

イミダゾ[1,2-a]ピリジン部分を有するスルホニル尿素系化合物の合成と除草活性

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Synthesis and Herbicidal Activity of Sulfonylurea Compounds with Imidazo [1,2-*a*]pyridine Moiety¹

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INTRODUCTION

In our previous papers,¹⁻⁴⁾ we have reported the synthesis and herbicidal activity of sulfonylureas **I** with imidazo[1,2-*a*]pyridine moiety against paddy weeds (Fig. 1).

In our continued study, we have found that some compounds showed a potential herbicidal activity against broadleaf weeds in cereal fields. Among them, compound **I** (X = MeSO₂, R¹ = R² = OMe) showed broad spectrum against not only broadleaf weeds but also grass weeds as a promising compound.

With much interest in the remarkable activity of this compound, we undertook the synthesis of the derivatives and tested herbicidal activities of them.

MATERIALS AND METHODS

1. Synthesis of Compounds

IR spectra were taken on a Shimadzu IR-420 spectrometer. ¹H NMR spectra were recorded at 200 MHz on a Bruker AC-200P spectrometer with tetramethylsilane as an internal standard. All melting points were uncorrected.

Sulfonylureas **I** were synthesized by the reaction of corresponding sulfonamides **II** with phenyl *N*-pyrimidinyl-carbamates **III** (Fig. 2).

1.1 General synthesis of sulfonamides **II**

The general synthetic routes of key intermediates, 2-sulfonyl-, sulfinyl- and sulfonyl imidazo[1,2-*a*]pyridine-3-sulfonamides **II**, are shown in Fig. 3.

Ethyl 2-methylsulfonylimidazo[1,2-*a*]pyridine-3-carboxylate **IV**⁵⁾ was substituted with various thiols to give



Fig. 1 Sulfonylureas with imidazo [1,2-*a*] pyridine moiety.

2-alkylsulfonyl or 2-arylsulfonyl derivatives **V**. The sequence of hydrolysis, decarboxylation, sulfonation, chlorination and aminolysis gave the sulfonamide derivatives **IIa**. Each step proceeded in a good yield but this sequence was circuitous. Therefore, we developed a simple synthetic route to the sulfonamide derivatives **IIa** from compound **VI**,⁶⁾ which is the intermediate of imazosulfuron.¹⁾

Compounds **IIb** and **IIc** were readily prepared by the oxidation with *m*-chloroperbenzoic acid (mCPBA) of **IIa**.¹⁾

1.1.1 Typical synthesis of 2-ethylthioimidazo [1,2-*a*] pyridine-3-sulfonamide **IIa** (R = Et)

To a suspension of sodium hydride (60%, 1.2 g, 30 mmol) in DMF (20 ml) was added dropwise a solution of ethanethiol (2.2 ml, 30 mmol) in DMF (15 ml) under ice cooling. After the solution was stirred for 1 hr, 2-chloroimidazo[1,2-*a*]pyridine-3-sulfonamide **VI** (2.3 g, 9.9 mmol) was added, and the resulting suspension was stirred at 115–120°C for 7 hr. The reaction mixture was poured into water (150 ml) and acidified with conc. HCl. The resulting precipitate was collected by filtration, washed with water and dried under reduced pressure to give 2.3 g (8.9 mmol, 90%) of **IIa** (R = Et) as brown solid. mp 169–171°C. ¹H NMR (DMSO-*d*₆) δ ppm: 1.38 (3H, t, *J* = 7.3 Hz), 3.20 (2H, q, *J* = 7.3 Hz), 7.15 (1H, ddd, *J* = 6.8, 6.8, 1.2 Hz), 7.50 (1H, dd, *J* = 8.9, 6.8 Hz), 7.69 (1H, dd, *J* = 8.9, 1.2 Hz), 7.75 (2H, def.s), 8.62 (1H, d, *J* = 6.8 Hz). IR (nujol) ν_{max} cm⁻¹: 3300 (NH), 1332 (SO₂), 1309 (SO₂), 1164 (SO₂), 1147, 756, 740. Anal. Found: C, 41.74; H, 4.20; N, 16.27. Calcd. for C₉H₁₁N₃O₂S₂: C, 42.01; H, 4.31; N, 16.33%.

1.2 General synthesis of sulfonylureas **I**

Sulfonylureas **I** were synthesized by the reaction of the corresponding sulfonamides **II** with carbamates **III**.

1.2.1 Typical synthesis of 1-(2-ethylsulfonylimidazo [1,2-*a*] pyridin-3-ylsulfonyl)-3-(4,6-dimethoxy-pyrimidin-2-yl) urea **6**

To a suspension of 2-ethylsulfonylimidazo[1,2-*a*]pyridine-3-sulfonamide **IIc** (R = Et; 2.0 g, 6.9 mmol) and phenyl *N*-(4,6-dimethoxy-pyrimidin-2-yl)carbamate **III** (R¹ = R² = OMe; 1.9 g, 6.9 mmol) in acetonitrile (20 ml) was added 1,8-diazabicyclo[5.4.0]-7-undecene (1.1 g, 6.9 mmol) and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into ice water (300 ml) and acidified with conc. HCl. The resulting precipitate was collected by filtration, washed with water and ether, and dried under reduced pressure to give 2.5 g (5.7 mmol, 83%) of **6** as a colorless solid. mp 197–199°C. ¹H NMR (DMSO-*d*₆) δ

¹ Studies on Sulfonylureas with Fused Heterocycles (Part 4). For Part 3, see Ref. 3.

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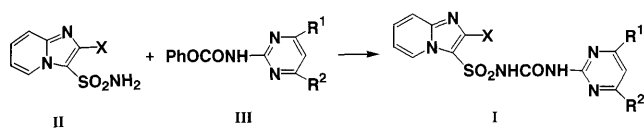


Fig. 2 Synthesis of sulfonylureas I.

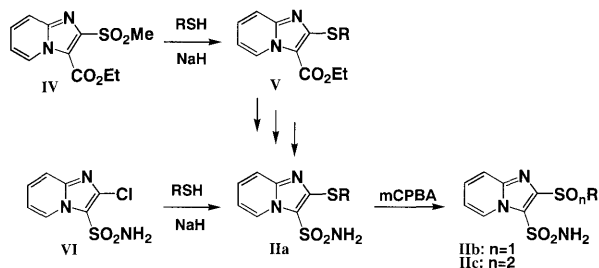


Fig. 3 Synthetic routes to sulfonamides II.

ppm: 1.17 (3H, t, $J=7.4$ Hz), 3.59 (2H, q, $J=7.4$ Hz), 3.96 (6H, s), 6.01 (1H, s), 7.50 (1H, ddd, $J=7.0, 7.0, 1.2$ Hz), 7.81 (1H, ddd, $J=9.0, 7.0, 1.1$ Hz), 8.01 (1H, dd, $J=9.0, 1.2$ Hz), 9.21 (1H, dd, $J=7.0, 1.1$ Hz), 10.80 (1H, def.s), 13.1 (1H, br). IR (nujol) ν_{\max} cm^{-1} : 3370 (NH), 1720 (C=O), 1318 (SO_2), 1165 (SO_2). Anal. Found: C, 41.01; H, 3.93; N, 17.75, Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_6\text{O}_7\text{S}_2$: C, 40.85; H, 3.86; N, 17.86%.

2. Herbicidal Activity

2.1 Greenhouse test for pre-emergence

Plastic pots (10 cm in diameter) were filled with sterilized sandy clay loam soil. Seeds of various kinds of plants (see Tables) were sown in the soil at a depth of about 0.5 cm. A solution, which was prepared by dissolving each compound

in acetone (containing 2 v/v% of Tween 20) and bringing the solution to volume in 0.1 v/v% Tween 20, was uniformly sprayed on the soil surface at a specified dose rate. Four weeks after the treatment, the herbicidal activity against each plant was evaluated visually by the following ratings.

Herbicidal effect, 5: 100% control (complete kill), 4: 88 to 99% control, 3: 76 to 87% control, 2: 51 to 75% control, 1: 1 to 50% control, 0: zero% control (no effect).

Phytotoxic effect, 5: 100% damage (complete damage), 4: 50 to 99% damage, 3: 25 to 49% damage, 2: 13 to 24% damage, 1: 1 to 12% damage, 0: zero% damage.

2.2 Greenhouse test for post-emergence

Plastic pots (10 cm in diameter) were filled with sterilized sandy clay loam soil. Seeds of various plants (see Tables) were sown in the soil at a depth of about 0.5 cm. When the plants were grown up to the 3-leaf stage, a solution, which was prepared by dissolving each compound in acetone (containing 2 v/v% of Tween 20) and bringing the solution to volume in 0.1 v/v% Tween 20, was uniformly sprayed on the foliage at a specified dose rate. Three weeks after the treatment, the herbicidal activity against each plant was evaluated visually using the value as mentioned above.

RESULTS AND DISCUSSION

1. Synthesis

The key intermediates, sulfonamide derivatives **IIa**, were synthesized by the reaction of compound **VI** with the corresponding thiols in the presence of more than 2 equivalents of base. It means that deprotonated **VI** could be substituted with thiolate to give **IIa**. Even though the sulfamoyl group at the 3-position was deprotonated in this reaction, it was still

Table 1 Structure, physical properties and herbicidal activities of sulfonylureas.

| No. | R | n | R ¹ | R ² | mp(°C) | Pre-emergence | | | | | | | | Post-emergence | | | | | | | |
|-----|--------------|---|----------------|----------------|---------------|---------------|---|---------------------|---|---|---|---|---|----------------|---|---------------------|---|---|---|---|---|
| | | | | | | Injury | | Herbicidal Activity | | | | | | Injury | | Herbicidal Activity | | | | | |
| | | | | | | a | b | c | d | e | f | g | h | a | b | c | d | e | f | g | h |
| 1 | Me | 0 | OMe | OMe | 183-187 | 0 | 0 | 1 | 0 | 4 | 1 | 2 | 2 | 0 | 0 | 1 | 1 | 3 | 4 | 1 | 0 |
| 2 | Me | 1 | OMe | OMe | 186-188 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 1 | 3 | 3 | 0 | 0 | 0 |
| 3 | Me | 2 | OMe | OMe | 199-203 | 0 | 1 | 3 | 3 | 4 | 5 | 2 | 1 | 1 | 1 | 3 | 3 | 4 | 4 | 3 | 1 |
| 4 | Et | 0 | OMe | OMe | 171-174 | 0 | 0 | 2 | 0 | 4 | 2 | 0 | 1 | 0 | 1 | 2 | 1 | 2 | 3 | 1 | 1 |
| 5 | Et | 1 | OMe | OMe | 179-180 | 0 | 0 | 1 | 0 | 4 | 1 | 1 | 1 | 0 | 0 | 1 | 2 | 3 | 2 | 1 | 1 |
| 6 | Et | 2 | OMe | OMe | 197-199 | 0 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 2 |
| 7 | <i>n</i> -Pr | 0 | OMe | OMe | 171-173 | 0 | 0 | 1 | 0 | 4 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 2 | 1 | 0 |
| 8 | <i>n</i> -Pr | 1 | OMe | OMe | 139-142 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 2 | 2 | 1 |
| 9 | <i>n</i> -Pr | 2 | OMe | OMe | 184-189 | 0 | 0 | 3 | 1 | 4 | 2 | 3 | 0 | 0 | 1 | 3 | 2 | 2 | 3 | 3 | 0 |
| 10 | <i>i</i> -Pr | 0 | OMe | OMe | 170-173 | 0 | 0 | 0 | 0 | 4 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 2 | 2 | 1 | 1 |
| 11 | <i>i</i> -Pr | 1 | OMe | OMe | 148-151 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| 12 | <i>i</i> -Pr | 2 | OMe | OMe | 180-184 | 0 | 1 | 4 | 2 | 4 | 4 | 2 | 3 | 0 | 1 | 4 | 2 | 2 | 3 | 1 | 1 |
| 13 | Ph | 0 | OMe | OMe | 154-159(dec.) | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 2 | 1 | 0 |
| 14 | Ph | 1 | OMe | OMe | 120-125(dec.) | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 2 | 1 | 0 |
| 15 | Ph | 2 | OMe | OMe | 205-208(dec.) | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0 |
| 16 | Et | 2 | OMe | Cl | 165-169 | 0 | 0 | 1 | 1 | 2 | 3 | 1 | 0 | 0 | 1 | 2 | 2 | 1 | 5 | 1 | 1 |
| 17 | Et | 2 | Me | Me | 198-201(dec.) | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 1 | 1 | 2 | 2 | 1 | 3 | 1 | 2 | 1 |

a: *Triticum aestivum* L. cv Nourin No.4 b: *Avena fatua* L. c: *Alopecurus myosuroides* Huds.
d: *Bromus tectorum* L. e: *Matricaria chamomilla* L. f: *Sinapis arvensis* L.
g: *Stellaria media* (L.) Cyr. h: *Chenopodium album* L. var. *centrorubrum* Makino

Table 2 Herbicidal activity (post-emergence) of TKM-19 and metribuzin.

| Compound | Dose (g/ha) | Injury | Herbicidal Activity | | | | | | |
|------------|-------------|--------|---------------------|---|---|---|---|---|-----------------|
| | | | a | b | c | d | e | f | g |
| TKM-19 | 400 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 2 |
| | 100 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 1 |
| | 25 | 0 | 4 | 4 | 4 | 4 | 4 | 4 | 1 |
| | 500 | 1 | 3 | 5 | 4 | 5 | 5 | 5 | - ¹⁾ |
| Metribuzin | 250 | 1 | 1 | 2 | 1 | 5 | 5 | 5 | - ¹⁾ |
| | 125 | 0 | 0 | 2 | 1 | 2 | 5 | 4 | - ¹⁾ |

1): not examined a: *Triticum aestivum* L. cv Nourin No.4
 b: *Avena fatua* L. c: *Alopecurus myosuroides* Huds. d: *Bromus tectorum* L.
 e: *Matricaria chamomilla* L. f: *Sinapis arvensis* L. g: *Stellaria media* (L.) Cyr.
 h: *Chenopodium album* L. var. *centrorubrum* Makino

able to increase the reactivity against nucleophilic attack at the 2-position.

Compounds **IIa** can be oxidized with one and two equivalent of mCPBA to give **IIb** and **IIc**, respectively. Sulfonamides **II** easily reacted with **III** to give **I**. Structures and physical properties of **I** are shown in Table 1.

2. Herbicidal Activity

As shown in Table 1, the herbicidal activity of sulfonylureas varied with the oxidation stage of sulfur atom and the substituent R at the 2-position.

In comparison with the oxidation stage of sulfur atom, sulfonyl compounds showed higher activity than sulfinyl and sulfenyl compounds. Alkylsulfonyl groups enhanced herbicidal activity especially against grass weeds including *Bromus tectorum* L. which is rampant in wheat fields. The relative order of activity with R was Et > Me > *i*-Pr > *n*-Pr, Ph.

Most of the compounds synthesized didn't show phytotoxicity to wheat by both pre- and post-emergence applications.

Among the substituents (R¹, R²) on the pyrimidine ring, dimethoxy compounds exhibited a potential activity. Compounds **16** and **17** showed less activity than **6**.

From these findings, 1-(2-ethylsulfonylimidazo[1,2-*a*]pyridin-3-ylsulfonyl)-3-(4,6-dimethoxypyrimidin-2-yl) urea **6** (TKM-19), which had the best combination of substituents and oxidation stage of sulfur atom, was selected for further evaluation as the promising compound (Table 2).

TKM-19 showed an excellent herbicidal activity against grass weeds as well as broadleaf weeds by post-emergence application at the rate of 25 g/ha. On the other hand, high

safety to wheat was evident even at the rate of 400 g/ha. TKM-19 showed more potential herbicidal activity against grass weeds and higher safety against wheat than metribuzin.

In conclusion, our study indicated that sulfonylureas containing 2-alkyl (especially ethyl) sulfonylimidazo[1,2-*a*]pyridine moiety showed a potential herbicidal activity against grass and broadleaf weeds, particularly against *Bromus tectorum* L., which is difficult to be controlled with herbicides on the market, with an excellent selectivity for wheat by pre- and post-emergence applications.

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要 約

イミダゾ[1,2-*a*]ピリジン部分を有するスルホニル尿素系化合物の合成と除草活性*

伊藤滋之, 太田一成, 山脇孝博, 石田泰雄
 イミダゾ[1,2-*a*]ピリジン環を有するスルホニル尿素系化合物の畑雑草に対する除草活性を調べたところ, 縮合環上2位にメチルスルホニル基を有する化合物が興味ある活性を示した。そこでその類縁化合物を合成し, それらの除草活性を調べた。また, 類縁体合成の過程で鍵中間体の簡便な合成法を見出した。合成したスルホニル尿素系化合物の中で1-(2-エチルスルホニルイミダゾ[1,2-*a*]ピリジン-3-イルスルホニル)-3-(4,6-ジメトキシピリジン-2-イル)ウレア (TKM-19) は出芽前, 出芽後処理のどちらでも高い除草活性を示し, 小麦に対して選択性を有していた。また, このものは既存の除草剤では防除が困難なウマノチャヒキに対しても卓効を示した。

* 縮合ヘテロ環スルホニル尿素に関する研究 (第4報)