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Novel diamide insecticides: Sulfoximines, sulfonimidamides and other new sulfonimidoyl derivatives

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ABSTRACT

Novel insecticidal anthranilamides with elaborated sulfur-containing groups are described. The synthesis of compounds with functional groups such as sulfoximines and scarcely reported groups such as sulfonimidoyl hydrazides and hydroxylamides, their in vitro and in vivo biological activity as well as their physical properties are reported.

The insecticidal diamides constitute a new class of crop protection agents, active against phytophagous insects.[1] They are activators of the ryanodine receptors (RyRs) which are ubiquitous calcium channels that regulate the Ca^{2+} release from intracellular stores located in the sarcoplasmic reticulum.[2] Due to the intrinsic selectivity for the insect receptor over the mammalian counterpart, the diamides have excellent toxicity and ecotoxicity profiles. The exceptionally high intrinsic activity is reflected in very low doses in agricultural practice, from about 5 g (!) to 100 g AI/ha (active ingredient/hectare) to fully control insect pests.

The first generation diamides recently introduced to the market comprise the phthalamide flubendiamide[3] (**1**) discovered by Nihon Nohyaku and the anthranilamide chlorantraniliprole (**2**) discovered by DuPont (Fig. 1).[1b] The compounds control lepidopteran and coleopteran pests. The reduced activity against hemipteran pests may be due to differences in the target RyRs across the species, selective metabolism by some insects or insufficient availability of the active ingredient (AI) at the target site (pharmacokinetics). In a discovery program at Syngenta, we realized that modifying the physical properties of the diamides had a significant impact on the insecticidal spectrum as well as on the plant and soil distribution of the AI, opening the door to applications against hemipteran pests (sucking pests such as aphids) and to soil and seed treatment applications. The second generation diamide cyantraniliprole (**3**) discovered by DuPont exhibits a similar enlarged spectrum.[4]

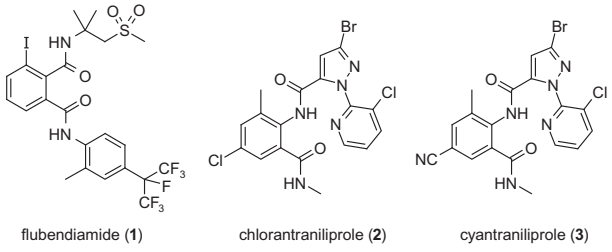

Figure 1. 1st and 2nd generation diamide insecticides.

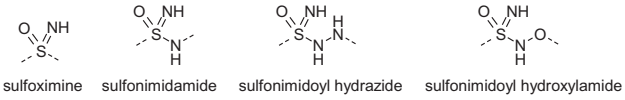

Figure 2. Elaborated sulfur-containing groups reported in this paper.

In this report we describe the synthesis and biological activity of novel diamide insecticides comprising elaborated sulfur-containing groups such as sulfoximines, sulfonimidamides and other sulfonimidoyl derivatives (Fig. 2).

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The sulfoximine functionality[5,6] has been known since 1946 and has been used in medicinal and agrochemical chemistry as a robust bioisosteric replacement for more traditional groups.[7] It has usually been synthesized from the corresponding sulfoxide by harsh methods such as sodium azide in concentrated sulfuric acid[8] or with hazardous electrophilic nitrogen sources such as *O*-mesityl sulfonyl hydroxylamine.[9] New methods have been described recently which allow the flexible and mild introduction of the sulfoximine group in the presence of various other sensitive functional groups. The Armstrong modification[10] of the electrophilic amination with an oxaziridine originally described by Collet is an expensive but extraordinary mild method for iminating a sulfur atom.[11]

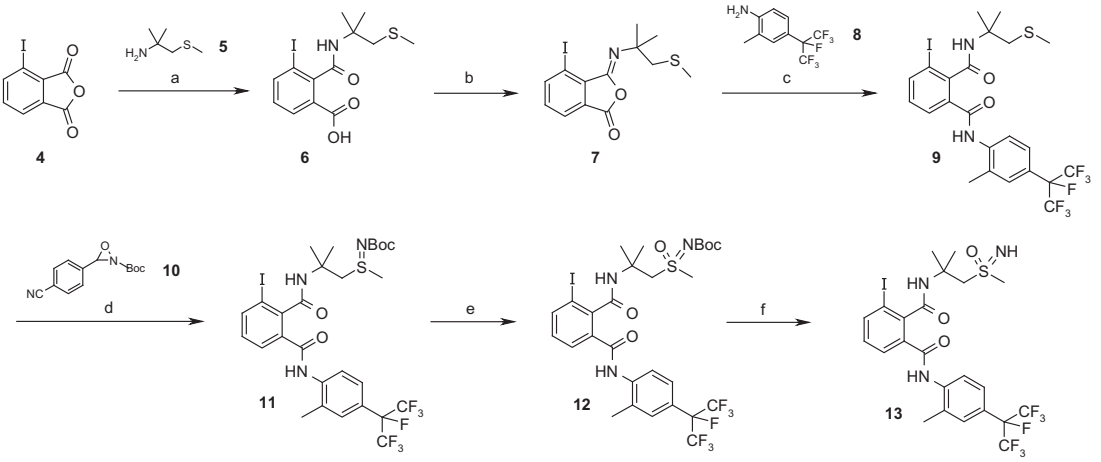
The Cu and Rh catalyzed iminations of sulfides or sulfoxides represent probably the most versatile and useful methods to date for use on the laboratory scale. Of special note here is the seminal paper by Bolm's group,[12] describing the easy imination of sulfoxides or sulfides to give sulfoximines or sulfilimines, respectively, with no substituent at the N atom, in the presence of trifluoroacetamide as a nitrogen source, phenyliodo diacetate, $Rh_2(OAc)_4$ and MgO.

The sulfonimidamide functional group can be seen as the imino analogue of a sulfonamide and is only sparingly described in the literature.[13] The corresponding sulfonimidoyl hydrazides[14] or hydroxylamides,[14a,15] respectively, are hardly known.

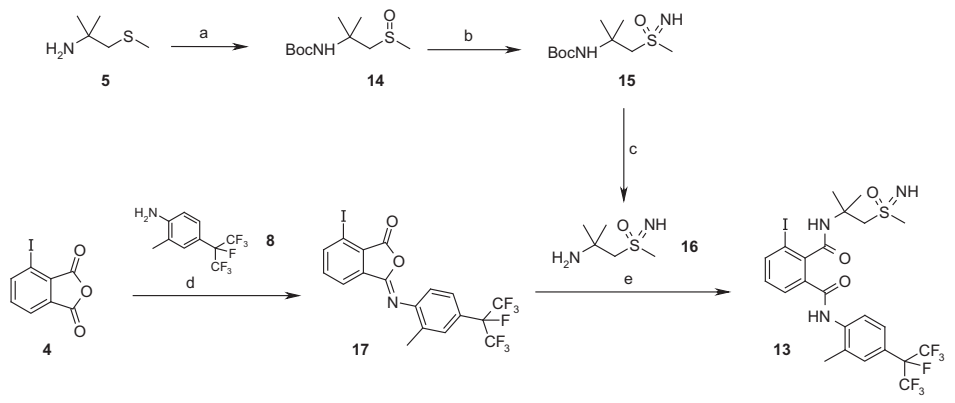
The sulfoximine analogue **13** of flubendiamide **1** was easily prepared by imination of the known sulfide **9**[3] using *N*-Boc-oxaziridine **10** in trifluoroethanol[10] (Scheme 1). The sulfilimine **11** was obtained in 57% yield together with 10% of the corresponding sulfoxide. Oxidation of **11** with $RuO_2/NaIO_4$ followed by *N*-Boc deprotection delivered the NH sulfoximine **13** in good yield. Alternatively, the $Rh_2(OAc)_4$-catalyzed imination of the sulfoxide **14** by Bolm's method[12] delivered the sulfoximine building block **15**, from which the flubendiamide sulfoximine analogue **13** was easily made (Scheme 2).

The same chemistry was applied to the anthranilamide derivatives (Scheme 3). The benzoxazinone intermediates **20** were prepared according to known procedures.[16] The anthranilamides **22** were made by opening the benzoxazinone **20** with the corresponding amino alcohols **21**. Mitsunobu reaction with thioacetic acid[17,18] and saponification of the thioester in the presence of methyl iodide allowed the introduction of the sulfide moiety in **23**, which was elaborated to the sulfoximines **25** according to Bolm's sulfoximination protocol.[12] Compound **25** (R^1 = CN, R^2 = Br, linker is $-C(CH_3)_2CH_2-$) was further derivatized via cyanation and nitration giving **26** and **27**, respectively. A wide range of anthranilamides **25a–o** containing a side chain with a sulfoximine group was prepared (Fig. 3).

The sulfonimidamide building block **33** was made in 7 steps from racemic alaninol **21** in multigram quantities, as depicted in Scheme 4. The sulfur functionality[19] was introduced by a Mitsunobu reaction as described above. Initial oxidation with 2 equiv of SO_2Cl_2[17,20], gave the sulfinyl chloride **29** which was



Scheme 1. Synthesis of sulfoximine **13** using the oxaziridine method. Reagents and conditions: (a) **5**, NEt_3, CH_3CONMe_2, 80%; (b) $(CF_3CO)_2O$, PhMe, quant.; (c) **8**, CH_3CN, 86%; (d) **10**, CF_3CH_2OH, 57% (+10% sulfoxide); (e) $NaIO_4$, RuO_2, H_2O, CH_2Cl_2, 86%; (f) TFA, CH_2Cl_2, 74%.



Scheme 2. Synthesis of sulfoximine **13** using Bolm's methodology. Reagents and conditions: (a) (i) Boc_2O, MeOH, NEt_3; (ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 60%; (b) (i) F_3CCONH_2, $PhI(OAc)_2$, MgO, $Rh_2(OAc)_4$, MeOH; (ii) K_2CO_3, MeOH, 65%; (c) (i) HCl, EtOH; (ii) NaOMe, MeOH, 70%; (d) **8**, $(CF_3CO)_2O$, PhMe, quant.; (e) **16**, CH_3CN, 40%.