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ORIGINAL PAPER

The Synthesis and Crystal Structure of a Novel Pesticide Intermediates

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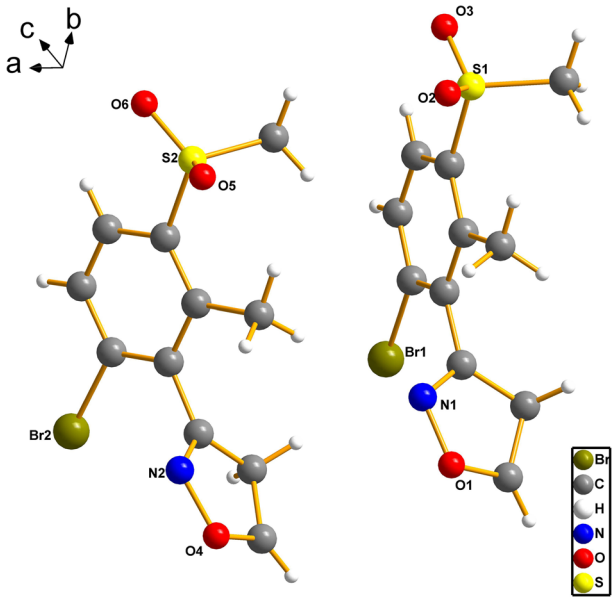
Abstract A novel pesticide intermediates 3-(6-bromo-2-methyl-3-(methylsulfonyl)phenyl)-4,5-dihydroisoxazole was synthesized with 2,3-dimethylaniline as the starting materials. The final product and intermediates were characterized by mass spectra, ^{1}H NMR, infrared and elemental analysis. The crystal structure of compounds **6** and **8** were determined by single crystal X-ray diffraction. Results shown that two oxazole compounds crystallize in the monoclinic (**6**) and triclinic (**8**) with the space group of *P* 21/*c* for **6** and *P*-1 for **8**, respectively.

Graphical Abstract A novel pesticide intermediates 3-(6-bromo-2-methyl-3-(methylsulfonyl)phenyl)-4,5-dihydroisoxazole was synthesized and characterized.



Keywords Synthesis · Characterization · Crystal structure · Pesticide intermediates · Oxazole

Introduction

1,2-Oxazole is also called isoxazole. It is a kind of heterocyclic compounds which possessed special physiological and pharmacological activities, such as antibacterial, antispasmodic, diminish inflammation, regulating plant growth and antiplatelet agglomeration, etc. [1]. As a medicine, the isoxazole compounds have been used as calcium regulating [2] and for treating Alzheimer disease [3], while some isoxazole compounds can kill microorganisms [4]. In the meantime, two isoxazole compounds

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clomazone and topramezone have been developed as herbicides, and isoxadifen-ethyl used as a herbicide safeners [5]. And there are other more isoxazole herbicides [6–9]. Furthermore, the excellent photoelectric properties and carrier transmission capacity of isoxazole compounds add to their wide use in photoelectric functional materials and organic photoconductors [10].

In this paper, a novel pesticide intermediates 3-(6-bromo-2-methyl-3-(methylsulfonyl)phenyl)-4,5-dihydroisoxazole was synthesized and the structure of these compounds were characterized by mass spectra (MS), ^{1}H NMR, infrared (IR) and single crystal X-ray diffraction.

Experiments

Instruments and Reagents

MS were determined with an Agilent 1100LC-MS mass spectrometer. IR spectra of synthetic compounds within 400–4000 cm^{-1} were recorded with a Nicolet 170 SXFT-IR spectrometer (mixed with KBr and pressed into pellets). ^{1}H NMR spectra in $CDCl_3$ or $(CD_3)_2SO$ solvent were recorded with an INOVA-400 spectrometer in the presence of tetramethylsilane as an internal standard. Intensity data were collected on Bruker Apex II CCD detector.

All chemicals and solvents are of commercial reagent grade and used without further purification except the bromine. While the single crystal specimens of **6** and **8** were acquired via slow evaporation of their methanol solutions at room temperature.

Synthesis Section

*Synthesis of 1,2-Dimethyl-3-methylsulfanyl-benzene (**1**)*

75 g (0.62 mol) 2,3-dimethylaniline and 70 g (1.09 mol) copper and 500 mL dimethyl disulfide was added into three-necked flask, heated to 55 °C, added a solution of 100 g (0.97 mol) *tert*butyl nitrite into the flask in 30 min at 55 °C, heated to 60 °C for 2 h, cooled to room temperature, filtered, the filtrate was washed by 10 % hydrochloric acid, saturated $NaHCO_3$ solution and water, dried, distilled under reduced pressure, and collected the component of 128–130 °C at 4 kPa (m.p. 16 °C, b.p. 213.369 °C [11]). Orange liquid 78.13 g. Yield 82.9 %.

*Synthesis of 2,3-Dimethyl-4-methylsulfanyl-bromobenzene (**2**)*

20 g (0.13 mol) 1,2-dimethyl-3-methylsulfanylbenzene and 125 mL 1,2-dichloroethane was added into three-necked flask, added 1 g anhydrous aluminum chloride, a solution of 21.6 g (0.136 mol) bromine in 125 mL 1,2-dichloroethane was added into the flask in 30 min, heated to 60 °C for 4 h, cooled to room temperature, washed by 10 % hydrochloric acid, saturated $NaHCO_3$ solution and water, dried, distilled off 1,2-dichloroethane under reduced pressure. Brown liquid 29.17 g (decompose, b.p. 266.717 °C [12]). Yield 95.9 %. MS ($M+H^+$): 231.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, $J = 8.5$ Hz, 1H, Ar–H), 6.92 (d, $J = 8.5$ Hz, 1H, Ar–H), 2.44 (s, 3H, SO_2–CH_3), 2.42 (s, 3H, Ar–CH_3), 2.38 (s, 3H, Ar–CH_3).

*Synthesis of 2,3-Dimethyl-4-methylsulfonyl-1-bromobenzene (**3**)*

15 g (65 mmol) 2,3-dimethyl-4-methylsulfonyl-1-bromobenzene and 150 mL acetic acid was added into three-necked flask, heated to 100 °C, added 150 mL 30 % hydrogen peroxide then placed at 100 °C for 2 h (the color of the solution changed from orange to colorless), cooled to room temperature, reaction mixture was added into 1200 mL water, placed overnight, filtered, dried. White powder 13.70 g. Yield 80.2 %. MS ($M+H^+$): 262.9. IR ν 3087 (Ar–CH_3), 3006 (Ar–H), 2924 (SO_2–CH_3), 1300, 1124 (–SO_2–); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, $J = 8.6$ Hz, 1H, Ar–H), 7.61 (d, $J = 8.5$ Hz, 1H, Ar–H), 3.09 (s, 3H, SO_2–CH_3), 2.71 (s, 3H, Ar–CH_3), 2.48 (s, 3H, Ar–CH_3).

*Synthesis of 3-Bromomethyl-2-methyl-4-methylsulfonyl-1-bromobenzene (**4**) and 2-Bromo methyl-3-ethyl-4-methylsulfonyl-1-bromobenzene (**5**)*

4 g (15.3 mmol) 2,3-dimethyl-4-methylsulfonyl-1-bromobenzene, 0.16 g azobisisobutyronitrile and 10 mL carbon tetrachloride was added in three-necked flask, heated to 80 °C, added 2.72 g NBS (15.3 mmol), reflow 4 h under lamp, suction filtered when it was hot, the filtrate was distilled under reduced pressure. The solid was separated by column chromatography (eluent was petroleum ether:-ethyl acetate = 5:1, *V*/*V*).

*3-Bromomethyl-2-methyl-4-methylsulfonyl-1-bromobenzene (**4**)* White powder 2.94 g (m.p. 99.3–100.1 °C), yield 56.5 %. MS ($M+H^+$): 341.1; IR ν 3084 (Ar–CH_3), 3012 (Ar–H), 2920 (SO_2–CH_3), 1303–1126 (–SO_2–); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.6$ Hz, 1H, Ar–H), 7.75 (d, $J = 8.6$ Hz, 1H, Ar–H), 4.91 (s, 2H, –CH_2Br), 3.28 (s, 3H, SO_2–CH_3), 2.62 (s, 3H, Ar–CH_3).

*2-Bromomethyl-3-methyl-4-methylsulfonyl-1-bromobenzene (**5**)* White powder 1.77 g (m.p. 157.6–158.1 °C), yield 34.5 %. MS ($M+H^+$): 341.1; IR ν 3081 (Ar–CH_3),

3007 (Ar–H), 2917 (SO_2–CH_3), 1303–1126 (–SO_2–); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, $J = 8.6$ Hz, 1H, Ar–H), 7.67 (d, $J = 8.6$ Hz, 1H, Ar–H), 4.74 (s, 2H, –CH_2Br), 3.12 (s, 3H, SO_2–CH_3), 2.86 (s, 3H, Ar–CH_3).

*Synthesis of 6-Bromo-2-methyl-3-methylsulfonyl-benzaldehyde (**6**)*

4 g (11.8 mmol) 2-bromomethyl-3-methyl-4-methylsulfonyl-1-bromo benzene and 30 mL acetonitrile was added in the flask, stirred at 25 °C, added 8 mL (35.4 mmol) *N*-methyl-morpholine-*N*-oxide aqueous (50 wt%) to the flask in 30 min at 25 °C, stirred for 12 h, poured into 100 mL water, tuned pH 3–4 by concentrated hydrochloric acid, placed overnight, filtered, dried. White powder 2.57 g (m.p. 122.7–124.1 °C). Yield 79.1 %. MS ($M+H^+$): 276.9; IR v 3074 (Ar–CH_3), 3014 (Ar–H), 2932 (SO_2–CH_3), 1705 (C=O), 1305 1121 (–SO_2–); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H, –CHO), 8.13 (d, $J = 8.6$ Hz, 1H, Ar–H), 7.73 (d, $J = 8.6$ Hz, 1H, Ar–H), 3.13 (s, 3H, SO_2–CH_3), 2.90 (s, 3H, Ar–CH_3).

*Synthesis of 6-Bromine-2-methyl-3-methylsulfonyl-benzaldehydoxime (**7**)*

4 g (14.5 mmol) 6-bromo-2-methyl-3-methylsulfonyl-benzaldehyde, 0.84 g (16.1 mmol) hydroxylamine hydrochloride and 60 mL methanol was added to the flask, stirred at 25 °C for 1.5 h, heated to 70 °C, reflow 2 h, distilled off methanol under reduced pressure, The residue was washed with a saturated aqueous sodium chloride, dried. White powder 4.09 g. Yield 96.9 %. MS ($M+H^+$): 292.2; IR v 3078 (Ar–CH_3), 3006 (Ar–H), 2930 (SO_2–CH_3), 1558 (C=N), 1305–1123 (–SO_2–); ^{1}H NMR (400 MHz, DMSO) δ 11.55 (s, 1H, –NOH), 8.03 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.86 (s, 1H, –CH=N–), 7.68 (d, $J = 8.4$ Hz, 1H, Ar–H), 3.28 (s, 3H, SO_2–CH_3), 2.68 (s, 3H, Ar–CH_3).

*Synthesis of 3-(6-Bromo-2-methyl-3-methylsulfonylphenyl)-4,5-dihydro-1,2-oxazole (**8**)*

2 g (6.9 mmol) 6-bromine-2-methyl-3-methylsulfonyl-benzaldehydoxime and 20 mL dichloromethane was added in three-necked flask, fed ethylene in the flask at room temperature for 30 min, then add 5 mL solution of sodium hypochlorite, stirred for 12 h in an atmosphere of ethylene. The organic phase was washed with water and dried, distilled off dichloromethane under reduced pressure. White powder 1.67 g (m.p. 160.8–161.7 °C). Yield 76.9 %. MS ($M+H^+$): 318.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, $J = 8.6$ Hz, 1H, Ar–H), 7.70 (d, $J = 8.6$ Hz, 1H, Ar–H), 4.61 (t, $J = 10.1$ Hz, 2H, –CH_2–), 3.29 (t, $J = 10.1$ Hz, 2H, –CH_2–), 3.11 (s, 3H, SO_2–CH_3), 2.69 (s, 3H, Ar–CH_3).

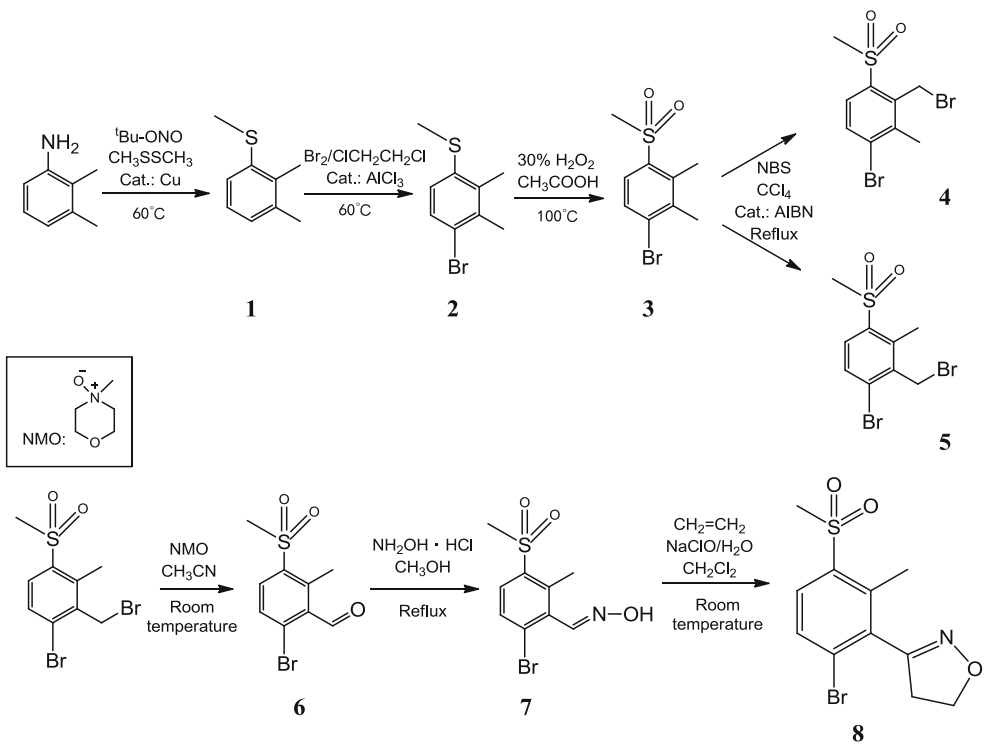

Fig. 1 The synthesis of 3-(6-bromo-2-methyl-3-methylsulfonylphenyl)-4,5-dihydro-1,2-oxazole

Table 1 The crystallographic data of and **6** and **8**

Items	**6**	**8**
CCDC deposit no.	1022672	1022874
Empirical formula	$C_9H_9O_3SBr$	$C_{11}H_{11}NO_3SBr$
Formula weight	277.13	317.18
Temperature (K)	296(2)	296(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Triclinic
Space group	*P* 21/*c*	*P*-1
a (Å)	17.9971(14)	9.3106(7)
b (Å)	7.6333(6)	10.2263(8)
c (Å)	7.7025(6)	14.3835(11)
α (°)	90	71.0940(10)
β (°)	98.3780(10)	76.4160(10)
γ (°)	90	87.8880(10)
Z	4	4
Density(calculated)	1.758 g/cm^3	1.674 g/cm^3
F(000)	552	636
Crystal size (mm^3)	0.36 × 0.31 × 0.25	0.37 × 0.26 × 0.12
Range for data collection (°)	2.288–26.419	2.25–25.33
Reflections collected/unique	5214/2094	6543/2154
R_{int}	0.0183	0.0231
Data/restraints/parameters	1855/0/129	4452/0/311
Goodness-of-fit on F^2	1.212	1.056
Volume (Å^3)	1046.86(14)	1258.22(17)
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0329$, $wR_2 = 0.1009$	$R_1 = 0.0415$, $wR_2 = 0.1187$
R indices (all data)	$R_1 = 0.0435$, $wR_2 = 0.1186$	$R_1 = 0.0615$, $wR_2 = 0.1348$
Largest diff. peak and hole (e/Å^3)	0.557, −0.749	0.483, −0.395

Results and Discussion

Synthetic

The synthetic route of 3-(6-bromo-2-methyl-3-methylsulfonylphenyl)-4,5-dihydro-1,2-oxazole (**8**) is shown in Fig. 1. In our paper, 2,3-dimethylaniline was used as materials, 3-(6-bromo-2-methyl-3-methylsulfonylphenyl)-4,5-dihydro-1,2-oxazole was synthesized through diazotization reaction [13], electrophilic bromination reaction [14, 15], oxidation reaction [16], radical bromination reaction, oxidation reaction [17], condensation reaction and 1,3-dipolar cycloaddition reaction [18–22].

There are four adjacent substituents on the phenyl ring of the target compound, It made some difficult for the synthesis of the target compound. So we chose changing the methyl group into an aldehyde group instead of introducing an aldehyde group directly on the phenyl ring.

There are two common methods to synthesize sulfide, the one is the reaction of halogenated hydrocarbon and sodium thiomethoxide, and the other is diazotization reaction. Because the 1-chloro-2,3-dimethylbenzene or 1-bromo-2,3-dimethylbenzene is much more expensive than 2,3-dimethylaniline, and the solubility of 2,3-dimethylaniline hydrochloride in water is so small that we cannot use it to synthesize the diazonium salt, so we choose the diazotization reaction to synthesize sulfide and use *tert*butyl nitrite as diazotization reagent, and the yield of sulfide is above 80 %.

The reaction of synthesis of 2,3-dimethyl-4-methylsulfanyl-bromobenzene is an electrophilic reaction, using Lewis acid as a catalyst. Bromination often uses iron as a catalyst (in fact, the catalyst is iron tribromide which is generated by iron and bromine). It was reported that bromination used the complexes which is generated by bromine and dioxane [14]. In this paper, considering the inconvenience of using iron as the catalyst or using the complexes which is generated by bromine and dioxane after the reaction, we chose aluminum chloride as the catalyst. Aluminum chloride is a fine catalyst in the electrophilic reaction. It has a high catalytic efficiency and a high reactivity. It is more important that aluminum chloride can dissolve in water, and we can remove it by water after the reaction. Considering the bromine we bought may

contain water which may affect the activity of aluminum chloride, we formulated as a solution of bromine in 1,2-dichloroethane and dried for the night by sodium sulfate before using the bromine.

In the reaction of oxidation from sulfide to sulfone, 30 % hydrogen peroxide is used as the oxidant and acetic acid is used as the solvent. We find that this reaction completed in 1.5–2 h at 100 °C, and the post-treatment is very simple while only pouring the reaction solution into water and the product can separate out.

The bromination reaction of side chain in benzene ring can generate two produces 3-bromomethyl-2-methyl-4-methylsulfonyl-1-bromobenzene (**4**) and 2-bromo methyl-3-ethyl-4-methylsulfonyl-1-bromobenzene (**5**), and we found that the yield of compound **4** is bigger than that of compound **5**. The reason may be that the steric hindrance of the bromine atom is bigger than the steric hindrance of the methylsulfonyl, so it is a little more difficult for the bromine radicals to offense the methyl in the *ortho* position of the bromine atom than the methyl in the *ortho* position of the methylsulfonyl. In this paper, we chose compound **5** as materials to synthesize the target compound **8**.

In theory, synthesis of compound **8** is a two-step reaction. The first step is that oxime generate chloro-oxime. And then, a 1,3-dipolar cycloaddition reactions occurs between ethylene and nitrile oxide which was generate by chloro oxime dehydrochlorination in an alkaline environment. Chlorine, NCS and sodium hypochlorite was usually used as the chlorinated reagents. Sodium hypochlorite solution is cheap and easy to use. The only problem is that the content of sodium hypochlorite solution is unstable. The concrete manifestation is the content of sodium hypochlorite solution between the one bought newly and placed for a period of time was different. However, when we search for the synthesis of it, we found that the excess of sodium hypochlorite does not cause side effects. So the sodium hypochlorite can be used excessively. For gas–liquid reaction, pressurization is necessary. However, when we tried to synthesize it, the 1,3-dipolar cycloaddition which

Table 2 Selected bond lengths (Å) and band angles (°) for **6**

Bonds	Lengths (Å)	Bonds	Lengths (Å)
Br–C6	1.898(3)	S1–O2	1.433(2)
S1–O3	1.433(3)	S1–C5	1.747(3)
S1–C7	1.782(3)	O1–C14	1.166(5)
Bonds	Angles (°)	Bonds	Angles (°)
O3–S1–O2	116.91(16)	C5–S1–O2	109.71(17)
C5–S1–O3	108.40(18)	C7–S1–O2	108.92(15)
C7–S1–O3	106.98(15)	C7–S1–C5	105.28(15)
C12–C6–Br1	119.3(3)	C13–C6–Br1	118.7(3)
C13–C6–C12	121.9(3)	C8–C7–S1	123.3(2)
C10–C7–S1	115.4(2)	C12–C14–O1	126.7(4)

Table 3 Selected bond lengths (Å) and band angles (°) for **8**

Bonds	Lengths (Å)	Bonds	Lengths (Å)
Br1–C5	1.891(4)	C8–S1	1.776(4)
C3–N1	1.261(6)	C11–S1	1.755(5)
C14–N2	1.273(5)	C12–O4	1.430(6)
N1–O1	1.414(5)	C19–S2	1.772(4)
O2–S1	1.432(3)	C22–S2	1.731(5)
O5–S2	1.429(4)	N2–O4	1.413(4)
Br2–C16	1.901(4)	O3–S1	1.439(4)
C1–O1	1.437(7)	O6–S2	1.434(3)
Bonds	Angles (°)	Bonds	Angles (°)
O1–C1–C2	105.0(4)	N1–C3–C2	113.4(4)
N1–C3–C4	121.2(4)	C6–C5–Br1	118.5(3)
C4–C5–Br1	119.7(3)	C9–C8–S1	123.1(3)
C7–C8–S1	116.1(3)	N2–C14–C15	119.9(4)
N2–C14–C13	114.2(4)	C15–C16–Br2	119.8(3)
C17–C16–Br2	118.7(3)	C18–C19–S2	115.9(3)
C20–C19–S2	123.1(3)	C14–N2–O4	109.7(3)
C3–N1–O1	109.8(4)	N2–O4–C12	108.8(3)
N1–O1–C1	107.8(4)	O2–S1–C8	108.9(2)
C11–S1–C8	105.7(2)	O2–S1–O3	117.6(2)
O2–S1–C11	109.3(2)	O3–S1–C11	107.0(3)
O3–S1–C8	107.7(2)	O5–S2–C19	108.2(2)
C22–S2–C19	105.2(2)	O5–S2–O6	118.2(2)
O5–S2–C22	108.7(3)	O6–S2–C22	106.5(3)
O6–S2–C19	108.2(2)		

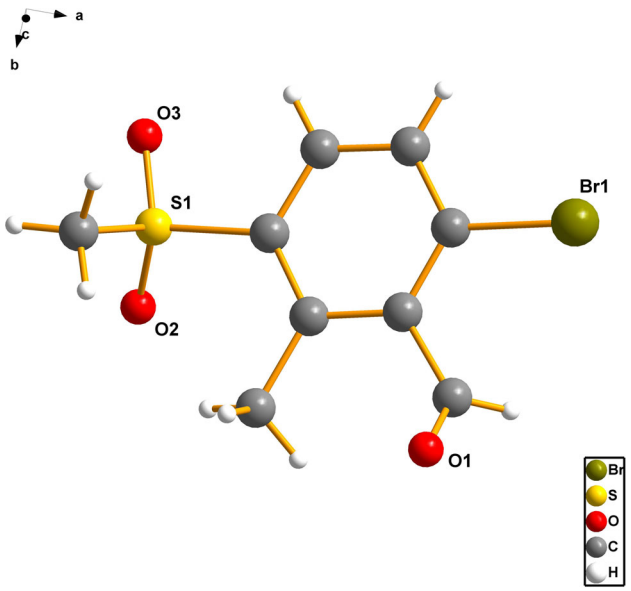

Fig. 2 The perspective view of compound **6**

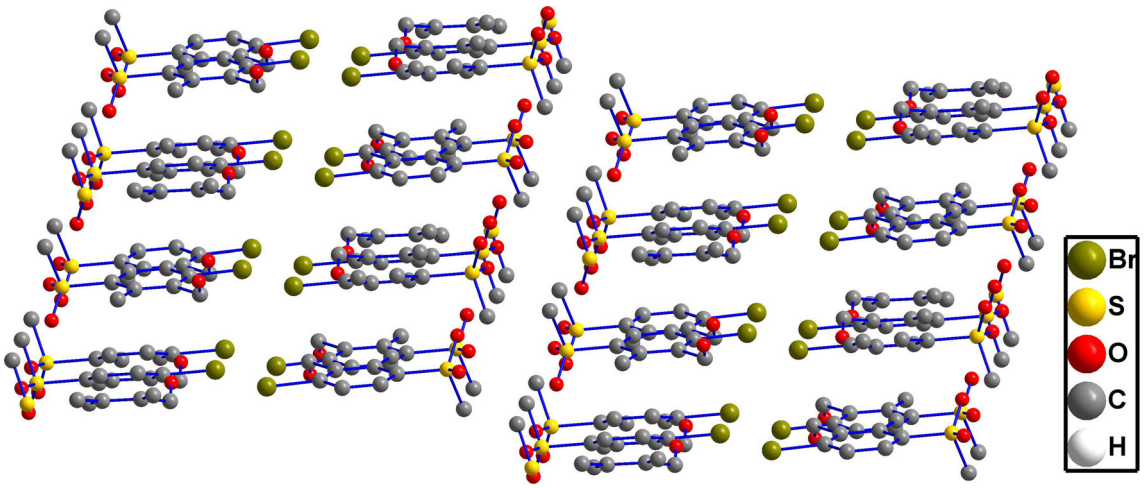

Fig. 3 The *stacking diagram* of compound **6** (hydrogen atoms are omitted for clarity)

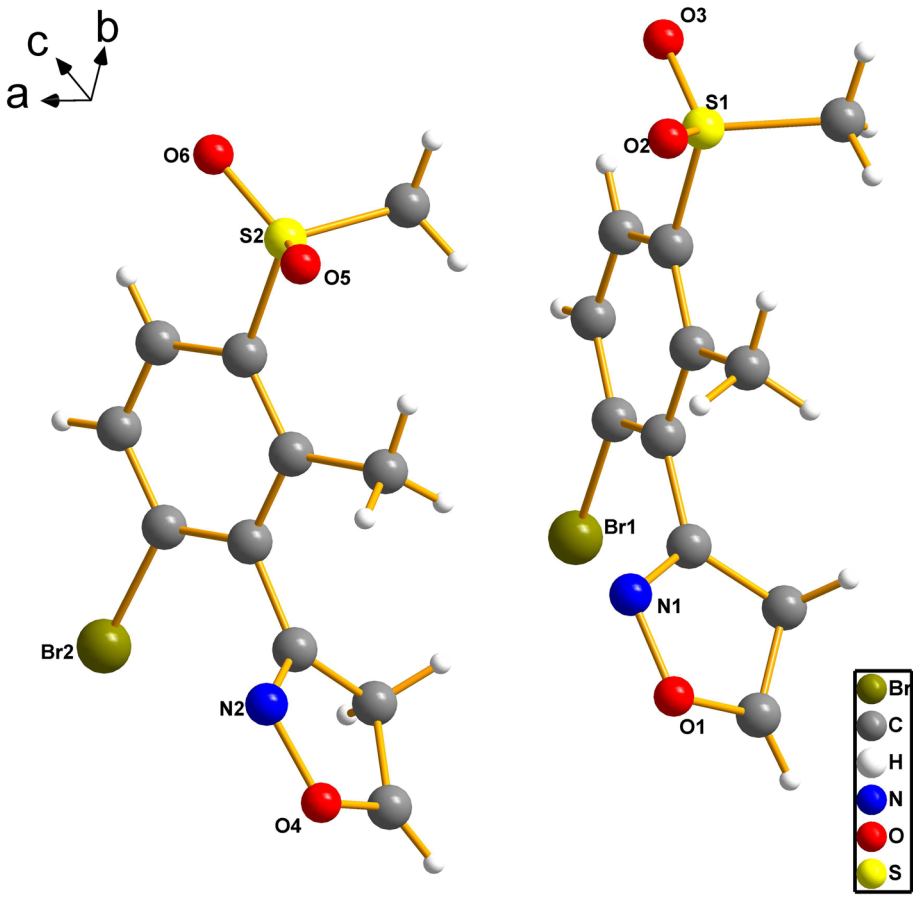

Fig. 4 The perspective view of compound **8**

used ethylene can occur at atmospheric pressure although it takes for a longer time, for example, 12 h.

Crystal Structure Determination and Analysis

Single-crystal X-ray diffraction measurements of compounds **6** and **8** were carried out on a Bruker Smart CCD X-ray single-crystal diffractometer. The reflection data were collected at 296(2) K in $\omega/2\theta$ scan mode with graphite monochromated Mo K radiation ($\lambda = 0.71073$ Å) as the excitation source. The reflections of single crystal **6** were measured in a 2θ range of 2.288°–26.419°, and those of single crystal **8** were measured in a 2θ range of 2.25°–25.33°; and 2094 and 2154 independent reflections were

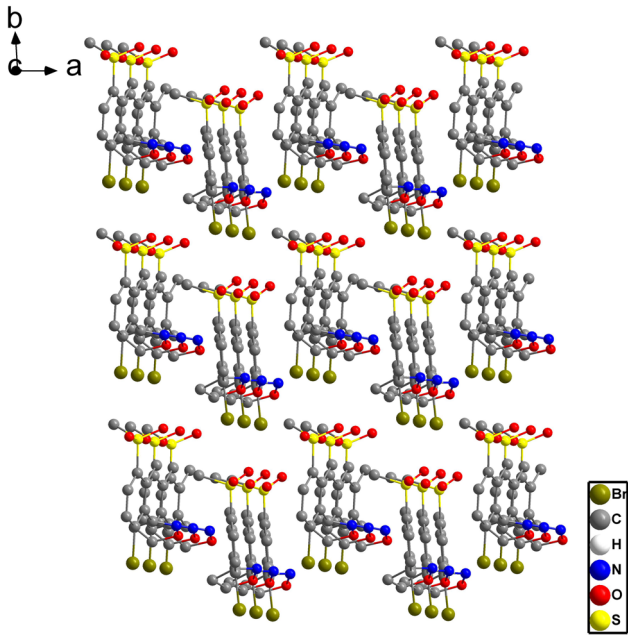

Fig. 5 The *stacking diagram* of compound **8** (hydrogen atoms are omitted for clarity)

measured for **6** and **8**, respectively. SADABS multi-scan empirical absorption corrections were adopted for data processing. The crystal structure was solved by direct method and refined based on full-matrix least-squares on F^2. The final least square cycle of refinement for **6** gave $R_1 = 0.0329$ and $wR_2 = 0.1009$; and that for **8** gave $R_1 = 0.0415$ and $wR_2 = 0.1187$. The crystallographic data and structural refinements for **6** and **8** are listed in Table 1, selected bond lengths and angles are listed in Tables 2 and 3, respectively.

Structure perspective of **6** and **8** was in Figs. 2 and 4; cell stacking diagram was in Figs. 3 and 5.

The perspective view of compound **6** is illustrated in Fig. 2. In the compound **6**, the length of the C=O bond is 1.166(5) Å, which is shorter than the theoretical value (1.20 Å). When C=O and benzene form conjugated system, the length of the C=O bond will elongate for the reason of equalization of the length; but in this case, the length of the C=O bond is shorter than the usual value, the steric effect of the *o*-position substituent of C=O can destroy the conjugated system that formed by C=O and benzene maybe the primary cause. That the torsional angles of C6–C12–C14–O1 is 128.3(5)° and C8–C12–C14–O1 is −52.3(5)° illustrate the C=O bond out of the plane of the aromatic ring. On the other hand, the electron drawing group in the *o*-position (Br) and *m*-position (–SO_2–CH_3) of C=O bond maybe another reason for shorten of C=O bond. All the other bond lengths in compound **6** are in normal ranges. As the C=O bond is not coplane with the aromatic ring suggesting that π–π conjugated system may not exist in the whole molecule. As a result, compound **6** presents two-dimensional (2D) layer structure based on the non-covalent intermolecular forces, as shown in Fig. 3. The perspective view of compound **8** is shown in Fig. 4. In the molecule **8**, the dihedral angle between benzene ring (C8–C11–C22–C9–C18–C19) and the heterocycle contained oxygen and nitrogen (C30–C24–N2–C32–O6) is 79.86°, indicating that π–π conjugation does not occur in the whole molecule. Finally, the zero-dimensional (0D) discrete molecules are stacked into a 2D sheet-like architecture, as illustrated in Fig. 5.

Conclusions

We synthesized 3-(6-bromo-2-methyl-3-methylsulfonylphenyl)-4,5-dihydro-1,2-oxazole, using MS, ^{1}H NMR, IR for their structure characterization and determination. At the same time, compounds **6** and **8** were got and obtained the related data of compounds **6** and **8** single crystal structure on the Bruker Apex II CCD plane diffraction, thus the structure of the compounds **6** and **8** was confirmed. However, the application of the matter is under the research.

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