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Synthesis of Some Arylsulfur Pentafluoride Pesticides and Their Relative Activities Compared to the Trifluoromethyl Analogues

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Abstract: Examples of pesticides containing an arylsulfur pentafluoride group were made and their biological activities compared to the corresponding trifluoromethyl analogues. A phenylsulfur pentafluoride analogue of the insecticide fipronil, screened against a resistant strain of *Musca domestica*, showed higher activity than the corresponding trifluoromethyl analogue.

Keywords: Arylsulfur pentafluorides · Biological activities · Insecticide · Pesticide · Resistant strain

Introduction

Trifluoromethyl-substituted aromatics have been found to be particularly useful for a range of applications in the Life Sciences. Incorporation of fluorine into molecules of interest often bestows unique properties to these compounds. These properties can translate into improved biological performance through interactions at the desired target site or by increased metabolic stability, uptake and distribution.

Like many companies in the late 1980s, ICI Agrochemicals was finding interesting activities with compounds bearing a trifluoromethyl group. This led us to investigate other related fluorine-containing analogues that might, through their different physical and electronic properties, further enhance the biological effects observed with the trifluoromethyl-substituted materials.

Literature searches revealed some pioneering work on the synthesis of arylsulfur pentafluorides carried out in the 1960s at the research laboratories of DuPont by Sheppard [1], who also reported on some of the properties that this substituent provides. Key observations by Sheppard's group were that arylsulfur pentafluorides are typically stable entities and have similar physical and electronic properties to trifluoromethylaromatics. Probably due to the lack of an accessible, efficient process to these materials incorporation of the sulfur pentafluoride substituent into potentially bioactive molecules had been little explored for over 30 years.

In order to test the biological effect of replacing a trifluoromethyl substituent with a sulfur pentafluoride group in compounds known to possess fungicidal, herbicidal or insecticidal activity we wanted to prepare a selection of compounds that have a variety of modes of actions. Examples of the syntheses of some of the compounds prepared by us have been reported [2] in detail.

Fluorination of Aryl Disulfides to Arylsulfur Pentafluorides

Our initial attempts at repeating the process described by Sheppard [1] to make arylsulfur pentafluorides gave inconsistent results and we wanted to devise a procedure that would be more amenable to scaling up. A procedure suitable to make 100 g amounts of materials that we required was developed by our process chemists, Williams and Foster [3]. The key improvement was preparing the arylsulfur trifluoride at ambient temperature from the diaryl disulfide and silver difluoride in an inert solvent, such as nonane, then heating this with further silver difluoride in a one-pot reaction and closely monitoring the conversion of the easily hydrolysed trifluoride into the much more stable pentafluoride. The reactions were typically conducted at atmospheric pressure under an atmosphere of dry nitrogen in vessels fabricated from copper. Using this procedure, we produced 3-nitro and 4-nitrophenylsulfur pentafluorides from the corresponding diaryl disulfides, for example as shown in Scheme 1.

The nitrophenylsulfur pentafluorides were reduced in high yield to the corresponding anilines, for example using hydrogen and Raney nickel. Further elaboration of these anilines gave us the building blocks for the synthesis of the required target pesticides (Schemes 2 and 3).

More recently, an alternative process to make arylsulfur pentafluorides using elemental fluorine has been reported by Bowden and co-workers [4], as well as some further chemical transformations of these molecules.

Synthesis and Insecticidal Activity of Arylsulfur Pentafluoride Compounds

During a research programme aimed at producing insecticides for the public health market, we discovered a series of insecticidal N-trifluoromethylphenyl pyrimidinones, *e.g.* **1** and **2**. The compounds were

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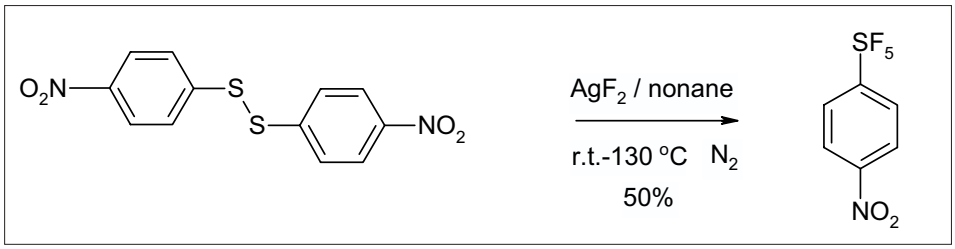
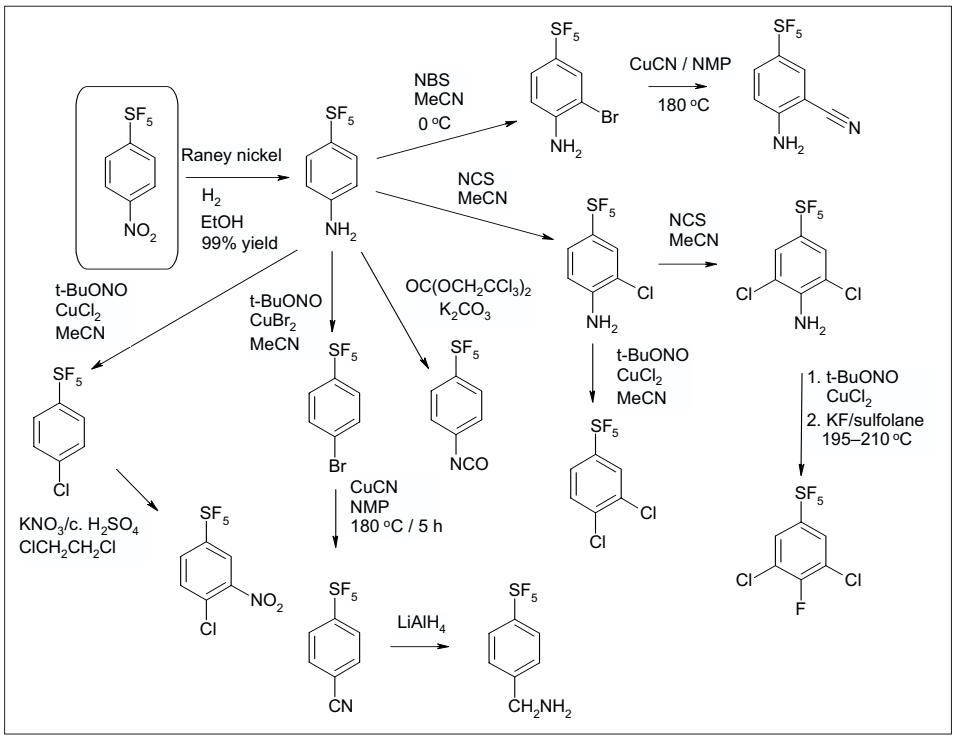
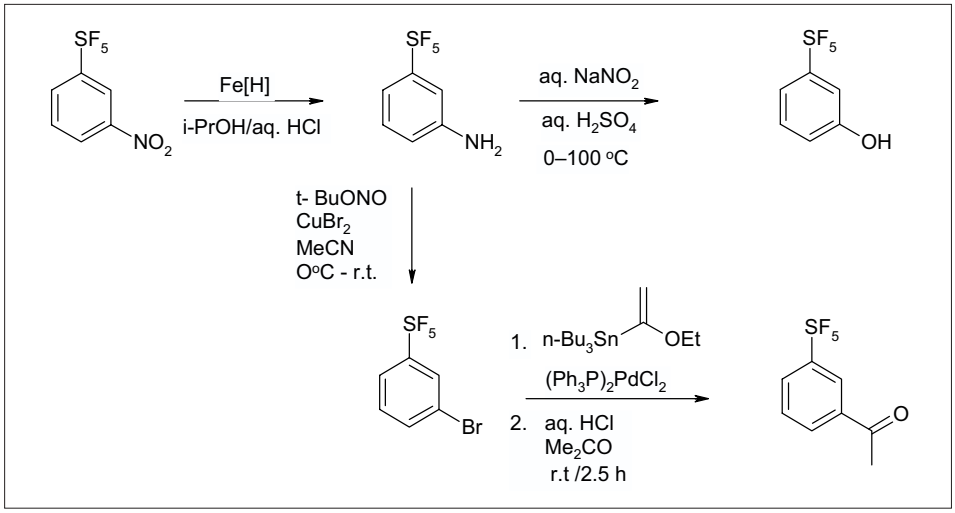


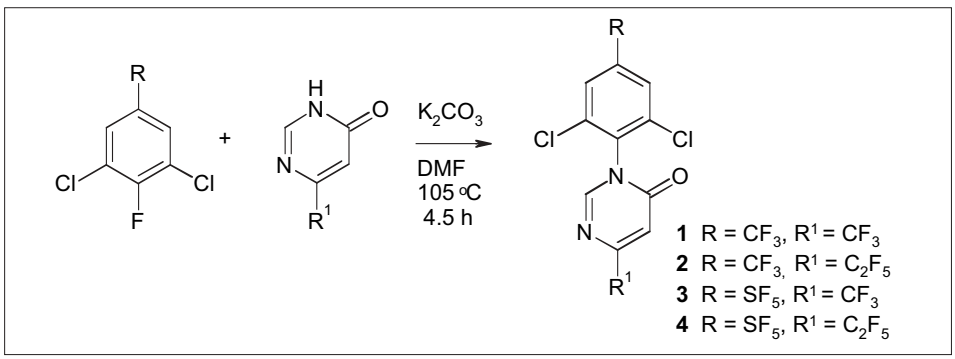
Scheme 1. Synthesis of 4-nitrophenylsulfur pentafluoride



Scheme 2. Chemical transformations of 4-nitrophenylsulfur pentafluoride



Scheme 3. Chemical transformations of 3-nitrophenylsulfur pentafluoride



Scheme 4. Synthesis of N-phenyl pyrimidinone insecticides

particularly active against laboratory strains of houseflies (*Musca domestica*) and German cockroaches (*Blattella germanica*). However, later testing against field strains of these pests revealed an inherent weakness that was found to be associated with an inherited resistance to another insecticide previously used commercially, dieldrin, which had the same mode of action as the N-aryl pyrimidinones. As part of our programme, we decided to investigate whether the corresponding phenylsulfur pentafluorides **3** and **4** could overcome this problem. As shown in Scheme 4, synthesis of the required targets was achieved using chemistry previously optimised for the corresponding trifluoromethylphenyl analogues.

As shown in Table 1, whilst **3** and **4** were more active than **1** and **2** against susceptible houseflies and cockroaches, they were also much less active against the dieldrin-resistant strain. Similarly, the laboratory strain of cockroaches was also more susceptible to the sulfur pentafluoride compounds than the corresponding trifluoromethylphenyl analogues.

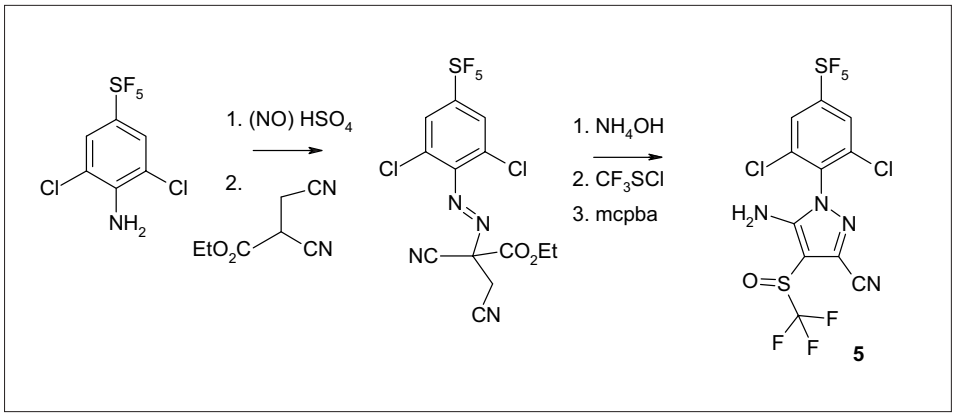
At the time of our studies, we noticed similarities between our series of pyrimidinones and some pyrazole analogues that had been claimed as insecticides in the patent literature [5]. We prepared some representative compounds from the patents as well as the analogue **5** of the insecticide fipronil, the synthesis of which is shown in Scheme 5, which contained a sulfur pentafluoride group rather than a trifluoromethyl substituent in the phenyl ring as disclosed in the patented examples.

As shown in Table 2, we screened the sulfur pentafluoride and trifluoromethyl analogues against both susceptible and resistant strains of houseflies and susceptible cockroaches. Surprisingly, the sulfur pentafluoride compound **5** was not only more active than the trifluoromethyl analogue but showed no loss of potency towards the resistant strain of housefly, in contrast to the trifluoromethyl compound fipronil.

Table 1. Relative activity of insecticidal compounds **1–4**

Compounds 1–4	R = SF_5 EC_{50} values (ppm)			R = CF_3 EC_{50} values (ppm)		
	Musca (S)[a]	*Musca* (R)[a]	*Blattella* (S)[a]	*Musca* (S)[a]	*Musca* (R)[a]	*Blattella* (S)[a]
$R^1 = CF_3$	0.4	300	1	2.5	>1000	17
$R^1 = C_2F_5$	0.3	>1000	1	1	>1000	6

[a](R) indicates a strain resistant to dieldrin and (S) is a susceptible strain.



Scheme 5. Synthesis of SF_5 analogue of the insecticide fipronil

Table 2. Comparison of the insecticidal activity of fipronil with its SF_5 analogue **5**

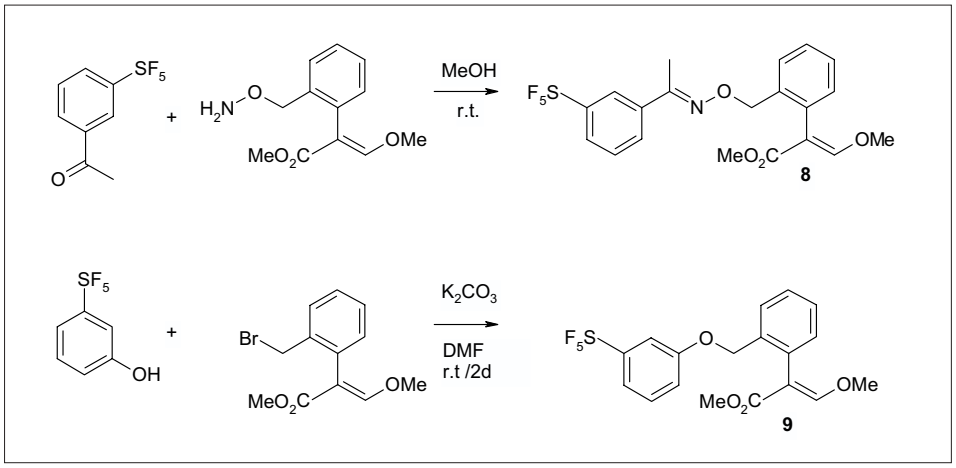
SF_5 Analogue **5** Relative potency		Fipronil Relative potency		SF_5 Analogue **5** Relative potency	Fipronil Relative potency
Musca (S)[a]	*Musca* (R)[a]	*Musca* (S)[a]	*Musca* (R)[a]	*Blattella* (S)[a]	*Blattella* (S)[a]
1	1	0.1	0.01	1	0.5

[a](R) indicates a strain resistant to dieldrin and (S) is a susceptible strain.

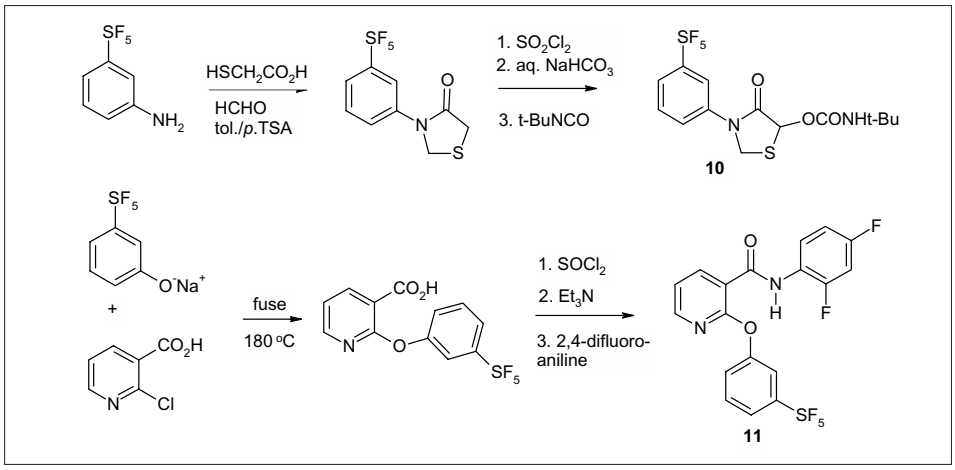
Synthesis and Fungicidal Activity of Arylsulfur Pentafluoride Compounds

We extended our research programme to include making arylsulfur pentafluoride compounds as potential plant fungicides. Two examples, **8** and **9**, we made were analogues of trifluoromethyl compounds from the strobilurin family of fungicides that had shown interesting activities. The synthetic routes we used are illustrated in Scheme 6.

As shown in Tables 3 and 4, although the sulfur pentafluorides retained some activity against the fungal pathogens in the tests, there was insufficient improvement upon the activity of the trifluoromethyl



Scheme 6. Synthesis of SF_5 strobilurin fungicide analogues



Scheme 7. Synthesis of SF_5 analogues of CF_3 herbicidal amides and carbamates

analogues to progress the compounds further.

Synthesis and Herbicidal Activity of Arylsulfur Pentafluoride Compounds

We also synthesised a range of arylsulfur pentafluorides as potential herbicides. The routes that we chose are given in Schemes 7 and 8 and typically follow those that had been devised for the corresponding trifluoromethyl analogues. Comparative screening for herbicidal activity of sulfur pentafluorides alongside their trifluoromethyl counterparts gave disappointing results for compounds **10**, **12** and **13**. No particularly useful improvements in the selectivities towards the crop species were observed for these sulfur pentafluorides and potencies against the weed species were typically a fifth to a tenth of the corresponding trifluoromethyl analogues. However, **11**, an analogue of the commercial herbicide diflufenican, did show levels of potency and selectivity that closely matched the trifluoromethyl analogue but we did not proceed further towards commercialisation with this compound.

Conclusions

Comparisons of pesticidal screening data obtained from trifluoromethyl and sulfur pentafluoride analogues showed that in some biological systems the differences in, for example, the electronic and steric properties of the sulfur pentafluoride group compared to a trifluoromethyl group can lead to improvements in potency and to influence more subtle effects such as the potential to overcome cross-resistance. At the time of our research programme, one major limitation we encountered in progressing arylsulfur pentafluoride analogues for use as commercial agrochemicals was the high

Table 3. Comparison of fungicidal activity of SF_5 and CF_3 oxime-ether strobilurin analogues

SF_5 Analogue **8**			CF_3 Analogue		
Fungal species: Potency relative to CF_3 analogue			Fungal species: Relative potency		
Wheat powdery mildew (Erad.)[a]	Wheat glume blotch (Prot.)[a]	Wheat brown rust (Erad.)[a]	Wheat powdery mildew (Erad.)[a]	Wheat glume blotch (Prot.)[a]	Wheat brown rust (Erad.)[a]
0.2	5	0.2	1	1	1

[a]Erad. indicates an eradicant test; Prot. indicates a protectant test.

Table 4. Comparison of fungicidal activity of SF_5 and CF_3 phenyl ether strobilurin analogues

SF_5 Analogue **9**			CF_3 Analogue		
Fungal species: Potency relative to CF_3 analogue			Fungal species: Relative potency		
Wheat powdery mildew (Erad.)[a]	Wheat glume blotch (Prot.)[a]	Wheat brown rust (Erad.)[a]	Wheat powdery mildew (Erad.)[a]	Wheat glume blotch (Prot.)[a]	Wheat brown rust (Erad.)[a]
1	2	0.2	1	1	1

[a]Erad. indicates an eradicant test; Prot. indicates a protectant test.

Table 5. Herbicidal activity of SF_5 analogue **11**

SF_5 Analogue **11** Pre-emergence test (Relative Potency)									
Weeds (Dicotyledons)							Crops (Monocotyledons)		
	POLAV	GALAP	AMARE	SETVI	BRAPP	PANDI	ZEAMX	ORYSA	TRZAW
SF_5	1	1	1	0.8	0.9	0.9	0	0	0
CF_3	1	1	1	1	1	1	0	0	0

POLVA = *Polygonum avencie* (bindweed), GALAP = *Gallium aparine* (cleavers), AMARA = *Amaranthus retroflexus* (pigweed), SETVI = *Setaria viridis* (green foxtail), BRAPP = *Brachiaria platphylla* (broadleaf signal grass), PANDI = *Panicum dichotomiflorum* (fall panicum), ZEAMX = *Zea mays* (maize), ORYSA = *Orysa sativa* (rice), TRZAW = *Triticum aestivum* (winter wheat).

cost of incorporating a SF_5 group into molecules relative to other substituents.

More recent patent publications by Huber, Chern and co-workers [6] indicate an interest in arylsulfur pentafluorides for the animal health sector.

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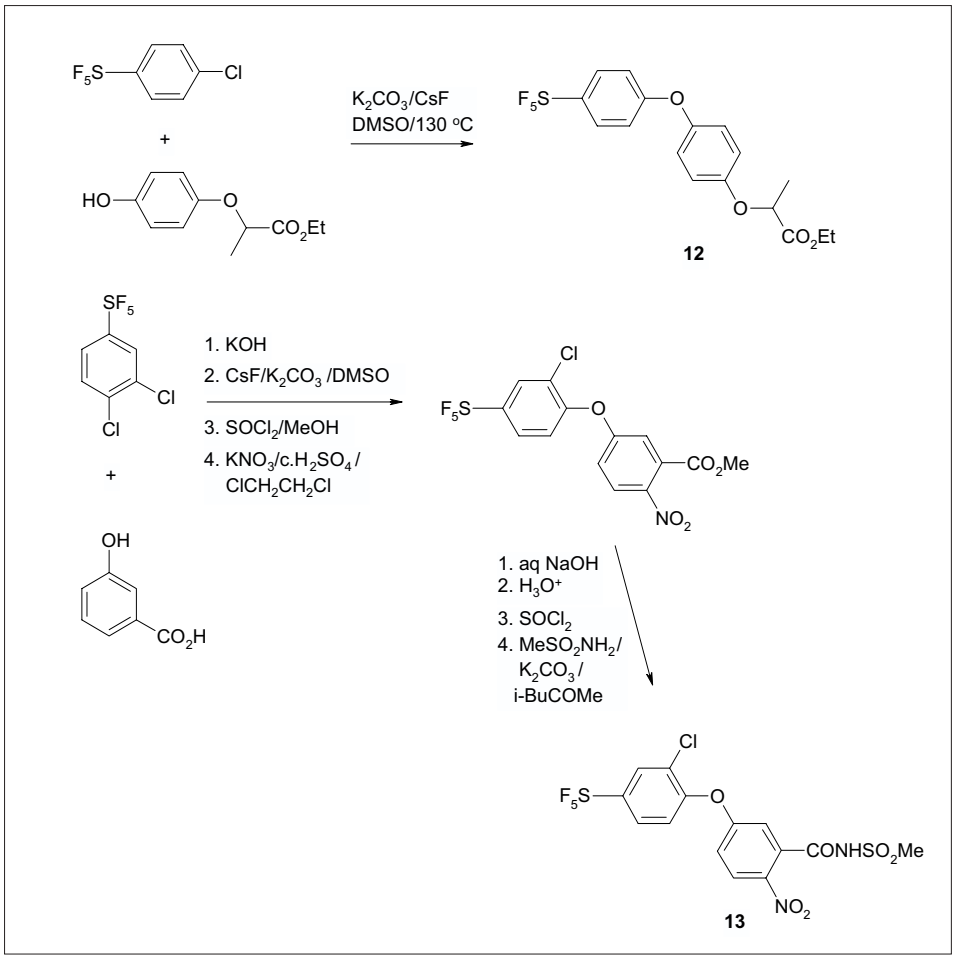

Scheme 8. Synthesis of SF_5 analogues of CF_3 herbicidal diphenyl ethers