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Tetrahydrophthalimidobenzoates as protoporphyrinogen IX oxidase inhibiting herbicides

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ABSTRACT

Tetrahydrophthalimidobenzoates are a class of protoporphyrinogen oxidase herbicides acting on the protoporphyrinogen oxidase enzyme. After the discovery of compound **1**, a series of novel tetrahydrophthalimidobenzoate derivatives were designed and synthesized, and some synthesized compounds exhibited good herbicidal activity in controlling broadleaf weeds. The structure activity relationship of the synthesized compounds was also determined. Substitution of a fluorine atom at the 4-position of benzene ring resulted in better herbicidal activity than that with non-substitution. Among the conjunctional groups, methylene group with more methyl substitutions was the best. Consequently, compound **9** was found as the best of all in the synthesized compounds, and it is worthy of being developed not only because of its good herbicidal activity against broadleaf weeds with selectivity for maize, but also for its low toxicity to mammals.

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1. Introduction

Herbicides are used widely across the world in protecting crops from competition from weeds [1]. Protoporphyrinogen oxidase (Protox) herbicides act on the protoporphyrinogen oxidase enzyme, which catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX. Inhibiting the Protox enzyme causes protoporphyrinogen IX to build up and leach out of the chloroplast, where protoporphyrinogen IX gets converted to protoporphyrin IX. In the presence of light, protoporphyrin IX generates singlet oxygen, which peroxidates the unsaturated bonds of fatty acids found in cell membranes. The end result of this peroxidation process is the loss of membrane integrity and leakage, pigment breakdown, and necrosis of the leaf that results in the death of the plant. This is a relatively fast process, with leaf symptoms such as a flaccid wet appearance observed within hours of plant exposure to the Protox herbicides under sunlight [2].

The first commercial inhibitor of Protox is the nitrofen that belongs to diphenyl ether (DPE) compound family, which was introduced in 1963 by Rohm & Hass [3]. Some years later, oxadiazon, as the first member in the 1,2,4,5-tetrasubstituted benzene (HTSB) compound family, was introduced in 1968 by Rhone-Poulenc [4]. Nitrofen and oxadiazon (Fig. 1) represent the earliest examples of Protox inhibiting herbicides. Although their chemical structures are completely different from each other, they share a common mode of action, inhibition of the protoporphyrinogen oxidase enzyme, though this was not known until the late 1980s.

Several early inventions of HTSB herbicide in 1960s had a significant impact on our understanding of the structure–activity of this kind herbicides. Rhone-Poulenc first introduced 3-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2(3H)-one in 1965 [5]. Further lead optimization at the phenyl ring soon led to the discovery in 1968 of the 2,4-dichloro-5-isopropoxyphenyl substitution pattern of the herbicide oxadiazon [6], which was then introduced into the market for the control of annual grasses and broadleaf weeds in pre-emergence or early post-emergence treatment by Rhone-Poulenc in 1969. The second cyclic imide herbicide, chlorophthalim, was introduced by Mitsubishi in 1972. The 2,4-dihalo-5-substituted pattern at the aromatic ring would become the basis for much of the 2,4,5-trisubstituted phenyl tetrahydrophthalimide research in this area of chemistry. A breakthrough discovery was the increasing biological activity caused by the replacement of chlorine by fluorine at the 2-phenyl position. In 1976, DuPont introduced the first example of a 2-fluoro-4-chlorophenyl tetrahydrophthalimide Protox inhibitor [7] (Fig. 2). In the next decade, the dramatic increase in biological activity had influenced on the lead optimization work in the HTSB area, such as the discovery of the 4-chloro-2-fluorophenyltetrahydrophthalimide herbicide S-23142 [8]. Flumiclorac pentyl was commercialized by Sumitomo as the first cyclic imide herbicide in Europe as early as 1993. It controlled annual broadleaf weeds such as *Abutilon*, *Euphorbia*, *Chenopodium*, *Datura*, *Ambrosia* and *Xanthium* at 30–60 g a.i. ha^{-1} in post-emergence treatment in soybean and maize fields, in particular, it showed excellent activity against *Abutilon* at progressed leaf stage at 60 g a.i. ha^{-1} [9–11].

In our previous work [12], a few tetrahydrophthalimidobenzoates were synthesized, in which 1-ethoxy-3-methyl-1-oxobut-3-en-2-yl 2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)benzoate (**1**, Fig. 3) was found to have good herbicidal activity, especially for the control

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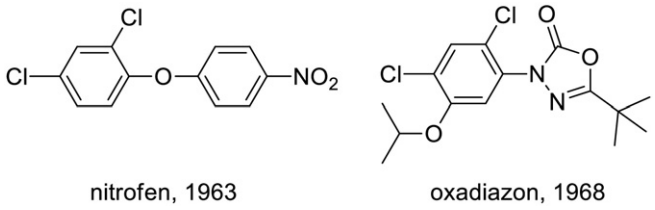

Fig. 1. Chemical structures of two early examples of Protox inhibitors.

of broadleaf weeds. It controlled *Abutilon*, *Amaranthus*, *Chenopodium*, *Polygonum*, *Potulaca*, *Solanum* and *Zinnia* at 30–45 g a.i. ha^{-1} in post-emergence treatment in soybean and maize fields. In order to find a better chemical compound with better herbicidal activity, further optimizations on **Cpd. 1** was carried out.

2. Materials and methods

2.1. Synthesis

2.1.1. Chemicals

Chemicals were purchased from Sigma-Aldrich Co. (Shanghai, China), Sinopharm Chemical Reagent Co., Ltd. (Shenyang, China) and Nanjing Boke Medicine Technology Development Co., Ltd. (Jiangsu, China). Anhydrous solvents were commercially available and stored over molecular sieves. Silica gel (100–140 meshes) used in column chromatography was afforded by Qingdao Haiyang Chemical Co., Ltd. (Shandong, China). NMR spectra were recorded on a Varian Mercury-300 or Varian Mercury-600 spectrometer. Tetramethylsilane (TMS) was used as the internal standard for ^{1}H NMR (0 ppm). Melting points were measured with a X-4 digital display melting point apparatus (Gongyi Yuhua Co., Ltd., Henan, China) and were uncorrected. IR spectra were recorded on a Nicolet Impact-400 spectrophotometer (Nicolet Co., USA). Elemental analyses were performed on a Yanaco Corder MT-3 elemental analyzer (Yanaco Co. Ltd., Japan).

2.1.2. Genaral procedure for the synthesis of tetrahydrophthalimidobenzoic acids (Scheme 1)

i) Methyl 5-amino-2-chlorobenzoate (Step a)

A solution of methyl 2-chloro-5-nitrobenzoate (2.16 g, 10 mmol) in tetrahydrofuran (20 mL) and water (20 mL) was cooled in an ice-bath. Zinc powder (3.25 g, 50 mmol) was added and concentrated hydrochloric acid (10 mL, 100 mmol) was then added dropwise into the mixture within 30 min. The reaction mixture was stirred at room temperature for 1 h, the solvent was then removed under vacuum. The residue was diluted with ethyl acetate (100 mL), washed with water (2 × 30 mL), saturated aqueous sodium carbonate (30 mL), saturated brine (30 mL), dried over anhydrous magnesium sulfate, and concentrated to give the crude methyl 5-amino-2-chlorobenzoate as an orange oil (1.0 g, 54%), which was used for the next reaction without further purification.

ii) 5-Amino-2-chlorobenzoic acid (Step b)

To a mixture of methyl 5-amino-2-chlorobenzoate (3.71 g, 20.0 mmol) in tetrahydrofuran (40 mL), was added a solution of sodium hydroxide (0.88 g, 22.0 mmol) in water (40 mL), and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was diluted with water (20 mL) and ethyl acetate (20 mL). The organic layer was washed with water (3 × 20 mL) and the combined aqueous layer was acidified to pH 2–3 with concentrated hydrochloric acid. The resulting precipitate was filtered off, washed with water and dried to afford 5-amino-2-chlorobenzoic acid (1.73 g, 51%) as an off-white solid, which was used for the next reaction without further purification.

iii) 2-Chloro-5-(3,4,5,6-tetrahydrophthalimido)benzoic acid (Step c)

A mixture of 5-amino-2-chlorobenzoic acid (1.72 g, 10.0 mmol) and 3,4,5,6-tetrahydrophthalic anhydride (1.52 g,10.0 mmol) in acetic acid (2.0 mL) was refluxed for 1 h. After cooling to room temperature, the precipitate in the reaction mixture was filtered off, washed with water and dried. 2-Chloro-5-(3,4,5,6-tetrahydrophthalimido)benzoic acid (2.80 g, 92%) was received as a light brown solid, m. p. 235–237 °C (lit [13]. 231–233 °C).

2-Chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)benzoic acid were synthesized in a similar manner as above.

2.1.3. General procedure for the synthesis of tetrahydrophthalimidobenzoates (Scheme 2)

2.1.3.1. Procedure A. Potassium carbonate (1.2 mmol) was added into the solution of tetrahydrophthalimidobenzoic acid (1.0 mmol) in DMF (2 mL) at room temperature. After stirring for 10 min, 2-chloroacetate (3.0 mmol) was added in and the resulting mixture was stirred at room temperature for 8 h. The reaction mixture was poured in to water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with aqueous sodium bicarbonate (20 mL) and brine (2 × 20 mL), dried over anhydrous magnesium sulfate, concentrated onto silica gel, and eluted by column chromatography to give the target compound.

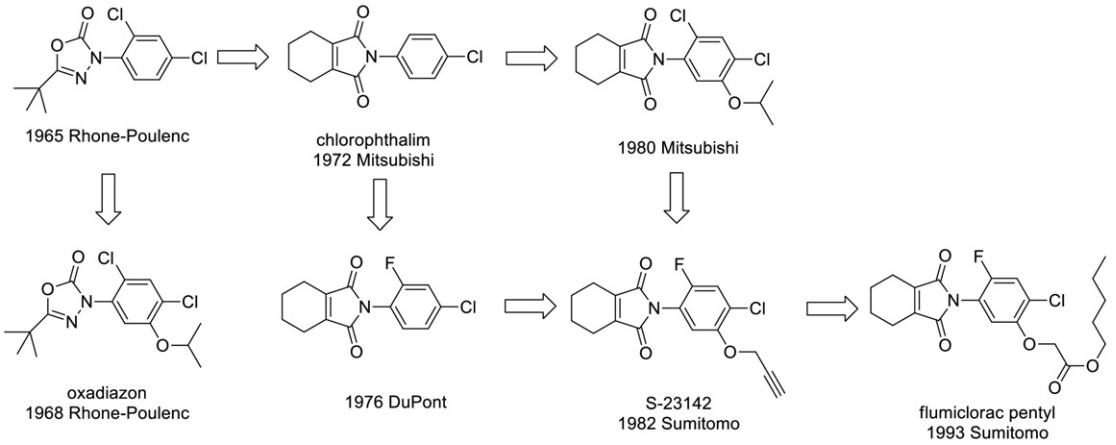

Fig. 2. Incorporation of the 2,4-dihalo-5-alkoxy aromatic pattern of oxadiazon into new phenyl tetrahydrophthalimide ring systems.

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