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Synthesis of fipronil sulfide, an active metabolite, from the parent insecticide fipronil

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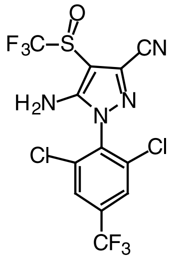
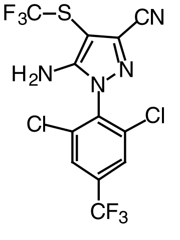
Abstract—A convenient procedure for the synthesis of fipronil sulfide, one of several active metabolites identified from the insecticide fipronil, has been developed. Reduction of fipronil with trifluoroacetic anhydride–sodium iodide in acetone, followed by flash chromatography afforded fipronil sulfide in 60% yield and >99.9 percent purity. This represents the first direct synthesis of this key metabolite from fipronil. © 2001 Elsevier Science Ltd. All rights reserved.

Fipronil (**1**), a second-generation *N*-phenylpyrazole insecticide and is a potent nanomolar inhibitor of the gamma-aminobutyric acid (GABA) gated chloride channel, exhibits high specificity toward insects and is effective against insects with resistance to first-generation insecticides.[1] Fipronil is effective against a host of insect pests of crops including grasshoppers, boll weevils, rice insects, termites, houseflies, fruit flies and thrips.[2–6]



Fipronil (**1**)



Fipronil Sulfide (**2**)

Fipronil is prone to both metabolic transformations and abiotic degradations to several key products: a sulfone metabolite, a desulfinyl photoproduct, and amide product resulting from the hydrolysis of the cyano group and a sulfide metabolite. Fipronil sulfone is the major metabolite identified in mice,[6] and has been identified as a major metabolite in field studies when applied to cotton crops.[3] Metabolism to the sulfone can be considered a bioactivation event, since the sulfone has been shown to be more potent than fipronil in freshwater fish, freshwater invertebrates and birds.[6] Desulfinyl fipronil is the principal photoproduct identified on plants and soils and equipotent to fipronil in toxicity to mice and houseflies.[7,8] The amide product is a result of the hydrolysis of the cyano group and has been identified in soil samples.[9] The sulfide metabolite (**2**), albeit a minor metabolite, has been identified and was found to be more potent than fipronil, the sulfone metabolite and the desulfinyl metabolite against boll weevils when applied topically.[10]

As part of our study aimed at determining the rank-order toxicity of fipronil and its metabolites against Louisiana crayfish (*Procambarus clarkii*), we required substantial quantities of the known fipronil metabolites. Although we were able to prepare sufficient amounts of the sulfone and desulfinyl metabolites based on literature precedents, we sought a more efficient procedure for the production of fipronil sulfide (**2**). The synthesis of this metabolite has been previously reported by Hainzl et al., who prepared the sulfide as an intermediate towards the synthesis of the sulfone metabolite, utilizing an appropriately functionalized aniline as the starting material in a three-step protocol.[7] This procedure was rather laborious and utilized the non-commercially available trifluoromethylsulfenyl chloride. An alternate procedure for the synthesis of the sulfide metabolite has also been reported, based on the reaction of fipronil disulfide dimer (lacking the -CF_3 group) with sulfoxylate anion radical precursors, followed by a trifluoromethylation reaction.[11]

Keywords: fipronil; sulfoxide; reduction; sulfide.

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Although each of these protocols are attractive in both scope and utility, we chose to investigate the direct reduction of fipronil sulfoxide to its corresponding sulfide, since an ample number of novel synthetic procedures are available for this synthetic transformation.[12] We investigated a wide array of sulfoxide deoxygenation reactions, including protocols utilizing phosphorous pentasulfide,[13] chlorotrimethylsilane–NaI,[14] Mg–methanol,[15] boron trifluoride etherate–NaI[16] and oxalyl chloride–NaI.[17] All of these procedures failed to produce the sulfide using the reported standard conditions.

However, the use of trifluoroacetic anhydride (TFAA)–sodium iodide (NaI)[18] in acetone afforded the sulfide product in 60% yield after 10 h at 0°C (optimized conditions), along with unreacted fipronil. The sulfoxide reduction was sensitive to the molar equivalents of TFAA used. For example, 2 equiv. of anhydride afforded 30 sulfide product and 65% unreacted fipronil, after stirring for 24 h at 0°C, while 4 equiv. of anhydride, or greater, resulted in the production of more polar reaction products in addition to a small amount of sulfide and unreacted fipronil. The optimal ratio of fipronil/TFAA/NaI was determined to be 1:3:3. Temperature and solvent also impacts the course of the reduction. The use of acetonitrile, rather than acetone, under identical conditions, affords the sulfide in only 20% yield in addition to polar by-products. Reactions performed at ambient temperatures lead to a decreased yield in the amount of sulfide. Although fipronil and the sulfide product co-elute on silica gel using a variety of mobile phases, we have found that they can be effectively resolved using 20 ethyl acetate/80% hexanes. This procedure represents an efficient and cost-effective method for the production of fipronil sulfide (**2**) in gram quantities from commercially available fipronil (**1**).

Synthesis of fipronil sulfide (2)

Fipronil (1.0 mmol, 437 mg) and sodium iodide (3.0 mmol, 450 mg) were dissolved in anhydrous acetone (5 mL) and cooled to 0°C under an argon atmosphere and trifluoroacetic anhydride (0.423 mL, 3.0 mmol) was added dropwise over 5 min. After stirring for 10 h at 0°C, the reaction mixture was quenched by the addition of dilute aqueous sodium thiosulfate, until the reaction mixture turned colorless. The solution was extracted three times with ethyl acetate (30 mL), washed successively with water (20 mL) and brine (20 mL) and the organic extract was dried over sodium sulfate and evaporated to yield a crude residue. Purification by flash chromatography (silica gel, 50×300 mm packed column, 20 ethyl acetate/80% hexanes) yielded the sulfide product (>99.9% purity, 60% yield). R_f fipronil = 0.42, R_f fipronil sulfide = 0.47. Mp: 169–170°C (lit: 169–171°C[7]). The remainder of the column effluent represented unreacted fipronil. HPLC analysis with synthetic standards, courtesy of Rhone Poulenc, confirmed the sulfide purity, R_t fipronil, 9.0 min, R_t fipronil sulfide, 13.3 min. (Alltech Econosil C_{18} reverse phase, 250×4.6×10 μM, 2.5 mL/min, 50% CH_3CN, 50% H_2O, 280 nm).

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