass spectrometry. The C, H, and N analyses were performed by microanalytical laboratory analysis. The melting points are uncorrected.

General procedure for synthesis of 4-alkanoyl/aroyl/hetaroyl-5-alkyl/allyl/benzylsulfanyl-1,2,3-thiadiazoles 3

An oven-dried round bottom flask was charged with the appropriate α-enolicdithioesters **1** (1.0 mmol), tosyl azide **2** (1.0 mmol), and Et_3N (1.0 mmol), and the reaction mixture was stirred in an ice bath at 0 °C for the stipulated period of time till the completion of the reaction (monitored by TLC). Methanol (1 ml) was added to the reaction mixture, followed by 1 ml of conc. HCl and 3 ml of water. The solid product obtained was filtered, washed with water, and finally recrystallized from MeOH–$CHCl_3$ mixture (1 : 1) to give the analytically pure sample. The liquid compounds and products **3ah** and **3ak** were purified by rapid filtration through a short column filled with silica gel using EtOAc–hexane as eluent.

The spectral and analytical data of all the compounds are given as follows.

4-Benzoyl-5-methylsulfanyl-1,2,3-thiadiazole (3aa). White solid; mp 106–107 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, J = 7.2 Hz, 2H, ArH), 7.61–7.50 (m, 3H, ArH), 2.71 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.7, 170.3, 153.0, 136.9, 133.1, 130.5, 128.2, 21.7. IR (KBr, cm^{-1}): 3072, 2916, 1624, 1568, 1592, 1447, 1392, 1218, 1087. HRMS (ESI) m/z calcd for $C_{10}H_8N_2OS_2$ [M + Na^+], 258.9970; Found 258.9866. Elemental analysis for $C_{10}H_8N_2OS_2$: calc. C, 50.83; H, 3.41; N, 11.85%. Found: C, 50.64; H, 3.24; N, 11.49%.

4-(4-Methylbenzoyl)-5-methylsulfanyl-1,2,3-thiadiazole (3ab). White solid; mp 168–169 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, J = 8.1 Hz, 2H, ArH), 7.32 (d, J = 8.1 Hz, 2H, ArH), 2.71 (s, 3H, SCH_3), 2.44 (s, 3H, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.3, 170.0, 144.1, 134.4, 130.8, 129.0, 100.5, 21.8, 21.7. IR (KBr, cm^{-1}): 3070, 2950, 1620, 1602, 1563, 1414, 1394, 1183, 1076.

5-Methylsulfanyl-4(4-trifluoromethylbenzoyl)-1,2,3-thiadiazole (3ac). White solid; mp 130–131 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, J = 8.1 Hz, 2H, ArH), 7.78 (d, J = 8.1 Hz, 2H, ArH), 2.74 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.6, 171.2, 152.6, 139.8, 134.2 (q, J = 33.3 Hz, 1C), 130.8, 125.2, 121.8, 21.8. IR (KBr, cm^{-1}): 3063, 2948, 1631, 1609, 1544, 1424, 1386, 1165, 1079.

4-(4-Methoxybenzoyl)-5-methylsulfanyl-1,2,3-thiadiazole (3ad). White solid; mp 169–170 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, J = 8.7 Hz, 2H, ArH), 7.00 (d, J = 8.7 Hz, 2H, ArH), 3.90 (s, 3H, OCH_3), 2.70 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.9, 169.7, 163.7, 153.4, 133.1, 129.7, 113.6, 55.4, 21.7. IR (KBr, cm^{-1}): 3075, 2984, 2916, 1619, 1596, 1565, 1426, 1393, 1255, 1173, 1085. Elemental analysis for $C_{11}H_{10}N_2O_2S_2$: calc. C, 49.61; H, 3.78; N 10.52%. Found: C, 49.93; H, 4.12; N, 10.24%.

4-(2-Furoyl)-5-methylsulfanyl-1,2,3-thiadiazole (3ae). White solid; mp 198–199 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 3.3 Hz, 1H, ArH), 7.70 (s, 1H, ArH), 6.57 (d, J = 1.8 Hz, 1H, ArH), 2.63 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 169.3, 151.6, 151.0, 148.0, 122.9, 112.5, 21.6. IR (KBr, cm^{-1}): 3089, 2979, 1666, 1587, 1516, 1418, 1268, 1049.

5-Methylsulfanyl-4-(2-thienoyl)-1,2,3-thiadiazole (3af). Yellow solid; mp 176–177 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.65 (d, J = 3.6 Hz, 1H, ArH), 7.78 (d, J = 4.8 Hz, 1H, ArH), 7.24 (dd, J = 5.7 Hz, J = 4.2 Hz, 1H, ArH), 2.72 (s, 3H, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 169.6, 152.2, 142.2, 136.2, 135.6, 128.4, 21.8. IR (KBr, cm^{-1}): 3087, 2980, 1656, 1599, 1507, 1420, 1270, 1057, 838.

5-Methylsulfanyl-4-(1-naphthoyl)-1,2,3-thiadiazole (3ag). White solid; mp 117–118 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 9.3 Hz, 1H, ArH), 8.04 (d, J = 3 Hz, 2H, ArH), 7.91 (d, J = 9.3 Hz, 1H, ArH), 7.58–7.52 (m, 3H, ArH), 2.73 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.6, 169.9, 154.1, 135.0, 133.6, 132.4, 130.7, 129.7, 128.4, 127.5, 126.3, 125.2, 124.2, 21.8. IR (KBr, cm^{-1}): 3049, 2909, 1629, 1505, 1436, 1409, 1274, 1058. HRMS (ESI) m/z calcd for $C_{14}H_{10}N_2OS_2$ [M + Na^+], 309.0127; Found 309.0003. Elemental analysis for $C_{14}H_{10}N_2OS_2$: calc. C, 58.72; H, 3.52; N, 9.78%. Found: C 58.79, H 3.74, N 9.93%.

5-Methylsulfanyl-4-(3-pyridoyl)-1,2,3-thiadiazole (3ah). White solid; mp 100–101 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 9.51 (s, 1H, ArH), 8.80–8.66 (m, 2H, ArH), 7.49–7.45 (m, 1H, ArH), 2.71 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.9, 171.2, 152.7, 152.5, 151.1, 138.3, 132.7, 123.3, 21.8. IR (KBr, cm^{-1}): 3047, 2923, 2853, 1625, 1579, 1428, 1397, 1274, 1012, 879.

4-(2-Chlorobenzoyl)-5-methylsulfanyl-1,2,3-thiadiazole (3ai). Yellow solid; mp 101–102 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.62–7.39 (m, 4H, ArH), 2.74 (s, 3H, SCH_3). ^{13}C NMR

(75 MHz, $CDCl_3$): δ 186.9, 169.5, 153.0, 138.2, 131.8, 131.7, 130.1, 129.6, 126.5, 21.7. IR (KBr, cm^{-1}): 3075, 2907, 1646, 1588, 1432, 1398, 1275, 1014, 878. HRMS (ESI) *m*/*z* calcd for $C_{10}H_7ClN_2OS_2$ [M + Na^+], 292.9580; Found 292.9460. Elemental analysis for $C_{10}H_7ClN_2OS_2$: calc. C, 44.36; H, 2.61; N, 10.35%. Found: C, 44.61; H, 2.94; N, 10.41%.

4-(3,4-Methylenedioxybenzoyl)-5-methylsulfanyl-1,2,3-thiadiazole (3aj). White solid; mp 190–191 °C. ^{1}H NMR (300 Hz, $CDCl_3$): δ 8.19 (dd, *J* = 8.1 Hz, *J* = 1.2 Hz, 1H, ArH), 7.89 (d, *J* = 1.5 Hz, 1H, ArH), 6.92 (d, *J* = 8.1 Hz, 1H, ArH), 6.07 (s, 2H, CH_2), 2.70 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.4, 169.8, 152.1, 147.9, 131.4, 127.8, 127.6, 110.4, 107.9, 101.8, 21.7. IR (KBr, cm^{-1}): 3054, 2924, 2890, 1641, 1608, 1499, 1439, 1398, 1266, 1075, 856. HRMS (ESI) *m*/*z* calcd for $C_{11}H_8N_2O_3S_2$ [M + Na^+], 302.9869; Found 302.9744.

4-(*N*-Methylpyrrol-3-oyl)-5-methylsulfanyl-1,2,3-thiadiazole (3ak). White crystalline solid; mp 148–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, ArH), 6.92 (s, 1H, ArH), 6.56 (s, 1H, ArH), 3.66 (s, 3H, NCH_3), 2.59 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8, 167.6, 153.5, 130.6, 123.8, 123.1, 111.1, 36.6, 21.6. IR (KBr, cm^{-1}): 3069, 2923, 2918, 1641, 1624, 1568, 1592, 1447, 1392, 1218, 1087. HRMS (ESI) *m*/*z* calcd for $C_9H_9N_3OS_2$ [M + Na^+], 262.0079; Found 261.9980.

5-Methylsulfanyl-4-(4-phenylbenzoyl)-1,2,3-thiadiazole (3al). White solid; mp 180–181 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.1 Hz, 2H, ArH), 7.66 (d, *J* = 8.4 Hz, 2H, ArH), 7.58 (d, *J* = 7.2 Hz, 2H, ArH), 7.42–7.29 (m, 3H, ArH), 2.63 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.1, 170.3, 153.2, 145.8, 139.8, 135.6, 131.2, 128.9, 128.1, 127.2, 126.9, 21.8. IR (KBr, cm^{-1}): 3071, 2921, 1638, 1559, 1583, 1439, 1386, 1223, 1076. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{12}N_2OS_2$ [M + Na^+], 335.0283; Found 335.0150. Elemental analysis for $C_{16}H_{12}N_2OS_2$: calc. C, 61.51; H, 3.87; N, 8.97%. Found: C 61.42, H 3.93, N 8.76%.

4-Acetyl-5-methylsulfanyl-1,2,3-thiadiazole (3am). White solid; mp 118–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 3H, CH_3), 2.68 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 167.0, 153.2, 28.5, 21.4. IR (KBr, cm^{-1}): 2974, 1638, 1386, 1211, 1017.

4-(2,2-Dimethylpropan-1-oyl)-5-methylsulfanyl-1,2,3-thiadiazole (3an). Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H, SCH_3), 1.49 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.9, 169.5, 151.7, 44.8, 26.8, 21.8. IR (KBr, cm^{-1}): 2967, 1634, 1592, 1392, 1218, 1007.

4-Benzoyl-5-ethylsulfanyl-1,2,3-thiadiazole (3ba). White solid; mp 102–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, *J* = 7.2 Hz, 2H, ArH), 7.61–7.51 (m, 3H, ArH), 3.09 (q, *J* = 7.4 Hz, 2H, CH_2), 1.52 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.7, 168.3, 153.3, 137.0, 133.0, 130.5, 128.2, 33.1, 13.1. IR (KBr, cm^{-1}): 3030, 2908, 2898, 1619, 1543, 1419, 1323, 1231, 1051, 853.

4-Benzoyl-5-(1-propylsulfanyl)-1,2,3-thiadiazole (3ca). Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, *J* = 7.2 Hz, 2H, ArH), 7.52–7.40 (m, 3H, ArH), 2.97 (t, *J* = 7.2, 2H, SCH_2), 1.85–1.65 (m, 2H, CH_2), 1.05 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.6, 168.6, 153.3, 137.0, 133.0, 130.5, 128.2, 41.0, 21.5, 13.4. IR (KBr, cm^{-1}): 3051, 2921, 1631, 1532, 1545, 1432, 1381, 1221, 1054.

4-Benzoyl-5-(1-butylsulfanyl)-1,2,3-thiadiazole (3da). Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, *J* = 7.2 Hz, 2H, ArH), 7.63–7.49 (m, 3H, ArH), 3.09–3.04 (t, *J* = 6.9 Hz, 2H, SCH_2), 1.89–1.67 (m, 2H, CH_2), 1.60–1.43 (m, 2H, CH_2), 0.98–0.94 (m, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.6, 168.7, 153.2, 137.0, 133.0, 130.5, 128.2, 38.8, 29.9, 21.9, 13.3. IR (KBr, cm^{-1}): 3148, 2903, 1629, 1521, 1548, 1427, 1359, 1218, 1061.

5-(1-Butylsulfanyl)-4-(2,2-dimethylpropan-1-oyl)-1,2,3-thiadiazole (3dn). Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01 (t, *J* = 7.2 Hz, 2H, SCH_2), 1.84–1.79 (m, 2H, CH_2); 1.57–1.45 (m, 11H, 1 × CH_2 and 3 × CH_3), 0.97 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.9, 168.0, 151.9, 44.8, 38.8, 30.0, 26.8, 21.9, 13.4. IR (KBr, cm^{-1}): 2931, 1641, 1447, 1389, 1239, 1087.

4-Benzoyl-5-(1-pentylsulfanyl)-1,2,3-thiadiazole (3ea). White solid; mp 65–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, *J* = 7.2 Hz, 2H, ArH), 7.63–7.49 (m, 3H, ArH), 3.06 (t, *J* = 7.2 Hz, 2H, SCH_2), 1.91–1.81 (m, 2H, CH_2), 1.55–1.32 (m, 4H, 2 × CH_2), 0.93 (t, *J* = 7.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.7, 168.7, 153.3, 137.1, 133.1, 130.5, 128.2, 39.1, 30.8, 27.7, 22.0, 13.8. IR (KBr, cm^{-1}): 2921, 1632, 1449, 1397, 1237, 1031.

5-Allylsulfanyl-4-benzoyl-1,2,3-thiadiazole (3fa). Yellow solid; mp 52–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, *J* = 7.2, 2H, ArH), 7.61–7.47 (m, 3H, ArH), 5.95–5.86 (m, 1H, CH), 5.48 (d, *J* = 16.2 Hz, 1H, CH), 5.36 (d, *J* = 10.2 Hz, 1H, CH), 3.70 (d, *J* = 6.3 Hz, 2H, SCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.7, 166.9, 153.8, 136.9, 133.1, 130.5, 129.8, 128.2, 121.5, 41.0. IR (KBr, cm^{-1}): 3122, 3089, 3010, 2929, 2903, 1625, 1516, 1408, 1361, 1229, 1069, 1048, 827.

5-Allylsulfanyl-4-(4-methylbenzoyl)-1,2,3-thiadiazole (3fb). Yellow solid; mp 70–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.1 Hz, 2H ArH), 7.24 (d, *J* = 8.1 Hz, 2H, ArH), 5.89–5.78 (m, 1H, CH), 5.42 (d, *J* = 16.8 Hz, 1H, CH), 5.30 (d, *J* = 10.2 Hz, 1H, CH), 3.64 (d, *J* = 6.6 Hz, 2H, SCH_2), 2.36 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.3, 166.6, 154.0, 144.1, 134.4, 130.8, 129.9, 129.0, 121.5, 41.05, 21.7. IR (KBr, cm^{-1}): 3118, 3059, 3015, 2929, 2903, 1624, 1536, 1429, 1345, 1241, 1061, 1002, 865. Elemental analysis for $C_{13}H_{12}N_2OS_2$: calc. C, 56.49; H, 4.38; N, 10.14%. Found: C, 56.28; H, 4.91; N, 9.83.

5-Allylsulfanyl-4-(4-methoxybenzoyl)-1,2,3-thiadiazole (3fd). White solid; mp 78–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (d, *J* = 9.0 Hz, 2H, ArH), 7.00 (d, *J* = 9.0 Hz, 2H, ArH), 5.97–5.86 (m, 1H, CH), 5.50 (d, *J* = 16.5 Hz, 1H, CH), 5.38 (d, *J* = 10.2 Hz, 1H, CH), 3.90 (s, 3H, OCH_3), 3.72 (d, *J* = 6.6 Hz, 2H, SCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.0, 166.3, 163.7, 133.2, 130.0, 129.7, 121.5, 113.6, 84.3, 55.5, 41.0. IR (KBr, cm^{-1}): 3029, 3073, 2919, 2901, 1624, 1515, 1409, 1335, 1215, 1089.

5-Allylsulfanyl-4-(1-naphthoyl)-1,2,3-thiadiazole (3fg). Yellow solid; mp 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 5.7 Hz, 1H, ArH), 8.03–7.88 (m, 3H, ArH), 7.57–7.51 (m, 3H, ArH), 5.98–5.89 (m, 1H, CH), 5.51 (d, *J* = 17.1 Hz, 1H, CH_2), 5.39 (d, *J* = 10.2 Hz, 1H, CH_2), 3.73 (d, *J* = 6.3 Hz, 2H, SCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.6, 166.6, 154.9, 135.1, 133.7,

132.4, 130.7, 129.7, 128.4, 127.5, 126.3, 125.3, 124.2, 121.6, 41.1. IR (KBr, cm^{-1}): 3125, 3079, 3010, 2956, 2905, 1631, 1606, 1516, 1419, 1349, 1237, 1081, 1001. Elemental analysis for $C_{16}H_{12}N_2OS_2$: calc. C, 61.51; H 3.87; N 8.97%. Found: C, 61.68; H, 4.24; N, 8.64%.

5-Allylsulfanyl-4-(2-furoyl)-1,2,3-thiadiazole (3fe). White solid; mp 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, J = 3.6 Hz, 1H, ArH), 7.74 (s, 1H, ArH), 6.61 (d, J = 1.5 Hz, 1H, ArH), 5.95–5.82 (m, 1H, CH), 5.47 (d, J = 16.8 Hz, 1H, CH_2), 5.35 (d, J = 9.9 Hz, 1H, CH_2), 3.69 (d, J = 6.3 Hz, 2H, SCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 166.0, 152.3, 151.0, 148.0, 129.8, 122.9, 121.5, 112.5, 40.9. IR (KBr, cm^{-1}): 3126, 3074, 3015, 2958, 2903, 1623, 1507, 1407, 1356, 1235, 1071, 1053. HRMS (ESI) m/z calcd for $C_{10}H_8N_2O_2S_2$ [M + H^+], 253.0100; Found 253.0108. Elemental analysis for $C_{10}H_8N_2O_2S_2$: calc. C, 47.60; H, 3.20; N, 11.10%. Found: C, 47.51; H, 3.16; N, 11.40%.

5-Allylsulfanyl-4-(2-thienoyl)-1,2,3-thiadiazole (3ff). White solid; mp 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, J = 3.6 Hz, 1H, ArH), 7.79 (d, J = 4.5 Hz, 1H, ArH), 7.28–7.22 (m, 1H, ArH), 6.00–5.87 (m, 1H, CH), 5.52 (d, J = 16.8 Hz, 1H, CH_2), 5.40 (d, J = 9.9 Hz, 1H, CH_2), 3.74 (d, J = 6.9 Hz, 2H, SCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 166.2, 152.8, 142.1, 136.0, 135.5, 129.8, 128.2, 121.5, 40.9. IR (KBr, cm^{-1}): 3121, 3084, 3005, 2948, 2913, 1604, 1503, 1418, 1352, 1231, 1072, 1031. Elemental analysis for $C_{10}H_8N_2OS_3$: calc. C, 44.75; H, 3.00; N, 10.44%. Found: C, 45.13; H, 3.39; N, 10.07%.

5-Allylsulfanyl-4-(2-methyl-propan-1-oyl)-1,2,3-thiadiazole (3fo). Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49–6.42 (m, 1H, =CH), 6.32–6.17 (m, 2H, CH_2), 3.99–3.91 (m, 1H, CH), 1.94 (d, J = 6.9 Hz, 2H, SCH_2), 1.30 (d, J = 6.6 Hz, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.9, 166.8, 151.6, 141.2, 120.6, 38.5, 38.4, 18.5. IR (KBr, cm^{-1}): 3061, 2927, 1639, 1586, 1382, 1221, 1078.

4-Benzoyl-5-benzylsulfanyl-1,2,3-thiadiazole (3ga). White solid; mp 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 7.2 Hz, 2H, ArH), 7.57 (d, J = 7.2 Hz, 1H, ArH), 7.51–7.41 (m, 4H, ArH), 7.33 (d, J = 6.6 Hz, 3H, ArH), 4.24 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.5, 167.0, 153.4, 136.8, 133.6, 133.1, 130.5, 129.0, 128.9, 128.4, 128.2, 42.7. IR (KBr, cm^{-1}): 3148, 2903, 1629, 1521, 1548, 1427, 1359, 1218, 1061.

5-Benzylsulfanyl-4-(2-naphthoyl)-1,2,3-thiadiazole (3gp). Yellow solid; mp 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, J = 3.6 Hz, 1H, ArH), 7.78 (d, J = 4.8 Hz, 1H, ArH), 7.48–7.37 (m, 9H, ArH), 7.28–7.22 (m, 1H, ArH), 4.29 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.8, 176.8, 166.3, 166.1, 156.2, 152.5, 146.9, 142.1, 136.0, 135.5, 133.6, 133.4, 129.3, 129.1, 128.9, 128.4, 128.2, 42.7. IR (KBr, cm^{-1}): 3101, 2921, 1631, 1519, 1537, 1461, 1356, 1221, 1058.

5-Benzylsulfanyl-4-(2-thienoyl)-1,2,3-thiadiazole (3gf). Yellow solid; mp 111–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H, ArH), 7.76 (d, J = 4.5 Hz, 1H, ArH), 7.43–7.35 (m, 5H, ArH), 7.21 (s, 1H, ArH), 4.27 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9, 166.3, 152.6, 142.1, 136.1, 135.6, 133.6, 129.1, 129.0, 128.5, 128.3, 42.7. IR (KBr, cm^{-1}): 3121, 2983, 1629, 1507, 1581, 1478, 1362, 1218, 1056.

5-Benzylsulfanyl-4-(2-methyl-propan-1-oyl)-1,2,3-thiadiazole (3go). Yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.33 (m, 5H, ArH), 4.22 (s, 2H, SCH_2), 3.95–3.90 (m, 1H, CH), 1.28 (d, J = 6.9 Hz, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 164.5, 152.7, 133.6, 129.0, 128.9, 128.4, 42.6, 38.5, 18.5. IR (KBr, cm^{-1}.): 3069, 2924, 1633, 1552, 1501, 1465, 1382, 1227, 1039.

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