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Synthesis of 1,3,4-thiadiazol-2(3*H*)-one derivatives via an unexpected intramolecular addition-elimination reaction of 1,3,4-thiadiazoles

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ABSTRACT

A new synthesis was developed for 1,3,4-thiadiazol-2(3*H*)-one derivatives, based on a new arrangement on the thiadiazole ring with an intramolecular addition-elimination reaction.

To this end, starting from 5-methyl-1,3,4-thiadiazole-2-thiol **(1)**, derivatives of 3-((un)substituted benzyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one **(7a-g)** and ((un)substituted phenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one **(10–15)** were synthesized (in yields of 81–88% and 63–71%, respectively). The structures of all synthesized compounds were characterized using IR, ^{1}H NMR, and ^{13}C NMR spectroscopy, and elemental analysis, mass spectroscopy and X-ray diffraction analysis (compounds **3c**, **7b-f** and **10**) techniques.

This study presents a new and effective reaction path for the synthesis of 1,3,4-thiadiazol-2(3*H*)-one derivatives.

1. Introduction

Heterocyclic molecules are widespread in nature and used in many fields. Among these molecules, thiadiazoles which have a significant place among 5-member heterorings containing nitrogen and sulfur are widely used in pharmaceutical chemistry, material science, and organic syntheses.[1,2]

1,3,4-Thiadiazole and its derivatives in particular represent a ring which has a broad spectrum of biological activities such as antimicrobial,[3] antifungal,[4] antibacterial,[5] analgesic,[6] anticonvulsant,[7] antioxidant,[8] anti-inflammatory,[9] anticancer,[10] antidepressant,[11] antihypertensive,[12] and antiviral[13] activities. Furthermore, 1,3,4-thiadiazole derivatives are widely used in many fields of agriculture and technology as pesticides, herbicides, fungicides, insecticides, and bactericides.[14,15] Such compounds have various optical and electrochemical applications due to their thermal and chemical stability.[16–18] In this study, (substituted benzyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one derivatives were synthesized. Very few compounds containing the 1,3,4-thiadiazole-2(3*H*)-one nucleus which we synthesized in the current study can be found in the literature.

In those literature studies, structures containing the 1,3,4-thiadiazole-2(3*H*)-one nucleus were synthesized by traditional methods but in low yields.[19] It was reported that such substances inhibit the Protoporphyrinogene oxidase (PPO) enzyme, especially in humans, and cause cancer cells to die and therefore are used in cancer treatment.[20–22] PPO enzymes are also used for haemoglobin and chlorophyll synthesis.[23] Mitochondrial PPO inhibitors inhibit mitochondrial Protoporphyrin IX (PPIX). As a result of this inhibition, the amount of PPIX in the mitochondria increases, PPIX enters the cytoplasm by diffusion and is oxidized. Thus, PPIX causes the circulation in veins from which tumour cells feed to slow down and eventually tumour cells shrink and die.[24,25]

There are various methods used for the synthesis of 1,3,4-thiadiazoles. Azides, hydrazines, diacyl hydrazines and thiosemicarbazides are the key compounds used in the synthesis of 1,3,4-thiadiazole and derivatives.[26–31]

In the present study, starting from 5-methyl-1,3,4-thiadiazole-2-thiol **(1)**, derivatives of 3-((un)substituted benzyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one **(7a-g)** and ((un)substituted phenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one **(10–15)** were unexpectedly obtained by a method not available in the literature. This unexpected result reveals a novel method for the synthesis of

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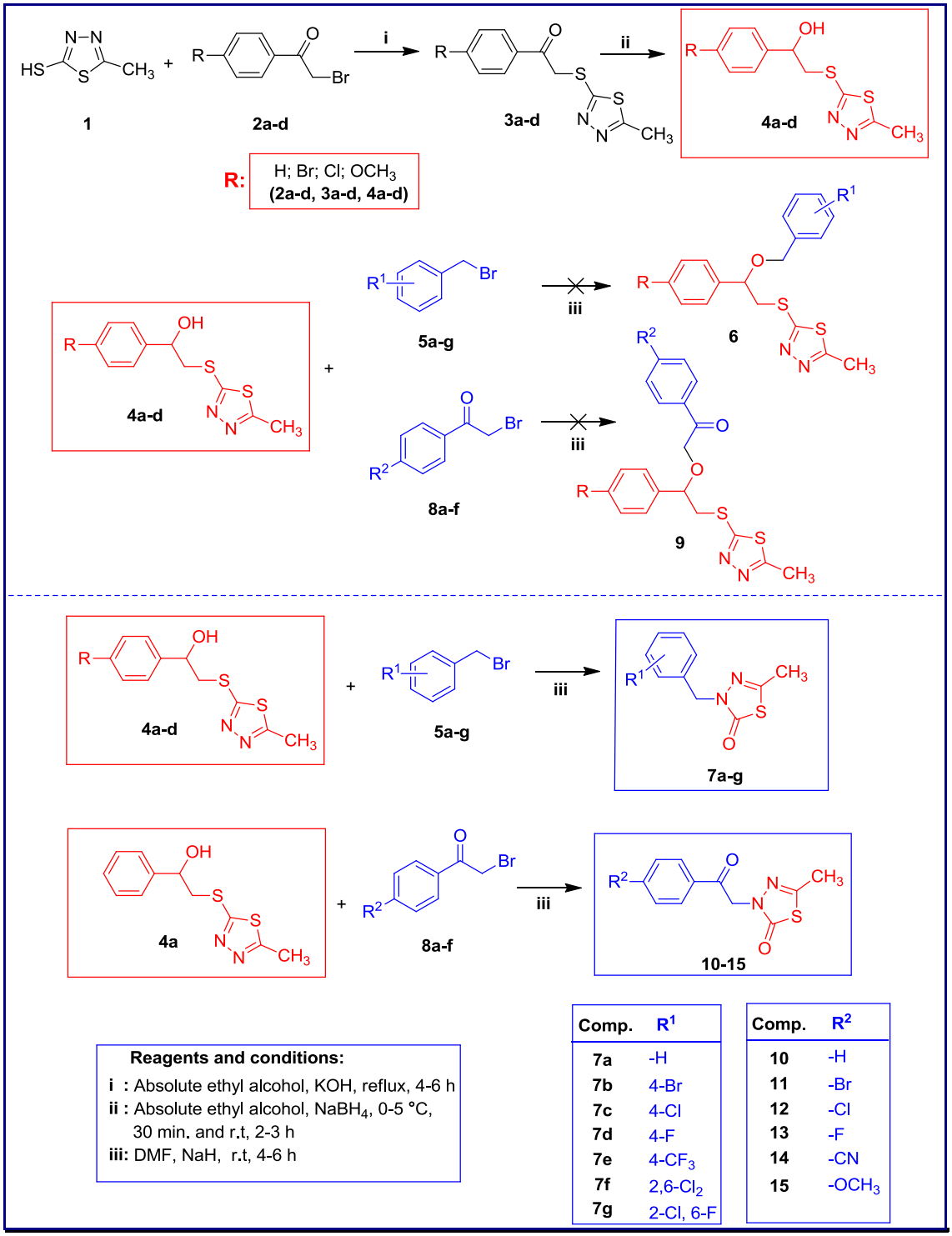
compounds containing the 1,3,4-thiadiazol-2(3*H*)-one nucleus (Scheme 1).

2. Results and discussion

In the first part of the study, 1-(substituted phenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethanone derivatives **(3a-d)** were obtained (in yields of 81–88%) from the reaction of 5-methyl-1,3,4-thiadiazole-2-thiol **(1)** with phenacyl bromide derivatives **(2a-d)** in presence of KOH in absolute ethyl alcohol. Compounds **3a-d** have been reported previously.[32,33]

Then, 1-(substituted phenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethanol derivatives **(4a-d)**, which are alcohol derivatives, were synthesized (in yields of 82–91%) by reduction of compounds



Scheme 1. Synthetic route for the synthesis of ((un)substituted benzyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one derivatives **(7a-g)** and ((un)substituted phenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one derivatives **(10–15)**.

3a-d with $NaBH_4$ in absolute ethyl alcohol.

Our next goal was to synthesize ether derivatives (compound **6**) by the reaction of these alcohol derivatives **(4a-d)** with various benzyl halides **(5a-g)** in the presence of NaH in DMF.

However, spectroscopic analyses of the synthesized compounds showed that, contrary to expectations, 3-((un)substituted benzyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one **(7a-g)** compounds were obtained (in yields of 71–82%) by a different mechanism. The resulting compounds and yields are shown in Fig. 1.

The reaction is believed to proceed starting from the formation of the benzyloxy group, which is a quite basic and strong nucleophile, through the deprotonation of secondary alcohol in compounds **4a-d** and then via the formation of a spiro compound following an S_Ni-type intramolecular nucleophilic substitution. In the next step, an S_N2-type nucleophilic substitution reaction between the new nucleophilic center formed on nitrogen in the spiro compound and benzyl bromide derivatives **(5a-g)** occurs and finally 3-((un)substituted benzyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one derivatives **(7a-g)** are obtained after the hydrolysis during work-up. The suggested reaction mechanism is shown in Scheme 2.

In an effort to prove the suggested reaction mechanism, 1-(4-methoxyphenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethanol **(4d)** was reacted with NaH in the absence of benzyl bromide derivatives **(5a-g)**. The resulting compound formed at the intermediate step was successfully isolated.

Another evidence that the reactions proceed through this proposed mechanism may be drawn from the following example: we obtained only compound **7a** by the reaction of alcohol derivatives **(4a-d)** with benzyl bromide **(5a)**. Thus, no matter which alcohol derivative is used, the result is determined by the benzyl halide derivatives used.

Furthermore, reactions of 2-((5-methyl-1,3,4-thiadiazol-2-yl) thio)-1-phenylethanol **(4a)** with phenacyl bromide derivatives **(8a-f)** were also carried out to show that the suggested reaction is possible with other compounds as well and reveal the functionality of the method.

As a result of these reactions, ((un)substituted phenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)-one derivatives **(10-15)** were synthesized (in yields of 63–71%) via a similar mechanism. The resulting compounds and yields are shown in Fig. 2.

In conclusion, it is believed that this reaction occurs through S_Ni-type intramolecular nucleophilic substitution of the benzyloxy group and involves a 7-substitued phenyl-3-methyl-6-oxa-4,9-dithia-1,2-diazaspiro[4.4]non-2-ene-1-ide type spiro intermediate step. In the second step, a nucleophilic substitution reaction occurs between the nitrogen atom of thiadiazolene in the spiro compound and benzyl bromide **(5a-g)** and/or phenacyl bromide **(8a-f)** derivatives. Finally, the resulting *N*-benzylated oxathiolan compound undergoes hydrolysis to the carbonyl group on work-up.

This mechanism is a new method for the synthesis of 5-methyl-1,3,4-thiadiazol-2(3*H*)-one derivatives **(7a-g** and **10–15)** with the formation of *N*-benzylated oxathiolan through two different substitutions (S_Ni and S_N2).

Structures of **7a-g** compounds were identified with IR, ^1H NMR, and ^{13}C NMR spectroscopy, elemental analysis, mass spectroscopy and X-ray diffraction analysis **(7b-f)** techniques. Disappearance of –OH absorption peaks observed in the 3340-3269 cm^{-1} range of alcohol derivatives **(4a-d)**, and emergence of carbonyl group (C=O) peaks observed in the 1679-1652 cm^{-1} range are important indicators for the formation of 5-methyl-1,3,4-thiadiazol-2(3*H*)-one derivatives **(7a-g)**.

We did not observe two different methylene ($-OCH_2$ and $-SCH_2$) and aromatic proton peaks, which are expected for ether derivatives (compound **6**), in the ^1H NMR spectra of **7a-g** compounds. Instead, we observed methylene peaks corresponding to two protons and proton peaks belonging to only a single aromatic ring in the 5.26–4.95 ppm range, which supports the structure that we suggest. Furthermore, the presence of carbonyl group peaks observed in the 170.32–169.36 ppm range in the ^{13}C NMR spectra of these compounds **(7a-g)** clearly supports the structure. Mass and elemental analysis results specified in the experimental section clearly indicates the structures that we suggest.

The fact that two different sharp carbonyl absorption bands were observed in the 1712-1691 and 1663-1646 cm^{-1} range in the IR spectra of compounds **10–15** clearly supports the suggested

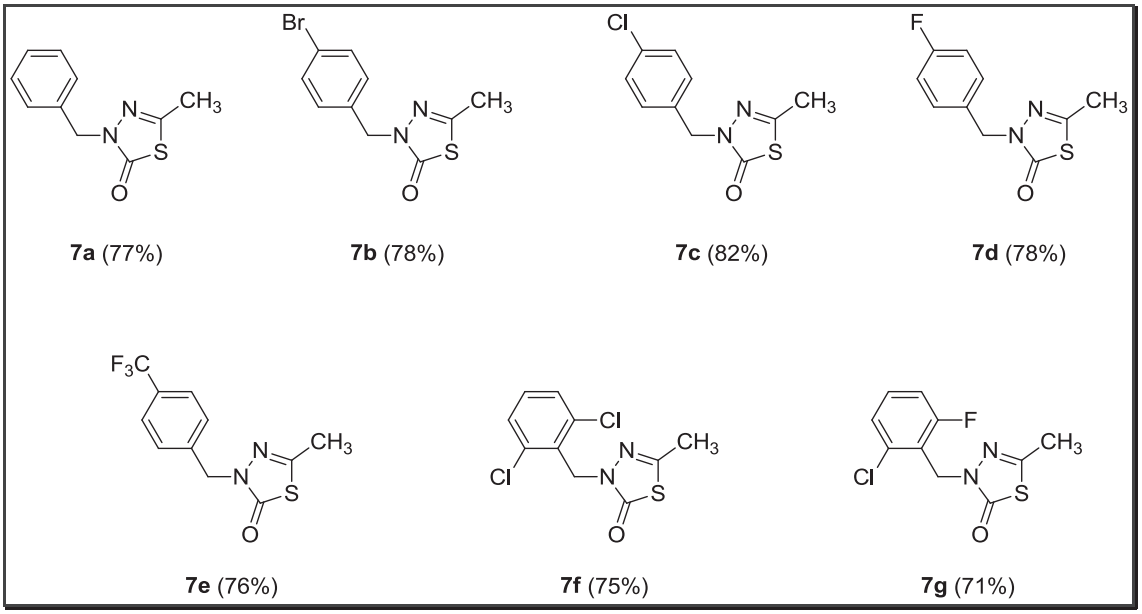
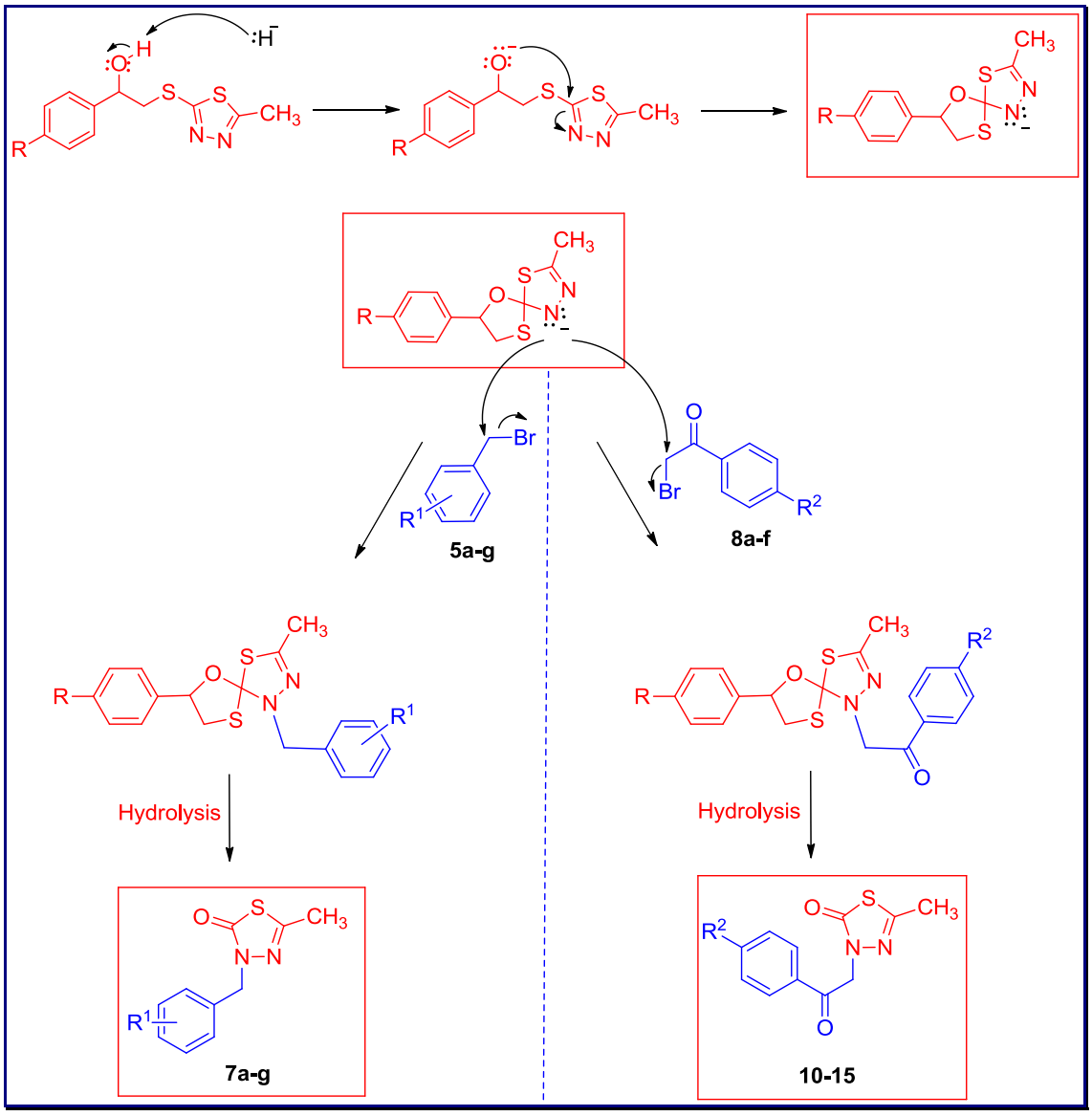


Fig. 1. Structures of the compounds **7a-g** (yields are given in the parentheses).



Scheme 2. A plausible mechanism for the formation of compounds (**7a-g**) and (**10**–**15**).

structures.

Also, two different carbonyl carbon peaks were observed in the ^{13}C NMR spectra of these compounds (**10**–**15**). One of the peaks is the amide carbonyl in the 170.93–170.46 ppm range. The other belongs to the ketone carbonyl in the 192.78–189.64 ppm range.

In ^{13}C NMR spectra of fluorine containing compounds **7d**, **7e**, **7g** and **13**, splittings were observed due to quite distinct C-F couplings. In coupling constants, it was observed that especially the coupling in the ^{1}J CF position was severe and splittings occurred corresponding to approximately 246–271 Hz range. C-F coupling constants for these compounds are given in the Experimental section. The spectra of all compounds are given in the Supplementary Material section.

Finally, the structures of compounds **3c**, **7b-f** and **10** were also confirmed by X-ray diffraction analysis. The crystal structures and crystallographic data of compounds **3c**, **7b-f** and **10** are given in the Supplementary Material Section. All trials and all spectroscopic data support the suggested mechanism and structure.

3. Conclusions

In conclusion, this study exhibits a new and effective method to synthesize compounds containing the 1,3,4-thiadiazol-2(3*H*)-one nucleus. Not only does this novel method take less time to perform, but it also costs less and allows the synthesis of the aforementioned compounds in higher yields. Most importantly, our method is not an alternative to other methods available in the literature, but a new method for synthesis, which is its most significant advantage.

4. Experimental section

4.1. General information

The ^{1}H NMR and ^{13}C NMR spectra of the compounds were measured in $CDCl_3$ using an Agilent NMR VNMRS spectrometer at 400 MHz and 100 MHz, respectively. Chemical shift values are given in ppm (parts per million) (δ) with tetramethylsilane (TMS) as internal standard. The peak patterns are indicated as follows: s,

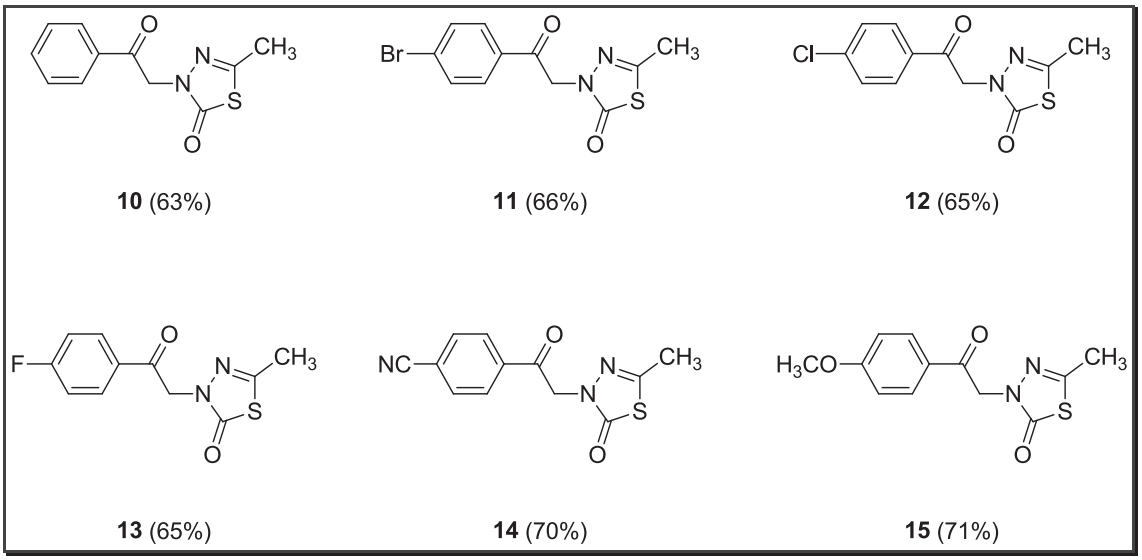


Fig. 2. Structures of the compounds **10**–**15** (yields are given in the parentheses).

singlet; bs, broad singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets. The coupling constants (*J*) are given in Hertz (Hz). The IR spectra were recorded in a Bruker Optics Alpha FT-IR in ATR. The mass spectra were measured with a Thermo TSQ Quantum Access Max LC-MS/MS spectrometer. Elemental analyses were performed on a Truspec Leco Micro CHNS elemental analyzer and the results were within ±0.4% of the theoretical values. Melting points were recorded on a Thermo Scientific IA9000 series apparatus and were uncorrected. For thin layer chromatography, 60 F_{254} Aluminum TLC plate were used. Column chromatography was performed using silica gel (70–230 mesh ASTM). All the chemicals, reagents and solvents were directly purchased from Sigma-Aldrich (St. Louis, MO) and were used without further purification, unless mentioned specifically.

*4.2. General procedure for the synthesis of 1-((un)substituted phenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethanone derivatives **(3a-d)***

In a two-necked flask, 5-methyl-1,3,4-thiadiazole-2-thiol **(1)** (0.06 mol; 7.93 g) and KOH (0.06 mol; 0.336 g) were dissolved in absolute ethanol (100 mL) and the solution was stirred for 30 min at room temperature. Phenacyl bromide derivative **(2a-d)** (0.06 mol) was dissolved in absolute ethanol (50 mL) and added dropwise to this solution at room temperature with the assistance of a dropping funnel. The mixture was then refluxed and stirred for 4–6 h. The progress of the reaction was monitored by TLC at appropriate time intervals. After completion of the reaction, the solution was filtered and recrystallized from the ethanol. The synthesized compounds were dried with P_2O_5 in a vacuum oven.

*4.2.1. 2-((5-Methyl-1,3,4-thiadiazol-2-yl)thio)-1-phenylethanone **(3a)***[32]

Yield: 13.21 g (88%), m.p. 86–87 °C (from EtOH). (lit[32] m.p. 83–85 °C).

*4.2.2. 1-(4-Bromophenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio) ethanone **(3b)***[33]

Yield: 16.79 g (85%), m.p. 111–113 °C (from EtOH) (lit[33] m.p. 106–109 °C).

*4.2.3. 1-(4-Chlorophenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio) ethanone **(3c)***[33]

Yield: 14.52 g (85%), m.p. 115–116 °C (from EtOH) (lit[33] m.p. 112–115 °C).

*4.2.4. 1-(4-Methoxyphenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl) thio)ethanone **(3d)***[33]

Yield: 13.63 g (81%), m.p. 105–106 °C (from EtOH) (lit[33] m.p. 106–108 °C).

*4.3. General procedure for the synthesis of 1-((un)substituted phenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)ethanol derivatives **(4a-d)***

In a two-necked flask, ketone derivatives **(3a-d)** (0.03 mol) were dissolved in absolute ethanol (100 mL) and cooled to 0–5 °C. Sodium borohydride ($NaBH_4$) (0.06 mol,; 2.27 g) was dissolved in absolute ethanol (20 mL) and added dropwise to this solution with the assistance of a dropping funnel. The mixture was stirred for 30 min at 0–5 °C. Then, the mixture was stirred for 2–3 h at room temperature. The progress of the reaction was monitored by TLC at appropriate time intervals. At the end of this period, the solvent was removed under reduced pressure. The crude residue was suspended in water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, filtered and then evaporated to dryness. The solid was recrystallized from the benzene/petroleum ether (2:1). The synthesized compounds were dried with P_2O_5 in a vacuum oven.

*4.3.1. 2-((5-Methyl-1,3,4-thiadiazol-2-yl)thio)-1-phenylethanol **(4a)***

Light yellow oil, yield: 6.89 g (91%). IR (ATR, cm^{-1}): 3274 (OH), 3066 (Ar–CH), 2922 (Aliph. CH), 1608 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.67 (s, 3H, $-CH_3$), 3.44 (dd, $J = 7.6$ Hz, $J = 7.2$ Hz, 1H, $-CH_2$ (A)), 3.67 (dd, $J = 7.6$ Hz, $J = 7.2$ Hz, 1H, $-CH_2$ (B)), 4.41 (d, $J = 2.0$ Hz, 1H, OH), 5.09 (t, $J = 4.0$ Hz, 1H, –CH–), 7.26 (t, $J = 6.4$ Hz, 1H), 7.32 (t, $J = 7.2$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 15.6 ($-CH_3$), 42.7 ($-CH_2$), 72.9 (–CH), 125.8 (CH), 127.9 (CH), 128.5 (CH), 142.4 (C), 165.4 (C), 166.2 (C). MS: *m/z* 252.72 (M^+, 100). *Anal.* Calcd. for $C_{11}H_{12}N_2OS_2$: C, 52.35; H, 4.79; N, 11.10. Found: C, 52.29; H, 4.76; N, 11.01.

4.3.2. 1-(4-Bromophenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio) ethanol **(4b)**

White solid, yield: 8.94 g (90%), m.p. 82–83 °C (from benzene-petroleum ether, 2:1). IR (ATR, cm^{-1}): 3340 (OH), 3046 (Ar–CH), 2918 (Aliph. CH), 1579 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.74 (s, 3H, $-CH_3$), 3.41 (dd, J = 8.4 Hz, J = 8.0 Hz, 1H, $-CH_2$ (A)), 3.69 (dd, J = 3.6 Hz, J = 2.8 Hz, 1H, $-CH_2$ (B)), 4.22 (d, J = 2.0 Hz, 1H, OH), 5.13 (t, J = 4.0 Hz, 1H, –CH–), 7.32 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 15.6 ($-CH_3$), 42.5 ($-CH_2$), 72.4 (–CH), 121.7 (C), 127.6 (CH), 131.6 (CH), 141.4 (C), 165.6 (C), 166.1 (C). MS: m/z 331.24 (M^+, 100), 333.14 (M+2, 97). *Anal.* Calcd. for $C_{11}H_{11}BrN_2OS_2$: C, 39.88; H, 3.35; N, 8.46. Found: C, 39.75; H, 3.31; N, 8.39.

4.3.3. 1-(4-Chlorophenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio) ethanol **(4c)**

White solid, yield: 7.05 g (82%), m.p. 80–81 °C (from benzene-petroleum ether, 2:1). IR (ATR, cm^{-1}): 3313 (OH), 3058 (Ar–CH), 2976 (Aliph. CH), 1586 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.73 (s, 3H, $-CH_3$), 3.35 (dd, J = 8.4 Hz, J = 8.0 Hz, 1H, $-CH_2$ (A)), 3.69 (dd, J = 3.6 Hz, J = 3.2 Hz, 1H, $-CH_2$ (B)), 4.24 (bs, 1H, OH), 5.14 (dd, J = 3.2 Hz, J = 2.8 Hz, 1H, –CH–), 7.32 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 15.6 ($-CH_3$), 42.6 ($-CH_2$), 72.5 (–CH), 127.2 (CH), 128.6 (CH), 133.6 (C), 140.9 (C), 165.5 (C), 166.1 (C). MS: m/z 286.81 (M^+, 100). *Anal.* Calcd. for $C_{11}H_{11}ClN_2OS_2$: C, 46.07; H, 3.87; N, 9.76. Found: C, 46.01; H, 3.92; N, 9.84.

4.3.4. 1-(4-Methoxyphenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl) thio)ethanol **(4d)**

White solid, yield: 7.21 g (85%), m.p. 71–72 °C (from benzene-petroleum ether, 2:1). IR (ATR, cm^{-1}): 3269 (OH), 3009 (Ar–CH), 2961 (Aliph. CH), 1609 (C=N), 1238-1057 ($-OCH_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.73 (s, 3H, $-CH_3$), 3.46 (dd, J = 8.4 Hz, J = 8.0 Hz, 1H, $-CH_2$ (A)), 3.68 (dd, J = 3.2 Hz, J = 3.2 Hz, 1H, $-CH_2$ (B)), 3.77 (d, J = 3.6 Hz, 1H, OH), 3.88 (s, 3H, $-OCH_3$), 5.09 (t, J = 4.0 Hz, 1H, –CH–), 6.89 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 15.6 ($-CH_3$), 42.7 ($-CH_2$), 55.2 ($-OCH_3$), 72.7 (–CH), 113.9 (CH), 127.1 (CH), 134.5 (C), 159.3 (C), 165.3 (C), 166.1 (C). MS: m/z 282.75 (M^+, 100). *Anal.* Calcd. for $C_{12}H_{14}N_2O_2S_2$: C, 51.04; H, 5.00; N, 9.92. Found: C, 51.11; H, 4.93; N, 9.85.

4.4. General procedure for the synthesis of 3-((un)substituted benzyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one **(7a-g)**

In a round-bottomed flask, alcohol derivatives **(4a-d)** (3.5 mmol) were dissolved in DMF (6 ml). NaH (60% mineral oil dispersion, 5.25 mmol; 0.126 g) was added in small fractions to prevent any heating. The appropriate benzyl halides **(5a-g)** (3.5 mmol) were dissolved in DMF (4 ml) and added dropwise to this solution. The mixture was stirred at room temperature for 4–6 h. The progress of the reaction was monitored by TLC at appropriate time intervals. After completion of the reaction, the excess hydride was decomposed with a small amount of methyl alcohol, then the solvent was removed under reduced pressure. The crude residue was suspended in water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, filtered and then evaporated to dryness. The crude residue was purified by column chromatography on a silica-gel column using chloroform as the eluent to obtain target compounds **(7a-g)**. The synthesized compounds were dried with P_2O_5 in a vacuum oven.

4.4.1. 3-Benzyl-5-methyl-1,3,4-thiadiazol-2(3H)-one **(7a)**[34]

Yellowish oil, yield: 0.55 g (77%), R_f = 0.64 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3033 (Ar–CH), 2925 (Aliph. CH), 1668 (C=O), 1562 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.36 (s, 3H, $-CH_3$), 5.01 (s, 2H, $-CH_2$), 7.34 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.1 ($-CH_3$), 50.5 ($-CH_2$), 128.0 (CH), 128.2 (CH), 128.7 (CH), 135.8 (C), 148.6 (C), 170.3 (C=O). MS: m/z 206.84 (M^+, 100). *Anal.* Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.15; H, 4.81; N, 13.49.

4.4.2. 3-(4-Bromobenzyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one **(7b)**

Colorless crystals, yield: 0.78 g (78%), m.p. 89–91 °C (from chloroform); R_f = 0.62 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3053 (Ar–CH), 2949 (Aliph. CH), 1652 (C=O), 1563 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.37 (s, 3H, $-CH_3$), 4.95 (s, 2H, $-CH_2$), 7.22 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.1 ($-CH_3$), 49.8 ($-CH_2$), 122.1 (C), 130.1 (CH), 131.8 (CH), 134.7 (C), 148.8 (C), 170.2 (C=O). MS: m/z 286.24 (M+1, 100). *Anal.* Calcd. for $C_{10}H_9BrN_2OS$: C, 42.12; H, 3.18; N, 9.82. Found: C, 42.05; H, 3.22; N, 9.76.

4.4.3. 3-(4-Chlorobenzyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one **(7c)**

Colorless crystals, yield: 0.69 g (82%), m.p. 80–82 °C (from chloroform); R_f = 0.67 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3055 (Ar–CH), 2932 (Aliph. CH), 1657 (C=O), 1563 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.37 (s, 3H, $-CH_3$), 4.97 (s, 2H, $-CH_2$), 7.28 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.1 ($-CH_3$), 49.8 ($-CH_2$), 128.9 (CH), 129.7 (CH), 130.0 (C), 134.2 (C), 148.8 (C), 170.2 (C=O). MS: m/z 241.05 (M+1, 100). *Anal.* Calcd. for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; N, 11.64. Found: C, 49.81; H, 3.68; N, 11.58.

4.4.4. 3-(4-Fluorobenzyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one **(7d)**

Light yellow crystals, yield: 0.61 g (78%), m.p. 76–78 °C (from chloroform); R_f = 0.67 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3081 (Ar–CH), 2960 (Aliph. CH), 1660 (C=O), 1559 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.36 (s, 3H, $-CH_3$), 4.97 (s, 2H, $-CH_2$), 7.02 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.1 ($-CH_3$), 49.7 ($-CH_2$), 115.5–115.7 (CH) ^3J CF = 21.0 Hz, 130.1–130.2 (CH) ^2J CF = 8.3 Hz, 131.6–131.7 (C) ^4J CF = 3.1 Hz, 148.7 (C), 161.2–163.7 (C) ^1J CF = 246.0 Hz, 170.2 (C=O). MS: m/z 224.83 (M^+, 100). *Anal.* Calcd. for $C_{10}H_9FN_2OS$: C, 53.56; H, 4.05; N, 12.49. Found: C, 53.49; H, 4.00; N, 12.57.

4.4.5. 5-Methyl-3-(4-(trifluoromethyl)benzyl)-1,3,4-thiadiazol-2(3H)-one **(7e)**

Light yellow crystals, yield: 0.73 g (76%), m.p. 50–52 °C (from chloroform); R_f = 0.69 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3078 (Ar–CH), 2946 (Aliph. CH), 1667 (C=O), 1558 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.38 (s, 3H, $-CH_3$), 5.06 (s, 2H, $-CH_2$), 7.45 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.1 ($-CH_3$), 49.9 ($-CH_2$), 119.9–122.6 (CF_3) ^1J CF = 271.0 Hz, 125.3 (CH), 125.6–125.7 (CH) ^3J CF = 4.0 Hz, 125.8–125.9 (CH) ^3J CF = 4.0 Hz, 128.0–128.5 (CH) ^1J CF = 51.0 Hz, 129.8–130.1 (C) ^2J CF = 35.0 Hz, 130.4–130.7 (C) ^2J CF = 32.0 Hz, 139.6 (C), 149.1 (C), 170.3 (C=O). MS: m/z 274.83 (M^+, 100). *Anal.* Calcd. for $C_{11}H_9F_3N_2OS$: C, 48.17; H, 3.31; N, 10.21. Found: C, 48.11; H, 3.26; N, 10.11.

4.4.6. 3-(2,6-Dichlorobenzyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one **(7f)**

Colorless crystals, yield: 0.72 g (75%), m.p. 130–132 °C (from chloroform); R_f = 0.70 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3076 (Ar–CH), 2959 (Aliph. CH), 1679 (C=O), 1561 (C=N). ^1H NMR

(400 MHz, $CDCl_3$) δ (ppm): 2.29 (s, 3H, $-CH_3$), 5.26 (s, 2H, $-CH_2$), 7.22 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.2 ($-CH_3$), 45.4 ($-CH_2$), 128.4 (CH), 130.0 (CH), 131.0 (C), 136.7 (C), 148.3 (C), 169.9 (C=O). MS: *m/z* 274.69 (M-1, 100), 276.79 (M+1, 74). *Anal.* Calcd. for $C_{10}H_8Cl_2N_2OS$: C, 43.65; H, 2.93; N, 10.18. Found: C, 43.54; H, 2.85; N, 10.15.

4.4.7. 3-(2-Chloro-6-fluorobenzyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one (7g)

Light yellow crystals, yield: 0.64 g (71%), m.p. 84–85 °C (from chloroform); R_f = 0.65 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3093 (Ar–CH), 2958 (Aliph. CH), 1665 (C=O), 1569 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.28 (s, 3H, $-CH_3$), 5.06 (s, 2H, $-CH_2$), 7.26 (t, J = 9.2 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 7.45–7.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.2 ($-CH_3$), 41.4–41.5 ($-CH_2$) ^4J CF = 4.6 Hz, 115.0–115.2 (CH) ^3J CF = 22.0 Hz, 121.6–121.8 (CH) ^4J CF = 17.5 Hz, 126.0–126.1 (CH) ^2J CF = 3.8 Hz, 131.6–131.7 (C) ^3J CF = 9.8 Hz, 135.1–135.2 (C) ^3J CF = 5.3 Hz, 149.2 (C), 160.6–163.3 (C) ^1J CF = 270.0 Hz, 169.3 (C=O). MS: *m/z* 260.88 (M+2, 100). *Anal.* Calcd. for $C_{10}H_8ClFN_2OS$: C, 46.43; H, 3.12; N, 10.83. Found: C, 46.38; H, 3.04; N, 10.76.

4.5. General procedure for the synthesis of ((un)substituted phenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one (10–15)

In a round-bottomed flask, 2-((5-methyl-1,3,4-thiadiazol-2-yl) thio)-1-phenylethanol **(4a)** (3.5 mmol; 0.88 g) was dissolved in DMF (6 ml). NaH (60% mineral oil dispersion, 5.25 mmol; 0.126 g) was added in small fractions to prevent any heating. The appropriate phenacyl bromide derivatives **(8a-f)** (3.5 mmol) were dissolved in DMF (4 ml) and added dropwise to this solution. The mixture was stirred at room temperature for 4–6 h. The progress of the reaction was monitored by TLC at appropriate time intervals. After completion of the reaction, the excess hydride was decomposed with a small amount of methyl alcohol, then the solvent was removed under reduced pressure. The crude residue was suspended in water and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, filtered and then evaporated to dryness. The crude residue was purified by column chromatography on a silica-gel column using chloroform as the eluent to obtain target compounds **(10–15)**. The synthesized compounds were dried with P_2O_5 in a vacuum oven.

4.5.1. 5-Methyl-3-(2-oxo-2-phenylethyl)-1,3,4-thiadiazol-2(3H)-one (10)

White crystals, yield: 0.52 g (63%), m.p. 102–103 °C (from chloroform); R_f = 0.38 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3057 (Ar–CH), 2937 (Aliph. CH), 1702 (C=O), 1651 (C=O), 1595 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.40 (s, 3H, $-CH_3$), 5.51 (s, 2H, $-CH_2$), 7.56 (t, J = 7.8 Hz, 2H), 7.70 (t, J = 8.0 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.1 ($-CH_3$), 53.6 ($-CH_2$), 128.6 (CH), 129.4 (CH), 134.5 (CH), 134.6 (C), 149.0 (C), 170.4 (C=O), 192.7 (C=O). MS: *m/z* 235.57 (M+1, 100). *Anal.* Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.29; H, 4.27; N, 11.92.

4.5.2. 3-(2-(4-Bromophenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one (11)

Yellowish solid, yield: 0.72 g (66%), m.p. 99–101 °C (from chloroform); R_f = 0.41 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3062 (Ar–CH), 2985 (Aliph. CH), 1703 (C=O), 1662 (C=O), 1587 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.42 (s, 3H, $-CH_3$), 5.26 (s, 2H, $-CH_2$), 7.65 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.2 ($-CH_3$), 52.6 ($-CH_2$), 129.4 (C), 129.5 (CH), 132.3 (CH), 133.0 (C), 149.2 (C), 170.8 (C=O), 190.4 (C=O). MS: *m/z* 314.28 (M+1, 100). *Anal.* Calcd. for $C_{11}H_9BrN_2O_2S$: C, 42.19; H, 2.90; N, 8.95. Found: C, 42.11; H, 2.88; N, 8.91.

4.5.3. 3-(2-(4-Chlorophenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one (12)

Yellow solid, yield: 0.61 g (65%), m.p. 90–91 °C (from chloroform); R_f = 0.40 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3043 (Ar–CH), 2986 (Aliph. CH), 1703 (C=O), 1663 (C=O), 1589 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.41 (s, 3H, $-CH_3$), 5.26 (s, 2H, $-CH_2$), 7.47 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.2 ($-CH_3$), 52.6 ($-CH_2$), 129.3 (CH), 129.4 (CH), 132.6 (C), 140.6 (C), 149.2 (C), 170.8 (C=O), 190.2 (C=O). MS: *m/z* 268.11 (M^+, 100). *Anal.* Calcd. for $C_{11}H_9ClN_2O_2S$: C, 49.17; H, 3.38; N, 10.42. Found: C, 49.11; H, 3.32; N, 10.45.

4.5.4. 3-(2-(4-Fluorophenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one (13)

Yellow solid, yield: 0.57 g (65%), m.p. 92–93 °C (from chloroform); R_f = 0.43 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3071 (Ar–CH), 2942 (Aliph. CH), 1703 (C=O), 1663 (C=O), 1598 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.42 (s, 3H, $-CH_3$), 5.27 (s, 2H, $-CH_2$), 7.17 (t, J = 8.4 Hz, 2H), 7.99 (t, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.2 ($-CH_3$), 52.6 ($-CH_2$), 116.1–116.3 (CH) ^3J CF = 22.0 Hz, 130.7–130.8 (C) ^2J CF = 9.1 Hz, 131.3–132.4 (C) ^4J CF = 3.1 Hz, 149.2 (C), 164.9–167.5 (C) ^1J CF = 255.0 Hz, 170.9 (C=O), 189.7 (C=O). MS: *m/z* 253.16 (M+1, 100). *Anal.* Calcd. for $C_{11}H_9FN_2O_2S$: C, 52.37; H, 3.60; N, 11.10. Found: C, 52.33; H, 3.52; N, 11.02.

4.5.5. 4-(2-(5-Methyl-2-oxo-1,3,4-thiadiazol-3(2H)-yl)acetyl) benzonitrile (14)

Yellow solid, yield: 0.63 g (70%), m.p. 133–135 °C (from chloroform); R_f = 0.38 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3079 (Ar–CH), 2981 (Aliph. CH), 2233 (C≡N), 1712 (C=O), 1660 (C=O), 1563 (C=N). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.41 (s, 3H, $-CH_3$), 5.28 (s, 2H, $-CH_2$), 7.80 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.2 ($-CH_3$), 52.8 ($-CH_2$), 117.3 (C≡N), 128.5 (CH), 129.5 (CH), 132.3 (C), 137.2 (C), 149.5 (C), 170.8 (C=O), 190.4 (C=O). MS: *m/z* 260.83 (M+1, 100). *Anal.* Calcd. for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21. Found: C, 55.48; H, 3.43; N, 16.33.

4.5.6. 3-(2-(4-Methoxyphenyl)-2-oxoethyl)-5-methyl-1,3,4-thiadiazol-2(3H)-one (15)

Yellow solid, yield: 0.66 g (71%), m.p. 70–72 °C (from chloroform); R_f = 0.36 ($CHCl_3$/MeOH 90:10). IR (ATR, cm^{-1}): 3063 (Ar–CH), 2942 (Aliph. CH), 1691 (C=O), 1646 (C=O), 1597 (C=N), 1181, 1118 ($-OCH_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.40 (s, 3H, $-CH_3$), 3.86 (s, 3H, $-OCH_3$), 5.25 (s, 2H, $-CH_2$), 6.95 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 9.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.2 ($-CH_3$), 52.4 ($-CH_2$), 55.5 ($-OCH_3$), 114.1 (CH), 127.3 (C), 130.3 (CH), 149.9 (C), 164.1 (C), 170.9 (C=O), 189.6 (C=O). MS: *m/z* 265.90 (M+1, 100). *Anal.* Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60. Found: C, 54.46; H, 4.51; N, 10.50.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.06.006.

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