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A simple and efficient approach for the synthesis of a novel class aliphatic 1,3,4-thiadiazol-2(3H)-one derivatives via intramolecular nucleophilic substitution reaction

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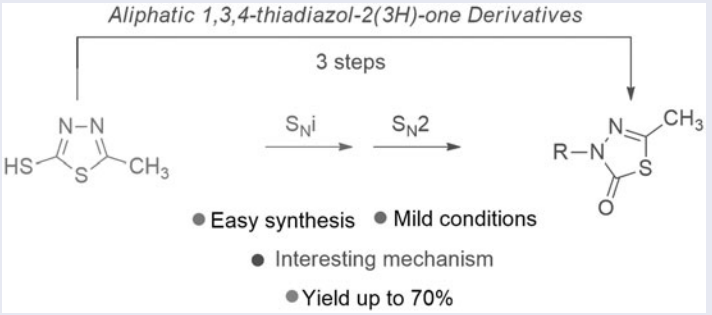
ABSTRACT

In this study, we synthesized a new series of substituted aliphatic 1,3,4-thiadiazol-2(3*H*)-one derivatives (**6-24**) in yields ranging from 42 to 70% with an interesting mechanism that involves internal nucleophilic substitution followed by an S_N2-type nucleophilic substitution. First, 1-(4-chlorophenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethanone (**3**) was synthesized from the reaction of 5-methyl-1,3,4-thiadiazole-2-thiol (**1**) with 2-bromo-1-(4-chlorophenyl)ethanone (**2**) in the presence of potassium hydroxide. Then, 1-(4-chlorophenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethanol (**4**) was synthesized by a reduction reaction of this compound using $NaBH_4$. Finally, 5-methyl-3-alkyl-1,3,4-thiadiazol-2(3*H*)-one derivatives (**6-24**), which are the target compounds, were synthesized from the reaction of this compound (**4**), which is a secondary alcohol with various alkyl halides (**5a-n**) in the presence of sodium hydride (NaH). This study presents an interesting reaction mechanism related to the synthesis of aliphatic 1,3,4-thiadiazol-2(3*H*)-one derivatives that is not recorded in the literature.

GRAPHICAL ABSTRACT



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Introduction

Compounds that contain one or more heteroatoms other than carbon and hydrogen, such as oxygen, nitrogen, or sulfur, and that have the maximum number of conjugated double bonds are referred to as heterocyclic compounds.[1]

Thiadiazole is a five-membered heterocyclic organic compound. Its molecular formula is $C_2H_2N_2S$. Thiadiazoles and their derivatives are commonly used in pharmaceutical chemistry, materials science, and organic syntheses due to their containing both an electron-withdrawing (–S) as well as electron-donating group (–C=N).[2,3] Thiadiazole has four isomers, including 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole.[4] The syntheses of 1,3,4-thiadiazole and its derivatives have become the focus of attention particularly in recent years due to their 2' and 5' positions being quite active against nucleophilic substitution reactions.[5–8]

The two-electron donor nitrogen system (–N=C–S), the sulfur atom, and the hydrogen binding domain in thiadiazole form the part that provides stability and are largely responsible for biological activity.[9–11] 1,3,4-Thiadiazole and its derivatives are commonly used in medicine and pharmacology due to their wide spectrum of biological and pharmaceutical properties, such as antifungal, antibacterial, antimicrobial, antiviral, anticancer, antidepressant, antioxidant, anti-inflammatory, anticonvulsant, antituberculosis, antiproliferative, and antihypertensive activities.[12–25]

Nitrogen and sulfur atoms in 1,3,4-thiadiazole contribute to its thermal properties and play a significant role in conductivity. 1,3,4-Thiadiazole and its derivatives are used for semiconductors and coatings in the polymer industry due to their electrical conductivity.[26,27]

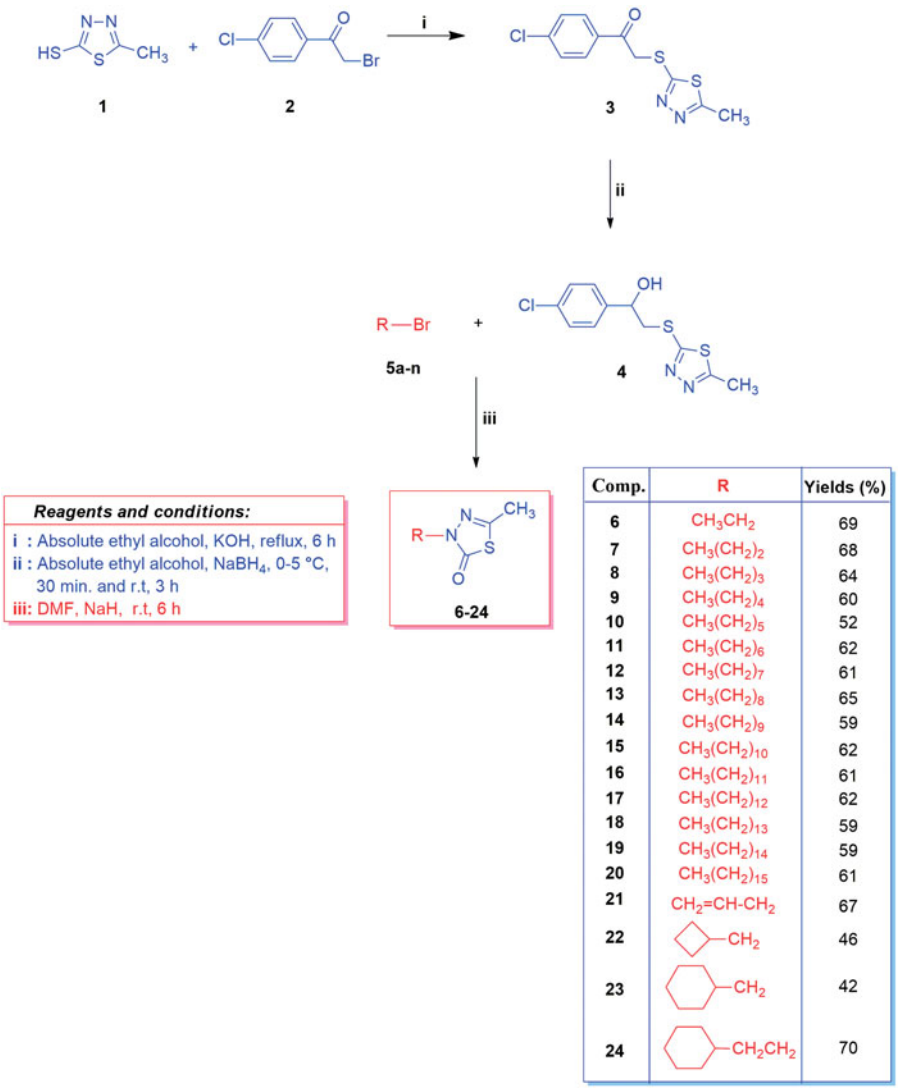
There are various methods in the literature used for the synthesis of 1,3,4-thiadiazole and its derivatives. Some compounds used as the starting compound in the synthesis of 1,3,4-thiadiazole and its derivatives include acylhydrazines, thiohydrazines, 1,3,4-oxadiazoles, and azides.[28–34]

In this study, we synthesized compounds containing a 1,3,4-thiadiazole-2(3*H*)-one nucleus. Only a limited number of studies in the literature involve such compounds. In those studies, aryl-substituted 1,3,4-thiadiazole-2(3*H*)-one compounds were synthesized using traditional methods, all of which featuring phosgene gas ($COCl_2$), which is a highly toxic chemical compound.[35–37] However, to the best of our knowledge, there is no study in the literature involving aliphatic 1,3,4-thiadiazole-2(3*H*)-one derivatives, which we synthesized in this study without using phosgene.

In light of the important data mentioned above, the primary purpose of this study is to synthesize 5-methyl-3-alkyl-1,3,4-thiadiazole-2(3*H*)-one derivatives (**6-24**), which are not found in the literature, using a method that has been used for the first time by our group through an interesting mechanism. The second purpose is to contribute to the literature by introducing compounds with new properties by characterizing these compounds using various analysis methods (^{1}H NMR, ^{13}C NMR, FT-IR, LC-MS, and elemental analysis). The synthetic pathway for the synthesis of target compounds is shown in Scheme 1.

Results and discussion

In the first part of the study, 1-(4-chlorophenyl)-2-((5-methyl-1,3,4-thiadiazole-2-yl)thio)ethanone (**3**) was synthesized (in yield of 87%) from the reaction of 5-methyl-1,3,4-



Comp.	R	Yields (%)
6	CH_3CH_2	69
7	$CH_3(CH_2)_2$	68
8	$CH_3(CH_2)_3$	64
9	$CH_3(CH_2)_4$	60
10	$CH_3(CH_2)_5$	52
11	$CH_3(CH_2)_6$	62
12	$CH_3(CH_2)_7$	61
13	$CH_3(CH_2)_8$	65
14	$CH_3(CH_2)_9$	59
15	$CH_3(CH_2)_{10}$	62
16	$CH_3(CH_2)_{11}$	61
17	$CH_3(CH_2)_{12}$	62
18	$CH_3(CH_2)_{13}$	59
19	$CH_3(CH_2)_{14}$	59
20	$CH_3(CH_2)_{15}$	61
21	CH_2=CH-CH_2	67
22		46
23		42
24		70

Scheme 1. Synthetic pathway for the synthesis of 5-methyl-3-alkyl-1,3,4-thiadiazol-2(3*H*)-one derivatives **(6-24)**.

thiadiazole-2-thiol (**1**) with 2-bromo-1-(4-chlorophenyl)ethanone (**2**) in the presence of potassium hydroxide in absolute ethyl alcohol.

Then, 1-(4-chlorophenyl)-2-((5-methyl-1,3,4-thiadiazole-2-yl)thio)ethanol (**4**) was synthesized (in yield of 86%) as a result of reduction reaction of this compound (**3**) with $NaBH_4$ in absolute ethyl alcohol. The starting materials (compounds **3** and **4**) were prepared in accordance with the existing methods.[38–40]

Finally, 5-methyl-3-alkyl-1,3,4-thiadiazole-2(3*H*)-one derivatives (**6-24**) were obtained from the reaction of this alcohol compound (**4**) with various alkyl halides (**5a-n**) in the presence of sodium hydride (NaH) in DMF, which is a polar aprotic solvent, with moderate-to-good yields (in yields of 42% to 70%). The target compounds and the yields are shown in Figure 1.

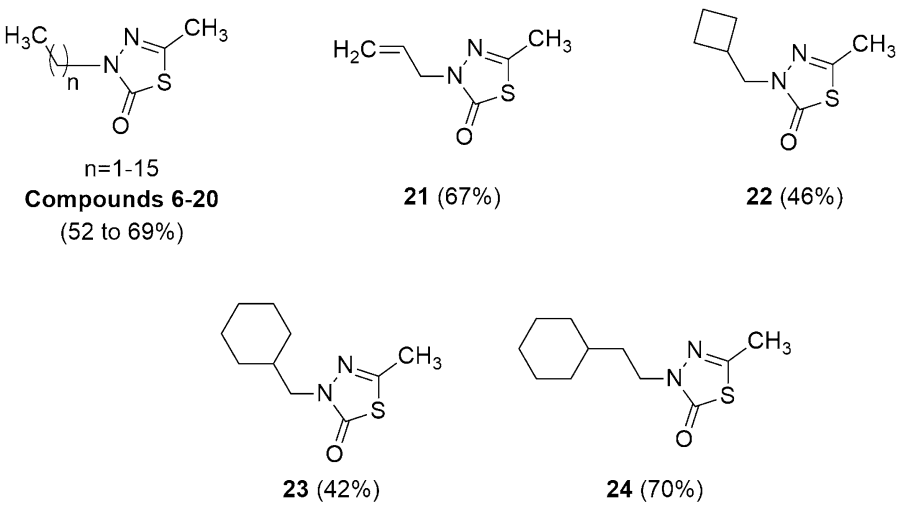


Figure 1. Structures of the target compounds **(6-24)** (yields are given in parentheses).

This reaction works with the formation of the benzyloxy group, which is quite a basic and strong nucleophile, through the deprotonation of the secondary alcohol (compound **4**). Then this benzyloxy group leads to an S_Ni-type intramolecular nucleophilic substitution reaction and forms a spiro intermediate A.

Subsequently intermediate B forms as a result of the S_N2-type nucleophilic substitution of the new nucleophilic center on the nitrogen atom of this spiro intermediate A formed in the intermediate step with alkyl halides (**5a-n**).

Finally, this compound (intermediate B) is converted to 5-methyl-3-alkyl-1,3,4-thiadiazole-2(3*H*)-one derivatives (**6-24**), the target compounds, with hydrolysis during work-up. This reaction involves two intermediate steps and appears to be an interesting mechanism. The suggested reaction mechanism related to the synthesis is shown in Scheme 2.

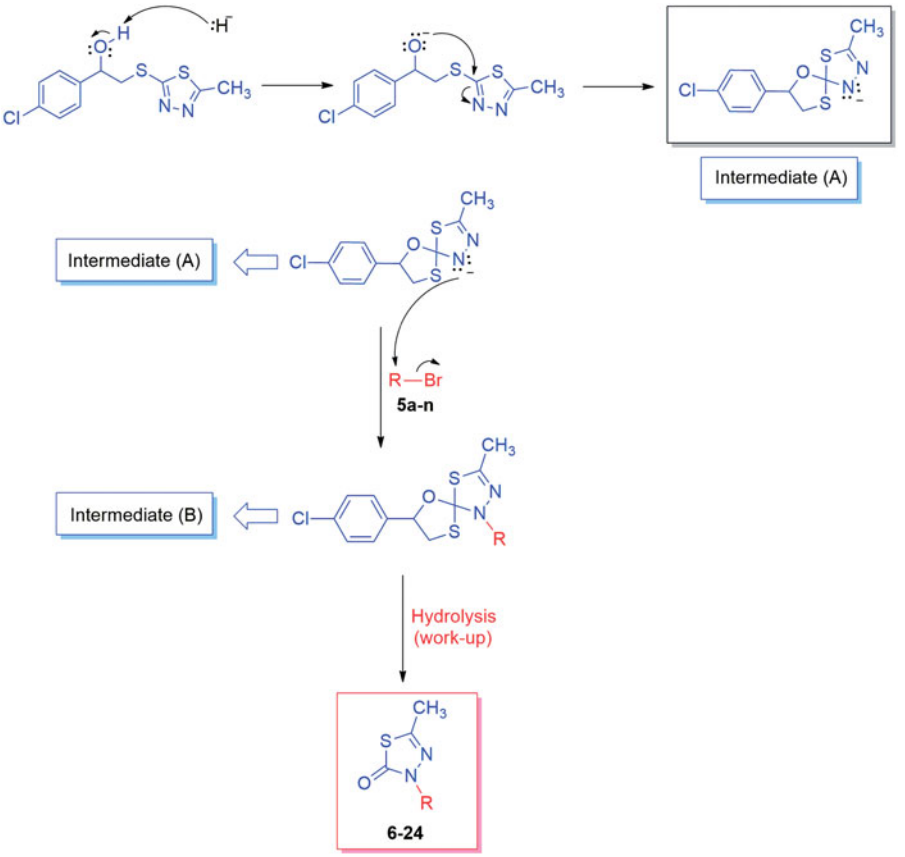
In a similar study previously conducted by our group, benzyl halides and phenacyl bromide derivatives were used instead of alkyl halides in this reaction. Substituted benzyl-5-methyl-1,3,4-thiadiazole-2(3*H*)-one derivatives were obtained through the same mechanism as a result of these reactions.[39] In this study, the secondary alcohol (compound **4**) was react with NaH without any benzyl bromide or phenacyl bromide derivatives in the reaction environment in order to prove that the reaction occurs through the suggested mechanism.

Thus, spiro intermediate A compound formed in the intermediate step and was isolated. The reaction mechanism shown in Scheme 2 was suggested based on this formation.

This study proves that the suggested reaction mechanism occurs in different derivatives (alkyl halides) other than benzyl halides and phenacyl bromide derivatives.

The suggested reaction mechanism shows that the target compounds are determined by the alkyl halides regardless of which alcohol derivative (**4**) with a similar principal structure is used at the beginning; this is shown in Figure 2.

This reaction mechanism involves an interesting reaction whereby exocyclic oxygen had transferred to the thiadiazole ring via two different substitution reactions (S_Ni and



Scheme 2. The reaction mechanism for the formation of the target compounds (**6-24**).

S_N2). The progress of this reaction mechanism, where the S_Ni and S_N2 reactions shown in Scheme 2 occur successively, relies on the alkoxide anion being a strong nucleophile as well as a strong base. This allows for the intramolecular nucleophilic substitution reaction (S_Ni). The suggested reaction mechanism appears to be a novel and interesting method for the synthesis of 5-methyl-3-alkyl-1,3,4-thiadiazole-2(3*H*)-one derivatives (**6-24**).

In this mechanism, first 7-(4-chlorophenyl)-3-methyl-6-oxa-4,9-dithia-1,2-diazaspiro[4.4]non-2-en-1-ide (spiro intermediate A) forms through the S_Ni-type intramolecular nucleophilic substitution reaction of the benzyloxy group. This compound is believed to then turn into the carbonyl group through the S_N2-type nucleophilic substitution reaction of the compound with various alkyl halides, and finally with the hydrolysis of this *N*-alkylated oxathiolane compound (intermediate B).

The 5-methyl-3-alkyl-1,3,4-thiadiazole-2(3*H*)-one derivatives (**6-24**) synthesized in this study are not found in the literature, similar compounds were synthesized with known methods,[35–37] which in turn makes our study unique.

The structures of the target compounds (**6-24**) synthesized in this study were elucidated using the ^{1}H NMR, ^{13}C NMR, FT-IR, elemental analysis, and mass spectroscopy.

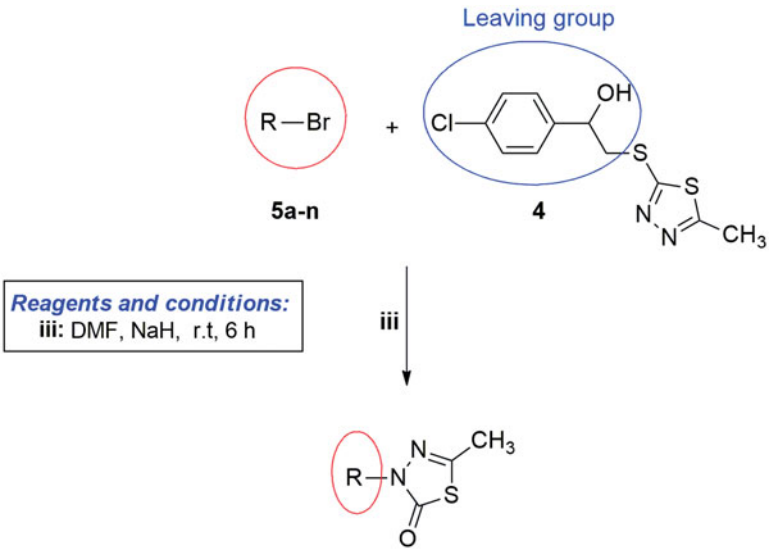


Figure 2. Synthetic route for the formation of the target compounds (**6-24**).

The broad −OH absorption band belonging to compound **4**, which was used as the starting compound, disappeared in the FT-IR spectra of the target compounds (**6-24**). The carbonyl group (C=O) peaks appeared in the 1679–1651 cm^{-1} range, which constitutes strong evidence for the formation of these compounds. Furthermore, aromatic –CH peaks were not observed in the 3100–3050 cm^{-1} range in the target compounds, which in turn supports the suggested structures.

The ^{1}H NMR spectra of the target compounds contained considerable evidence for the formation of these compounds. The AB system observed at 3.69 and 3.35 ppm in the starting compound and the broad singlet peak belonging to OH observed at 4.24 ppm in the starting compound disappeared, and this indicates the formation of the target compounds.

No peak was observed in the domain belonging to the aromatic structures in the 7.5–8.0 ppm range. Instead, peaks belonging to the aliphatic groups were observed in the 1–3 ppm range depending on the compound structure, which is the most significant evidence for the formation of the target compounds. It can be said that the ^{1}H NMR spectra of the target compounds were similar. The main difference was the increased integration value of the protons belonging to the aliphatic $-CH_2$ groups in the 1.39–1.18 ppm range with the elongation of the aliphatic chain.

Detailed data related to the ^{1}H NMR spectra can be found in the experimental section together with the coupling constants, and the relevant spectra are given in the Supporting Information.

The presence of peaks belonging to the carbonyl group carbon observed in the 170.43–169.92 ppm range in the ^{13}C NMR spectra of the target compounds (**6-24**) supports the structures that we suggest. These values are very consistent with the literature.[39,41] The data related to the ^{13}C NMR spectra can be found in the experimental section, while all the spectra are given in the Supporting Information.

The mass spectra belonging to the target compounds were also observed as expected with molecular ion peaks.

Conclusions

In summary, this study presents an interesting mechanism where exocyclic oxygen transferred to the thiadiazole ring via two different substitution reactions. In this study, aliphatic 1,3,4-thiadiazole-2(3*H*)-one derivatives, which were not previously recorded in the literature, were synthesized and characterized using various analysis techniques.

The advantages and novelties of this study include synthesizing aliphatic 1,3,4-thiadiazole-2(3*H*)-one derivatives under mild conditions with simple synthetic procedures, and obtaining them without using phosgene ($COCl_2$).

We further believe that the novel compounds synthesized, and the interesting reaction mechanism suggested in this study, may pave the way for other study groups synthesizing novel heterocyclic compounds.

Experimental section

Materials and methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded on an Agilent NMR VNMRS spectrometer at 400 and 100 MHz, respectively in $CDCl_3$ with tetramethylsilane as internal reference. Chemical shift values are provided in ppm (parts per million) (δ) and the designation of signals were as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. The IR spectra were measured in ATR with a Bruker Optics Alpha FT-IR. A Thermo TSQ Quantum Access Max LC-MS/MS spectrometer was used for the measurement of the mass spectra. It was Truspec Leco Micro CHNS elemental analyzer on which elemental analyses were carried out and the results were within ±0.4% of the theoretical values. A Thermo Scientific IA9000 series apparatus was utilized for recording the melting points (uncorrected). Thin layer chromatography (TLC) was carried out on the glass backed silica-gel sheets (Silica Gel 60 F_{254} Aluminum TLC plate) and imaged in UV light (254 nm and 365 nm). Silica gel (70–230 mesh ASTM) eluting with chloroform was used to carry out column chromatography.

General procedure for the synthesis of 5-methyl-3-alkyl-1,3,4-thiadiazol-2(3H)-one derivatives (6-24)

The compound **(4)** (3.48 mmol) was dissolved in DMF (about 5 mL) in a round-bottomed flask. NaH (60% mineral oil dispersion, 5.23 mmol; 0.2092 g) was added in small fractions. The alkyl halides **(5a-n)** (3.48 mmol) were dissolved in DMF (about 3 mL) and added drop by drop into this solution. For a period of about 6 h, the reaction mixture was stirred at room temperature. TLC was used to observe the progress of the reaction at appropriate time intervals. After the reaction was ended, the excess sodium hydride was decomposed with methyl alcohol (5 mL), and then the solvent was evaporated with rotary evaporator. The residue of the crude was suspended in brine and extracted with chloroform (×3). The organic portion was dried over anhydrous sodium

sulfate, filtered, and then evaporated by using rotary evaporator. The crude residue was purified using column chromatography on a silica-gel column with chloroform as the eluent to obtain target compounds **(6-24)**. The pure matter was dried with phosphorus pentoxide in a vacuum oven.

Selected characterization data

3-Ethyl-5-methyl-1,3,4-thiadiazol-2(3H)-one (6)s

Yellowish oil, yield: 0.348 g (69%), R_f = 0.60 ($CHCl_3$). IR (ATR, cm^{-1}): 2929 (Aliph. CH), 1667 (C=O), 1563 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.28 (t, J = 8.0 Hz, 3H, $-CH_3$), 2.34 (s, 3H, $-CH_3$), 3.86 (q, J = 8.0 Hz, 2H, $-CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 13.8 ($-CH_3$), 18.0 ($-CH_3$), 42.0 ($-CH_2$), 148.15 (Thiadiazole-C), 169.9 (C=O). MS: *m/z* 144.86 (M^+, 100). Anal. Calcd. for $C_5H_8N_2OS$: C, 41.65; H, 5.59; N, 19.43. Found: C, 41.54; H, 5.49; N, 19.38.

5-Methyl-3-propyl-1,3,4-thiadiazol-2(3H)-one (7)

Light oil, yield: 0.376 g (68%), R_f = 0.61 ($CHCl_3$). IR (ATR, cm^{-1}): 2941 (Aliph. CH), 1670 (C=O), 1563 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.89 (t, J = 8.0 Hz, 3H, $-CH_3$), 1.73–1.71 (m, 2H, $-CH_2$), 2.34 (s, 3H, $-CH_3$), 3.76 (t, J = 8.0 Hz, 2H, $-CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 10.9 ($-CH_3$), 18.0 ($-CH_3$), 21.9 ($-CH_2$), 48.5 ($-CH_2$), 147.9 (Thiadiazole-C), 170.2 (C=O). MS: *m/z* 158.79 (M^+, 100). Anal. Calcd. for $C_6H_{10}N_2OS$: C, 45.55; H, 6.37; N, 17.71. Found: C, 45.50; H, 6.45; N, 17.59.

3-Butyl-5-methyl-1,3,4-thiadiazol-2(3H)-one (8)

Light oil, yield: 0.386 g (64%), R_f = 0.62 ($CHCl_3$). IR (ATR, cm^{-1}): 2943 (Aliph. CH), 1670 (C=O), 1562 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (t, J = 4.0 Hz, 3H, $-CH_3$), 1.34–1.32 (m, 2H, $-CH_2$), 1.72–1.68 (m, 2H, $-CH_2$), 2.36 (s, 3H, -CH_3), 3.82 (t, J = 4.0 Hz, 2H, $-CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 13.5 ($-CH_3$), 18.0 ($-CH_3$), 19.6 ($-CH_2$), 30.6 ($-CH_2$), 46.7 ($-CH_2$), 147.9 (Thiadiazole-C), 170.1 (C=O). MS: *m/z* 172.93 (M^+, 100). Anal. Calcd. for $C_7H_{12}N_2OS$: C, 48.81; H, 7.02; N, 16.26. Found: C, 48.76; H, 6.91; N, 16.34.

5-Methyl-3-pentyl-1,3,4-thiadiazol-2(3H)-one (9)

Light oil, yield: 0.39 g (60%), R_f = 0.64 ($CHCl_3$). IR (ATR, cm^{-1}): 2936 (Aliph. CH), 1673 (C=O), 1563 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (t, J = 8.0 Hz, 3H, $-CH_3$), 1.37–1.30 (m, 4H, $-CH_2$), 1.72–1.68 (m, 2H, $-CH_2$), 2.37 (s, 3H, $-CH_3$), 3.81 (t, J = 4.0 Hz, 2H, $-CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 13.8 ($-CH_3$), 18.0 ($-CH_3$), 22.1 ($-CH_2$), 28.3 ($-CH_2$), 28.5 ($-CH_2$), 47.0 ($-CH_2$), 147.9 (Thiadiazole-C), 170.1 (C=O). MS: *m/z* 187.00 (M + 1100). Anal. Calcd. for $C_8H_{14}N_2OS$: C, 51.58; H, 7.58; N, 15.04. Found: C, 51.45; H, 7.65; N, 15.00.

3-Hexyl-5-methyl-1,3,4-thiadiazol-2(3H)-one (10)

Light oil, yield: 0.367 g (52%), R_f = 0.67 ($CHCl_3$). IR (ATR, cm^{-1}): 2931 (Aliph. CH), 1674 (C=O), 1563 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.85 (t, J = 4.0 Hz, 3H, $-CH_3$), 1.28–1.25 (m, 6H, $-CH_2$), 1.72–1.68 (m, 2H, $-CH_2$), 2.36 (s, 3H, $-CH_3$), 3.80 (t, J = 8.0 Hz, 2H, $-CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 13.9 ($-CH_3$), 18.0 ($-CH_3$), 22.4 ($-CH_2$), 26.1 ($-CH_2$), 28.5 ($-CH_2$), 31.2 ($-CH_2$), 47.0 ($-CH_2$), 147.9 (Thiadiazole-C), 170.1 (C=O). MS: m/z 200.98 (M^+, 100). Anal. Calcd. for $C_9H_{16}N_2OS$: C, 53.97; H, 8.05; N, 13.99. Found: C, 53.89; H, 7.98; N, 13.87.

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