Synthesis and herbicidal activity of a pentafluorosulfanyl analog of trifluralin

Dong Sung Lim, Jung Sup Chol, Chwang Siek Pak and John T. Welch*

Department of Chemistry, University at Albany, 1400 Washington Avenue, Albany, New York 12222, USA
† Bioorganic Science Division, Korea Research Institute of Chemical Technology, Yuseong-Ku, Jang-Dong 100, Taejeon 305–600, Korea

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The synthesis of 2,6-dinitro-4-pentafluorosulfanyl-1,N,N-dipropylaniline, 2, was achieved in a straightforward manner from commercially available 1-nitro-4-pentafluorosulfanylbenzene. In post-emergence screening 2 was found to be approximately twice as potent as trifluralin with the same general spectrum of activity. In contrast, in pre-emergence tests, 2 was nearly 5 fold more potent against quackgrass and crabgrass. Given the existing structure–activity-relationship for adverse properties of the dinitroaniline herbicides 2, it is proposed to have properties quite comparable to that of trifluralin 1. The steric demand and symmetry of the SF5 group can be compared and contrasted with both the t-butyl and trifluoromethyl groups. The volume of the SF5 group is slightly less than that of a t-butyl group5,6 and therefore considerably greater than that of a trifluoromethyl group (CF3). However the electrostatic surface presented by SF5 is comparable to CF3 in that it presents a highly fluorinated surface, a pyramid of electron density as opposed to the inverted cone of density associated with CF3 group. When the electronic influence of a SF5 group is compared with that of a CF3 group, the electron withdrawing effect, as assessed by the carbon 1s photoelectron spectra, is similar in magnitude.7,8 However, the electronegativity of the SF5 group has been proposed to be as high as 3.65 in comparison to a value of 3.36 for the CF3 group.9 In electrophilic substitution reactions the Hammet σp value for SF5 was determined to be 0.68 in contrast to σp value for CF3 of 0.54.9 This has been further refined to a σp value for SF5 of 0.55 and a σp value of 0.11 in contrast to σp value for CF3 of 0.39 and a σp value of 0.12.10 The decreased resonance and increased inductive contributions are consistent with the electronic effects observed in the estimation of electronegativity.7,8 The organic chemistry of the SF5 group, previously reviewed6,11 and extensively developed by Gard, has only recently come under more widespread investigation with the ready availability of previously difficultly accessible building blocks or reagents.14 To date pentafluorosulfanyl arenes have found applications in liquid crystalline displays15,16 and in agrochemicals.4,17 However, given the absence information about on a side-by-side comparison of the relative efficacy of the SF5 group substituted for a CF3 group in dinitroaniline herbicides we have prepared 2 and tested it alongside trifluralin against a representative panel of plant species.

Materials and Methods

1. Analytical instruments

Infrared (IR) spectra were obtained on a Perkin-Elmer 1600 Series FTIR spectrometer. All 1H, 13C and 19F NMR spectra were recorded on a Gemini-300 MHz NMR spectrometer at 300, 75.43 and 282.20 MHz respectively. The chemical shifts of 1H and 13C NMR are reported relative to the residual signal of CDCl3 (for 1H: δ=7.24; 13C: δ=77.00) or C6D6 (for 1H: δ=7.15; 13C: δ=128.00). All 13C NMR spectra were acquired in the proton-decoupled mode. 19F NMR spectra are reported relative to the resonance assigned to CFC13 (δ=0). Thin layer chromatography was performed with silica gel F254 (Merck) as the adsorbent on 0.2 mm thick, plastic-backed plates. The chromatograms were visualized under UV (254 nm) or by staining with a KMnO4 aqueous solution followed by heating. Column chromatography was performed using silica gel 60 (70–230 mesh, Merck). Melting points were determined in open capillaries using a Büchi 510...
melting point apparatus and are reported uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

2. **Synthesis**

2.1. **1-Amino-4-pentafluorosulfanylbenzene (4)**

To a solution of 1-nitro-4-pentafluorosulfanylbenzene (Air Products and Chemicals Inc.) 3 (1 eq, 5.00 g, 20 mmol) in ethanol (200 mL) was slowly added HBr (0.600 g, 2.12 mmol) in conc. H\(_2\)SO\(_4\) (11 mL) at 0°C. The reaction mixture was stirred for 30 min at room temperature. The reaction mixture was quenched with water (20 mL) then made basic (pH 10) by the addition of saturated aqueous sodium carbonate. The reaction mixture was extracted with dichloromethane and water. The combined organic layers were dried over MgSO\(_4\) and then concentrated. The crude product was purified by chromatography to afford the colorless liquid product in 67% (1.30 g) yield. 1H NMR (300 MHz, CDCl\(_3\), ppm): \(\delta\) 8.16 (s, 2H), 2.94 (t, 4H, \(J_{HF} = 7.4\) Hz), 1.59 (sxt, 4H, \(J_{HF} = 7.3\) Hz), 0.86 (t, 6H, \(J_{HF} = 7.4\) Hz); 19F NMR (282 MHz, CDCl\(_3\), ppm): \(\delta\) 80.67 (m, 1F, \(J_{SF, SF} = 150.0\) Hz, SF), 63.81 (d, 4F, \(J_{SF, SF} = 150.0\) Hz, SF). 13C NMR (75 MHz, CDCl\(_3\), ppm): \(\delta\) 143.9, 142.8 (t, \(J_{CF} = 22.8\) Hz), 140.9, 127.7 (quintet, \(J_{CF} = 4.6\) Hz), 54.0, 20.7, 11.1; Anal. Calcd for C\(_5\)H\(_4\)F\(_2\)N\(_2\)S\(_2\): C, 36.64; H, 4.10. Found : C, 36.60; H, 4.09.

2.2. **1-Bromo-4-pentafluorosulfanylbenzene (5)**

To a solution of 1-amino-4-pentafluorosulfanylbenzene (1 eq, 1.5 g, 6.84 mmol) in acetonitrile (7 mL) was added HNO\(_3\) (fuming) (11 mL) at 0°C. The reaction mixture was stirred for 30 min at room temperature. The reaction mixture was quenched with water (20 mL) then made basic (pH 10) by the addition of saturated aqueous sodium carbonate. The reaction mixture was extracted with dichloromethane and water. The combined organic layers were dried over MgSO\(_4\) and then concentrated. The crude product was purified by chromatography to afford the white solid of product in 96% (4.25 g, 10.3 mmol) yield. 1H NMR (300 MHz, CDCl\(_3\), ppm): \(\delta\) 8.9 Hz), 7.80 (dd, 1H, \(J_{HF} = 8.9, 2.5\) Hz); 19F NMR (282 MHz, CDCl\(_3\), ppm): \(\delta\) 77.30 (m, 1F, \(J_{SF, SF} = 152.6\) Hz, SF), 62.98 (d, 4F, \(J_{SF, SF} = 152.6\) Hz, SF).

2.3. **1-Bromo-2-nitro-4-pentafluorosulfanylbenzene (6)**

To a solution of 1-bromo-2-nitro-4-pentafluorosulfanylbenzene (1 eq, 0.600 g, 2.12 mmol) in conc. H\(_2\)SO\(_4\) (11 mL) at 0°C was slowly added HNO\(_3\) (fuming) (4.8 mL) at room temperature. The reaction mixture was stirred for 1 hr at room temperature. The reaction mixture was extracted with dichloromethane and water. The organic layer was washed with saturated sodium bicarbonate solution (2 times). The organic layer was dried over MgSO\(_4\) and then concentrated. The crude product was purified by chromatography to afford the white solid in 73% (0.250 g, mp = 95–96.5°C) yield. 1H NMR (300 MHz, CDCl\(_3\), ppm): \(\delta\) H 8.28 (s, Ar); 19F NMR (282 MHz, CDCl\(_3\), ppm): \(\delta\) 77.30 (m, 1F, \(J_{SF, SF} = 152.6\) Hz, SF), 62.98 (d, 4F, \(J_{SF, SF} = 152.6\) Hz, SF).

2.4. **2-Bromo-3-dinitro-5-pentafluorosulfanylbenzene (7)**

To a solution of 1-bromo-2-nitro-4-pentafluorosulfanylbenzene (1 eq, 0.300 g, 0.91 mmol) in conc. H\(_2\)SO\(_4\) (4.8 mL) was slowly added HNO\(_3\) (fuming) (4.8 mL) at room temperature. The reaction mixture was stirred for 18 hr at 80°C. The reaction mixture was extracted with dichloromethane and water. The organic layer was washed with saturated sodium bicarbonate solution (2 times). The organic layer was dried over MgSO\(_4\) and then concentrated. The crude product was purified by chromatography to afford the yellow-orange solid product in 99% (0.167 g, mp = 66–68°C) yield. 1H NMR (300 MHz, CDCl\(_3\), ppm): \(\delta\) H 8.16 (s, 2H), 2.94 (t, 4H, \(J_{HF} = 7.4\) Hz), 1.59 (sxt, 4H, \(J_{HF} = 7.3\) Hz), 0.86 (t, 6H, \(J_{HF} = 7.4\) Hz); 19F NMR (282 MHz, CDCl\(_3\), ppm): \(\delta\) 80.67 (m, 1F, \(J_{SF, SF} = 150.0\) Hz, SF), 63.81 (d, 4F, \(J_{SF, SF} = 150.0\) Hz, SF); 13C NMR (75 MHz, CDCl\(_3\), ppm): \(\delta\) 143.9, 142.8 (t, \(J_{CF} = 22.8\) Hz), 140.9, 127.7 (quintet, \(J_{CF} = 4.6\) Hz), 54.0, 20.7, 11.1; Anal. Calcd for C\(_5\)H\(_4\)F\(_2\)N\(_2\)S\(_2\): C, 36.64; H, 4.10. Found : C, 36.60; H, 4.09.

3. **Evaluation of herbicidal activity**

Seeds of eight grass species, corn, wheat, rice, shattercane, barnyardgrass, large crabgrass, quack grass, and fall panicum, as well as seven broad leaf species, soybean, cotton, black nightshade, yardgrass, large crabgrass, quack grass, and fall panicum, as well as seven broad leaf species, are required for seed germination. The results are shown in Figs. 2–5.

Various concentrations of trifluralin (1) and 2,6-dinitro-4-pentafluorosulfanyl-N,N-dipropylaniline (2) dissolved in 50% acetone solution containing 0.1% Tween 20 were sprayed onto the surface of soil at 1 day after planting for pre-emergence application, or solutions of 2 were sprayed onto the plants at 12 days after planting for post-emergence application. The spray volume was equivalent to 5000 L ha\(^{-1}\), and the spray pressure was 50 kPa using a laboratory spray gun. After the spray application, the pots were placed in a vented cabinet until the treated chemical solution was dried, and then the pots were returned into the same greenhouse. The plants were watered from overhead to the soil surface as required, except the first day after the chemical treatment. The plants were allowed to grow for 2 weeks and then the degree of plant damage was estimated by percent (%) visual injury ranging from 0% (no injury) to 100% (complete inhibition of growth). The results are shown in Figs. 2–5.
Results

2,6-Dinitro-4-pentafluorosulfanyl-\(N,N\)-dipropylaniline (2), the pentafluorosulfanyl analog of trifluralin was prepared from commercially available 1-nitro-4-pentafluorosulfanylbenzene (Fig. 1).

Reduction with either zinc and acetic acid or sodium sulfide resulted in only low or incomplete reduction, however, treatment with iron powder and HCl led to isolation of aniline 4 in 96% yield. Diazotization and dediaziative bromination formed the desired 1-bromo-4-pentafluorosulfanylbenzene 5 in 67% yield. Conversion of 5 to 2 followed the procedures of Kwiatkowski.18) Nitration was effected successfully stepwise in good yield, resulting in 6 and 7, 99% and 73%, respectively. Displacement of the bromide by dipropylamine formed 2 in a nearly quantitative yield.

The herbicidal activity of both trifluralin 1 and the pentafluorosulfanyl analog 2 is illustrated in the bar graphs below. The activity is reported in terms of percent inhibition of growth based on primary screening and is derived from the results of single experiments as is normal in our primary screening procedures.

Discussion

1. Synthesis

The synthesis of 2 reported above differs from that described by...
Thrasher in that Thrasher’s synthesis was dependent upon the use of silver (II) fluoride for fluorination of a chloro,dinitro-arenedisulfide precursor. The ready availability of the 1-nitro-4-pentafluorosulfanylbenzene (3) obviated the need for expensive and aggressive fluorinating reagents, making the synthesis of 2 and other analogs conveniently accessible to practicing synthetic chemists.

2. Herbicidal activity
A side-by-side comparison of the spectrum of herbicidal activity of 1 and 2, clearly demonstrates that in post-emergence applications, the pentafluorosulfanyl replacement of the trifluoromethyl group affords no apparent advantage. However in pre-emergence applications, the herbicidal performance of 2 is greater than the parent trifluralin as assessed by visual injury estimation. When parent trifluralin was applied at 4 and 1 kg/ha, crop injury for corn in pre-emergence was 100% (complete death) and 20% damage, respectively. Compared to the parent trifluralin as assessed by visual injury estimation. When parent trifluralin, the crop injury was much less in crops treated with 2. For example, crop injury for corn on treatment with 2 at 2.68 kg/ha resulted only 10% growth inhibition. Therefore, the observation that crops were relatively more tolerant of 2 than trifluralin, might at least account for the differential selectivity to the parent trifluralin 1. Although trifluralin 1 effectively controlled the several weeds at 4 kg/ha application rates, the herbicidal activity of 2 toward grass weeds was greater than that of parent trifluralin. At 0.67 kg/ha application rate, the herbicidal activity of 2 afforded the same level of control as trifluralin at 4 kg/ha. Moreover, herbicidal activity in barnyardgrass and crabgrass at 0.168 kg/ha resulted in over 90% damage. In conclusion, our results indicate that herbicidal activity of 2 on pre-emergence application, in terms of crop injury and weed control, is nearly 5 fold greater than the parent trifluralin 1.

3. Mechanism of action
The mechanism of action of dinitroaniline herbicides is thought to occur in the vicinity of Thr239 of α-tubulin19) with interactions of the electron dense areas of the inhibitor with charged Arg2 essential.

The electron rich surface of trifluralin is associated with the trifluoromethyl group. A comparison of the electrostatic potential surface models of 1 and 2 clearly indicates that a similar interaction is possible with the pentafluorosulfanyl containing dinitroaniline 2.

4. Carcinogenicity
The utility of dinitroaniline herbicides has always been clouded by the known carcinogenicity of dinitroaromatics. To facilitate an understanding of the important physico-chemical properties that might be associated with carcinogenicity, a quantitative-structure activity relationship model has been developed.20) In this model although it was determined that while hydrophobicity, as measured by the octanol/water partition coefficient, had a major influence on the potency of carcinogens, the principal predictor of carcinogenicity was the magnitude of the HOMO-LUMO gap. In a comparison of 1 and 2, the ClogP values of 5.322 and 5.636 respectively, are very close. Likewise the HOMO-LUMO gap was calculated to be 0.303 and 0.132 (B3LYP 6-31G**) respectively for 1 and 2. The parity of these values suggests that this model predicts little difference in carcinogenicity between the two compounds.

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