Ultrasonic irradiated synthesis and herbicidal activities of 5,7-disubstituted-2-(substituted pyridine-3-formylimino)-2H-1,2,4-thiadiazolo[2,3-a]pyrimidine derivatives

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Eight new substituted-pyridine-3-formylimino-2H-1,2,4-thiadiazolo[2,3-a] derivatives containing substituted pyrimidine ring were synthesized in good yield under ultrasonic irradiation (USI). The structures of all newly synthesized compounds were elucidated and confirmed by IR, $^1$H NMR and elemental analysis. The target compounds have been screened for activity against a number of monocotyledones and dicotyledones. The preliminary herbicidal tests show that some of the target compounds have better inhibitory activities against weeds.

In the 20th century, the advent of sulfonylurea herbicide was a very important milestone in the development history of pesticide chemistry, because of super high activity, low toxicity and low residue content, especially after people found the biochemical mechanism of this kind of herbicides, acetolactate synthase (ALS) has been a very attractive target for herbicides. It is reported that $^2$, 2H-1,2,4-thiadiazolo[2,3-a]pyrimidine derivatives are another kind of remarkable ALS inhibitor after the advent of sulfonylurea herbicides, and their herbicidal activities are comparable to sulfonylurea herbicides. Moreover, because of containing an inherently weak N-S bond which benefits plant’s absorption and metabolism, the former’s selective activities are superior to the latter. In addition, nitrogen heterocycles are extremely versatile building blocks for the manufacture of active compounds such as herbicides, fungicides, and insecticides in the agrochemical industry. Among these, substituted nicotinic acid and its derivatives as agricultural and pharmaceutical intermediates have been well established. Moreover, acylthiourea derivatives are well known for a wide range of biological activities such as bactericidal, fungicidal, herbicidal, insecticidal action and regulating activity for plant growth. More recently, new technologies have provided innovative synthetic routes. Sonochemistry is presented as a technology in itself and can be used to improve the efficiency of synthesis, the interest of synthetic chemists is becoming increasing focused on the use of sonochemical methods in organic synthesis. A survey of literature shows that many organic reactions have recently been accelerated by ultrasonic irradiation. To create new herbicide which accords with pesticide criterion and to design alternative synthetic strategies to improve the synthetic efficiency, we introduced substituted-nicotinyl into the structure of 2H-1,2,4-thiadiazolo[2,3-a]pyrimidine derivatives, and synthesized a series of substituted-pyridine-3-formylimino-2H-1,2,4-thiadiazolo[2,3-a] derivatives containing substituted pyrimidine ring under ultrasonic irradiation with a frequency of 35 kHz. Our ultrasonic irradiation method apparently improves the efficiency of the synthetic process with a good yield and a shorter reaction time compared the typical heating method. The structures of all newly synthesized compounds were elucidated by elemental analysis, IR and $^1$H NMR spectral data. The preliminary herbicidal activity tests show that some of the target compounds have better inhibitory activities against weeds.

The title compounds were synthesized by the method in Scheme 1.

Experimental

Apparatus:

The structures of the newly synthesized compounds were characterized by IR, $^1$H NMR and elemental analysis. The melting points were determined on an XT4A micro digital melting point apparatus and are uncorrected. The IR spectra were recorded in the region 4000–400 cm$^{-1}$ KBr discs on a Nicolet 5DX FT-IR spectrophotometer. The $^1$H NMR spectra were obtained on a Varian-300-54 spectrometer in $d_6$-DMSO using TMS as internal reference. The C, H and
Reagents:

All starting materials are commercial products of analytical grade purity. Thionyl chloride was distilled and potassium thiocyanate was baked before use. 2-Amino-4,6-disubstituted-pyrimidine 4 were prepared by the literature method 7.

General procedures for the preparation of the target compounds 6a-h were as follows:

Substituted-nicotinic acid (0.05 mol), 10 mL of toluene and thionyl chloride (15 mL) were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred at about 50°C for 2 h. Then the excess of thionyl chloride was removed under reduced pressure to give a clear solution of substituted-nicotinyl chloride 2. To a solution of potassium thiocyanate (0.15 mol) in 10 mL of acetonitrile, the clear solution of substituted-nicotinyl chloride 2 and 3% PEG-400 were added. The flask with the reaction mixture was immersed into the water bath of an ultrasonic cleaner at refluxed temperature for about 0.5 h and then the reaction mixture was filtered off to yield an orange-red solution 3. Then equimolar quantity of 4,6-disubstituted-2-amino pyrimidine 4 was added and under ultrasonic irradiation for about 15–20 min and the reaction was monitored by TLC. At the end of the reaction, the resulting precipitate was collected by filtration and recrystallized from DMF-EtOH-H₂O to yield compound 5. To a solution of compound 5 in 15 mL of CHCl₃, equimolar quantity of bromine was added dropwise at water-ice bath. After addition, the flask with the reaction mixture was immersed into the water bath of an ultrasonic cleaner at room temperature for about 1.5 h. At the end of the reaction, the resulting precipitate was collected by filtration and recrystallized from DMF-EtOH-H₂O to yield target compound 6.

Hericidal activity test:

The herbicidal activity was evaluated by flat-utensil method according with the standard bioactivity test procedures of Shanghai Branch of National Pesticide R & D South Central in China. A stock solution was prepared by dissolving 3mg/mL of each compound in DMSO, was diluted by distilled water up to three dilutions, giving concentrations of 10, 50 and 100 ppm. *Digitaria sanguinalis* (L.) Scop, *Chenopodium serotinum* L., *Echinochloa crusgallis* (L.), *Sorghum bicolot* and *Amaranthus retroflexus* L. were selected as test plants for measuring the herbicidal activity of 6a-h. After spraying, the plants placed in the temperature between 20 and 25°C under natural light conditions for a week. The inhibition percentage of some active compounds to kinds of plants was given in Table 1. The inhibition percentage was calculated by the following equation:

\[
\text{Inhibition percentage} = 1 - \frac{\text{comparison}}{\text{treatment}} \times 100\%
\]
Table 1. Inhibition percentage of 6a-h to different kinds of plants

| Compd. | Conc. (ppm) | Inhibition (%) | Echinochloa crus-galli | Sorghum bicolor | Digitaria sanguinalis (L.) Scop. | Chenopodium serotinum | Amaranthus retroflexus |
|--------|-------------|----------------|------------------------|----------------|----------------------------------|----------------------|------------------------|
|        |             |                | L.                     | L.             | L.                               | L.                   | L.                     |
| 6b     | 10          | The stalk      | 0                      | 30             | 70                               | 70                   | 80                     |
|        |             | The root       | 50                     | 90             | 60                               | 80                   | 85                     |
|        | 50          | The stalk      | 0                      | 40             | 80                               | 80                   | 85                     |
|        |             | The root       | 90                     | 90             | 80                               | 90                   | 90                     |
|        | 100         | The stalk      | 10                     | 40             | 90                               | 100                  | 90                     |
|        |             | The root       | 90                     | 90             | 80                               | 100                  | 90                     |
| 6e     | 50          | The stalk      | 0                      | 10             | 60                               | 20                   | 20                     |
|        |             | The root       | 20                     | 70             | 20                               | 20                   | 20                     |
|        | 100         | The stalk      | 30                     | 10             | 70                               | 100                  | 20                     |
|        |             | The root       | 80                     | 30             | 80                               | 100                  | 20                     |
|        | 10          | The stalk      | 10                     | 0              | 0                                | 0                    | 0                      |
|        |             | The root       | 20                     | 0              | 0                                | 0                    | 0                      |
|        | 6g          | 50             | 10                     | 0              | 10                               | 70                   | 80                     |
|        |             | The root       | 10                     | 0              | 0                                | 0                    | 0                      |
|        | 100         | The stalk      | 30                     | 20             | 30                               | 80                   | 90                     |
|        |             | The root       | 30                     | 80             | 50                               | 80                   | 90                     |

Results and discussion

The intermediate substituted-nicotinyl chloride 2 obtained by the reaction of substituted-nicotinic acid with thionyl chloride was treated with potassium thiocyanate using PEG-400 as solid-liquid phase transfer catalyst under ultrasonic irradiation to give substituted-nicotinyl isothiocyanate 3. It was found that the acyl chloride was quantitatively converted to the corresponding acyl isothiocyanate. This intermediate was then treated with 4,6-disubstituted-2-amino pyrimidine 4 to give compound 5 in good yield. Then the intermediate 5 was treated with bromine under ultrasonic irradiation to give the target compounds 5,7-disubstituted imino 2H-1,2,4-thiadiazolo[2,3-a]pyrimidine derivatives (6a-h).

We know that the use of ultrasonic irradiation as a method of agitating heterogeneous reaction system is gaining recognition. In search of improving methods to prepare the intermediate acylthiourea by reacting acyl isothiocyanates with nucleophiles, we have found the ultrasonic vibration of a mixture of acyl chloride, potassium thiocyanate and 3% PEG-400 in acetonitrile can provide acyl isothiocyanates in good yield. In this paper, we have conducted our reaction using PEG-400 as solid-liquid phase transfer catalyst under ultrasonic irradiation to synthesis the intermediate acylthiourea 5, then the intermediate 5 undergoes a fast reaction with bromine under ultrasonic irradiation to give target compounds, this is a facile and convenient method for the synthesis of substituted-pyridine-3-formylimino-2H-1,2,4-thiadiazolo[2,3-a] derivatives containing substituted pyrimidine ring, with the advantages of simple operation, short reaction times and high yield over the traditional heating method.

All the structures of the newly synthesized compounds 6 were assigned on the basis of their elemental analyses and spectroscopic data, IR and 1H NMR. The IR (KBr) spectrum displayed absorptions at about 1600, 1650 and 1200 cm⁻¹, which are assigned to C=N, C=O and C=S functions, respectively. The medium-strong Vc=O band in the IR spectra of all the compounds appears at about 1650 cm⁻¹, apparently decreasing in wavenumber compared with the ordinary carbonyl absorption (1710 cm⁻¹). The 1H NMR (DMSO-d₆) spectrum exhibited the singlet and multiplet signals at about δ 6.50 and 7.20-8.50 were assigned to pyrimidine-CH and pyridine-CH protons, respectively. All the compounds can be dissolved in DMF, DMSO and other nonprotonic solvents, but insoluble in chloroform and dichloromethane.

Characterization data for target compounds:
5,7-Disubstituted-2-(substituted pyridine-3-formyl-
imino)-2H-1,2,4-thiadiazolo[2,3-a]pyrimidine derivatives (6a-h):

(6a) Yield 86%, m.p. 240–243°C; IR (cm⁻¹) 1690 (C=O), 1630 (C=N); ¹H NMR (d₆-DMSO) δ 3.80 (6H, s, OCH₃), 6.68 (1H, s, pyrimidine-5-H), 7.45–8.27 (3H, m, pyridine-H) (Found: C, 44.30; H, 2.76; N, 19.98. Calcd. for C₁₃H₁₀ClN₅O₂S: C, 44.38; H, 2.84; N, 19.91%).

(6b) Yield 80% m.p. 252–254°C; IR (cm⁻¹) 1688 (C=O), 1626 (C=N); ¹H NMR (d₆-DMSO) δ 2.25 (6H, s, OCH₃), 6.72 (1H, s, pyrimidine-5-H), 7.32–8.18 (3H, m, pyridine-H) (Found: C, 40.52; H, 2.06; N, 19.54. Calcd. for C₁₂H₁₀ClN₅O₂S: C, 40.45; H, 1.97; N, 19.66%).

(6c) Yield 75%, m.p. 248–251°C; IR (cm⁻¹) 1692 (C=O), 1624 (C=N); ¹H NMR (d₆-DMSO) δ 3.76 (3H, s, OCH₃), 6.75 (1H, s, pyrimidine-5-H), 7.30–8.24 (3H, m, pyridine-H) (Found: C, 42.08; H, 2.36; N, 18.85. Calcd. for C₁₃H₁₀ClN₅O₂S: C, 42.16; H, 2.43; N, 18.92%).

(6d) Yield 78%, m.p. 234–238°C; IR (cm⁻¹) 1688 (C=O), 1628 (C=N); ¹H NMR (d₆-DMSO) δ 4.30 (2H, q, OCH₂CH₃), 1.62 (3H, t, OCH₂CH₃), 6.58 (1H, s, pyrimidine-5-H), 7.35–8.22 (3H, m, pyridine-H) (Found: C, 40.52; H, 2.06; N, 19.54. Calcd. for C₁₂H₁₀ClN₅O₂S: C, 40.45; H, 1.97; N, 19.66%).

(6e) Yield 82%, m.p. >260°C; IR (cm⁻¹) 1683 (C=O), 1627 (C=N); ¹H NMR (d₆-DMSO) δ 3.75 (6H, s, OCH₃), 6.60 (1H, s, pyrimidine-5-H), 7.36–8.28 (3H, m, pyridine-H) (Found: C, 44.30; H, 2.76; N, 19.98. Calcd. for C₁₃H₁₀ClN₅O₂S: C, 44.38; H, 2.84; N, 19.91%).

(6f) Yield 75%, m.p. 254–257°C; IR (cm⁻¹) 1687 (C=O), 1620 (C=N); ¹H NMR (d₆-DMSO) δ 3.72 (3H, s, OCH₃), 6.82 (1H, s, pyrimidine-5-H), 7.38–8.15 (3H, m, pyridine-H) (Found: C, 40.52; H, 2.06; N, 19.54. Calcd. for C₁₂H₁₀ClN₅O₂S: C, 40.45; H, 1.97; N, 19.66%).

(6g) Yield 80%, m.p. >260°C; IR (cm⁻¹) 1680 (C=O), 1625 (C=N); ¹H NMR (d₆-DMSO) δ 3.78 (6H, s, OCH₃), 6.64 (1H, s, pyrimidine-5-H), 7.42–8.36 (2H, m, pyridine-H) (Found: C, 40.34; H, 2.41; N, 18.02. Calcd. for C₁₃H₁₀ClN₅O₂S: C, 40.41; H, 2.33; N, 18.13%).

(6h) Yield 77%, m.p. >260°C; IR (cm⁻¹) 1685 (C=O), 1618 (C=N); ¹H NMR (d₆-DMSO) δ 3.65 (3H, s, OCH₃), 6.70 (1H, s, pyrimidine-5-H), 7.32–8.24 (2H, m, pyridine-H) (Found: C, 36.75; H, 1.60; N, 17.84. Calcd. for C₁₂H₁₀ClN₅O₂S: C, 36.88; H, 1.54; N, 17.93%).

Herbicidal efficiency:

The preliminary herbicidal test results showed that the target compound 6b has high inhibitory activities against root and stalk of dicotyledon plant (such as Amaranthus retroflexus L.) in higher concentration (100 ppm), compound 6e and 6g have good inhibitory activities against root and stalk of dicotyledon plant (such as Chenopodium serotinum L.). None of the tested compounds were well active against the root and stalk of monocotyledon plant species used.

The inhibition percentage of some active compounds to different kinds of plants was given in Table 1.

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