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Ultrasound-assisted synthesis and preliminary bioactivity of novel 2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine derivatives containing fluorine

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Abstract

Eight novel 5,7-disubstituted-2-{5-methyl-3-(4-trifluoromethylphenyl)isoxazol-4-ylcarbonylimino}-2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidines were synthesized by multi-step reactions in yields 68−85%. Reactions were carried out either by ultrasound irradiation or conventional method, and found it was faster and more efficient under ultrasonic irradiation. Preliminary herbicidal activities against *Echinochloa crus-galli*, *Digitaria sanguinalis* and *Chenopodium serotinum* were also evaluated by flat-utensil method, and the results indicated that the target compounds exhibited significant activities, some were even higher than the control herbicide.

Keywords: 2*H*-1,2,4-Thiadiazolo[2,3-*a*]pyrimidine; Synthesis; Ultrasound; Bioactivity

The fused heterocycles with a pyrimidine ring are important pyrimidine derivatives and exhibit excellent biological activities, such as anti-virus, antitumor, antihypertensive, antifungal and herbicidal activities [1–5]. Among the derivatives, substituted 2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidines possess high herbicidal activity, being inhibitors of acetohydroxyacid synthase (AHAS) [6–8].

On the other hand, isoxazole derivatives are widely used in medicine and pesticide fields owing to their exceptional biological activities. Many isoxazole compounds have been developed into herbicide, fungicide, insecticide and other agricultural chemicals [9,10]. In particular, their excellent herbicidal activity attracts many pesticide chemists' attention, and more than 10 isoxazole herbicides have been discovered, such as isoxaben [11] and isoxaflutole [12].

Nowadays, ultrasound-assisted synthesis as an effective technique is widely used in chemical reactions, which exhibits many advantages including higher yield, shorter reaction time and milder reaction condition when compared with conventional methods [13]. Motivated by these findings, herein we introduced a trifluoromethyl phenyl moiety to the isoxazole ring, followed by linking a 2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine moiety though a carbonylimino bridge, to synthesize eight novel 2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine derivatives. Their herbicidal activities were evaluated against selected weeds.

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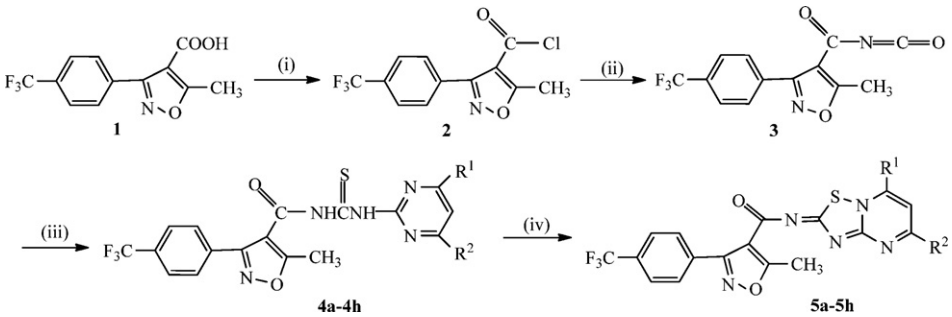


Scheme 1. Reagents and conditions: (i) $SOCl_2$, reflux 4 h; (ii) KSCN, CH_3CN, PEG-400, reflux 3 h; (iii) 2-amino-4,6-disubstituentedpyrimidines, TBAB, CH_3CN, reflux 2 h; (iv) Br_2, $CHCl_3$, USI, r.t. 1–2 h.

The target compounds were synthesized using the strategy described in Scheme 1. The starting materials 5-methyl-3-(4-trifluoromethylphenyl)isoxazole-4-formic acid **1** and 2-amino-4,6-disubstituented pyrimidines were prepared according to the literature [14] and [15], respectively. The synthesis began by treating **1** with $SOCl_2$ to yield 5-methyl-3-(4-trifluoromethylphenyl)isoxazole-4-carbonyl chloride **2**, followed by reacting with KSCN in anhydrous acetonitrile to give acyl isothiocyanate **3** [7]. Then, the unpurified isothiocyanate solution was slowly added to a mixture of 2-amino-4,6-disubstituented pyrimidine and tetrabutyl ammonium bromide (TBAB) in acetonitrile to afford corresponding acyl thiourea **4**. Finally, **4** was cyclized using Br_2 as oxidant in chloroform to generate the target compound **5**, and the reaction was carried out either by ultrasound irradiation with power 250 W (USI method) or stir at room temperature (conventional method). The use of ultrasound irradiation could afford the target compounds in short time and moderate to good yield (Table 1). For example, the yields of **5a**, **5b**, **5d** and **5e** were more than 80%, and their reaction times were 60–100 min. However, the yields were only 48–57%, and the reaction times were from 180 to 300 min by conventional method.

The structures of the target compounds were confirmed by IR, NMR and elemental analyses as shown in Ref. [16].

The reaction mechanism of acyl thiourea **4** with Br_2 may be that a bromine molecule attacks the two active H atoms in the N–H bonds, while the S atom in C=S bond attacks one N atom in the pyrimidine ring. Moreover, if two substituents at 4,6-positions of pyrimidine are different, the S atom will mainly attacks the N atom with larger charge density to generate the target compound [7]. Herein, we calculated the charges of the two N atoms in the pyrimidine ring by B3LYP/6-31G(d) according to density functional theory, and the result was listed in Table 2. In compounds **4c**–**4h**, when R^1 was OCH_3, OH, Cl, SCH_3, Cl and OCH_3, respectively, the charge density of N1 atom was larger, so the S atom linked with N1 atom. Therefore, we assigned the positions of R^1 and R^2 as shown in Table 1 and suggested a possible reaction mechanism (Scheme 2).

In vitro herbicidal activity of the target compound **5** was evaluated by flat-utensil method according to the literature [7]. Three kinds of weeds, *Digitaria sanguinalis*, *Chenopodium serotinum* and *Echinochloa crus-galli*, were used in

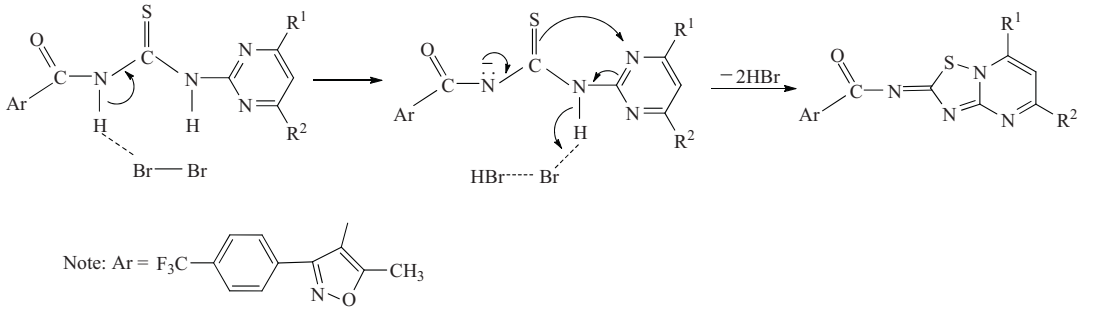
Table 1
Data of synthesis (USI), *in vitro* herbicidal activity[a] for the target compounds **5a**–**5h**.

Compd.	R^1	R^2	Time (min)	Yield (%)	*C. serotinum*			*D. sanguinalis*			*E. crus-galli*		
					I	II	III	I	II	III	I	II	III
5a	CH_3	CH_3	60	85	93.7	81.9	53.8	88.9	73.5	56.1	87.1	84.9	54.8
5b	OCH_3	OCH_3	60	85	89.8	82.5	55.3	83.2	67.0	37.5	84.3	59.8	46.4
5c	OCH_3	CH_3	60	72	95.1	86.5	58.9	65.4	61.7	50.3	77.1	64.8	48.6
5d	OH	CH_3	90	83	70.4	47.6	36.6	58.1	50.7	25.4	76.2	65.9	49.7
5e	Cl	CH_3	100	80	77.1	63.6	50.6	80.1	64.9	43.9	86.6	58.6	43.0
5f	SCH_3	CH_3	90	68	83.8	70.4	46.8	60.3	45.5	29.4	85.5	61.5	50.3
5g	Cl	OCH_3	90	76	75.3	64.7	54.1	73.5	50.0	29.7	90.5	84.3	50.9
5h	OCH_3	SCH_3	90	68	68.2	57.3	50.6	77.9	42.6	30.8	79.3	63.7	58.1
CK					90.5	87.5	55.7	80.7	52.4	33.8	82.2	49.2	36.8

[a] Herbicidal activities are expressed with inhibition rate for root length (%); I, II and III represent the tests at concentrations of 100, 50 and 10 mg/L, respectively.

Table 2
Atom charges of N1 and N2 for compounds **4c**–**4h**.

Compd.	R^1	R^2	Atom charge	
			N1	N2
4c	OCH_3	CH_3	−0.599	−0.508
4d	OH	CH_3	−0.601	−0.509
4e	Cl	CH_3	−0.525	−0.487
4f	SCH_3	CH_3	−0.565	−0.498
4g	Cl	OCH_3	−0.548	−0.525
4h	OCH_3	SCH_3	−0.577	−0.559



Scheme 2. A suggested mechanism for synthesis of the target compound.

the test. Nicosulfuron, a commercial herbicide, was used as control (*CK*). As seen from Table 1, **5a** and **5b** exhibited good herbicidal activities against the three tested weeds at a dose of 100 mg/L, with inhibitory rates of 84.3–93.7%, near to or higher than nicosulfuron. In addition, **5c** possessed excellent activity against *Chenopodium serotinum* at 100 mg/L and 50 mg/L; **5e** displayed good activity against *Digitaria sanguinalis* at the two doses. Moreover, **5e, 5f** and **5g** showed considerable activities against *Echinochloa crus-galli* in comparison with the control.

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[16] Analytic data for target compounds. **5a**: mp 220–221 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H), 2.53 (s, 3H), 2.72 (s, 3H), 7.03 (s, 1H), 6.80–7.45 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.6, 166.5, 162.7, 161.0, 158.6, 158.1, 152.9, 135.2, 133.9, 132.4, 129.7, 128.0, 125.5, 112.8, 21.4, 20.7, 12.0. Anal. Calcd. for $C_{19}H_{14}F_3N_5O_2S$: C 52.65, H 3.26, N 16.16; found: C 52.45, H 3.16, N 16.20. **5b**: mp 233–

234 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.75 (s, 3H), 3.82 (s, 3H), 3.95 (s, 3H), 5.25 (s, 1H), 6.85–7.45 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.8, 166.4, 162.9, 160.5, 159.1, 158.3, 153.4, 135.5, 133.2, 132.1, 130.5, 128.6, 125.0, 112.7, 55.3, 54.7, 11.8. Anal. Calcd. for $C_{19}H_{14}F_3N_5O_4S$: C 49.03, H 3.03, N 15.05; found: C 49.43, H 3.01, N 15.36. **5c**: mp 240–241 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.62 (s, 3H), 2.79 (s, 3H), 3.93 (s, 3H), 5.75 (s, 1H), 6.96–7.38 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.9, 166.0, 163.0, 160.6, 159.1, 158.6, 153.1, 134.9, 133.2, 132.1, 130.8, 128.6, 125.0, 112.7, 54.6, 21.4, 11.8. Anal. Calcd. for $C_{19}H_{14}F_3N_5O_3S$: C 50.78, H 3.14, N 15.58; found: C 50.63, H 3.28, N 15.28. **5d**: mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H), 2.82 (s, 3H), 6.10 (s, 1H), 6.95–7.35 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7, 165.4, 162.4, 160.5, 158.6, 158.4, 153.6, 135.7, 133.2, 132.3, 130.2, 128.3, 125.3, 113.5, 21.9, 11.8. Anal. Calcd. for $C_{18}H_{12}F_3N_5O_3S$: C 49.66, H 2.78, N 16.09; found: C 49.48, H 2.52, N 16.18. **5e**: mp 252–254 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H), 2.72 (s, 3H), 5.90 (s, 1H), 7.16–7.42 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7, 165.4, 162.4, 160.5, 158.6, 158.4, 153.6, 135.7, 133.2, 132.4, 130.2, 128.3, 125.3, 113.5, 21.4, 12.2. Anal. Calcd. for $C_{18}H_{11}ClF_3N_5O_2S$: C 47.64, H 2.44, N 15.43; found: C 47.54, H 2.45, N 15.32. **5f**: mp 242–244 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 3H), 2.63 (s, 3H), 2.72 (s, 3H), 5.91 (s, 1H), 7.34–7.48 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.8, 165.9, 163.0, 160.4, 159.2, 158.5, 153.6, 135.2, 133.2, 132.1, 130.1, 128.6, 125.1, 112.7, 21.6, 20.4, 11.9. Anal. Calcd. for $C_{19}H_{14}F_3N_5O_2S_2$: C 49.03, H 3.03, N 15.05; found: C 49.23, H 3.19, N 15.33. **5g**: mp 255–256 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.72 (s, 3H), 3.92 (s, 3H), 5.70 (s, 1H), 7.02–7.35 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.9, 166.0, 163.0, 160.6, 159.1, 158.5, 153.4, 135.1, 133.4, 132.1, 130.5, 128.7, 125.0, 112.6, 54.5, 11.9. Anal. Calcd. for $C_{18}H_{11}ClF_3N_5O_3S$: C 46.02, H 2.36, N 14.91; found: C 46.11, H 2.36, N 14.87. **5h**: mp 228–230 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (s, 3H), 2.79 (s, 3H), 3.90 (s, 3H), 5.91 (s, 1H), 6.96–7.38 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.8, 165.2, 162.9, 159.6, 159.1, 158.3, 153.0, 135.5, 132.8, 132.1, 130.4, 128.8, 125.1, 112.3, 54.7, 20.6, 12.0. Anal. Calcd. for $C_{19}H_{14}F_3N_5O_3S_2$: C 47.40, H 2.93, N 14.55; found: C 47.50, H 2.85, N 14.42.