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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]

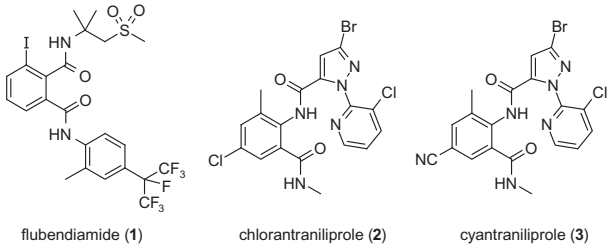

Figure 1. 1st and 2nd generation diamide insecticides.

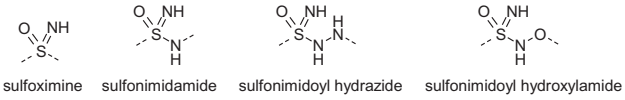

Figure 2. Elaborated sulfur-containing groups reported in this paper.

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]

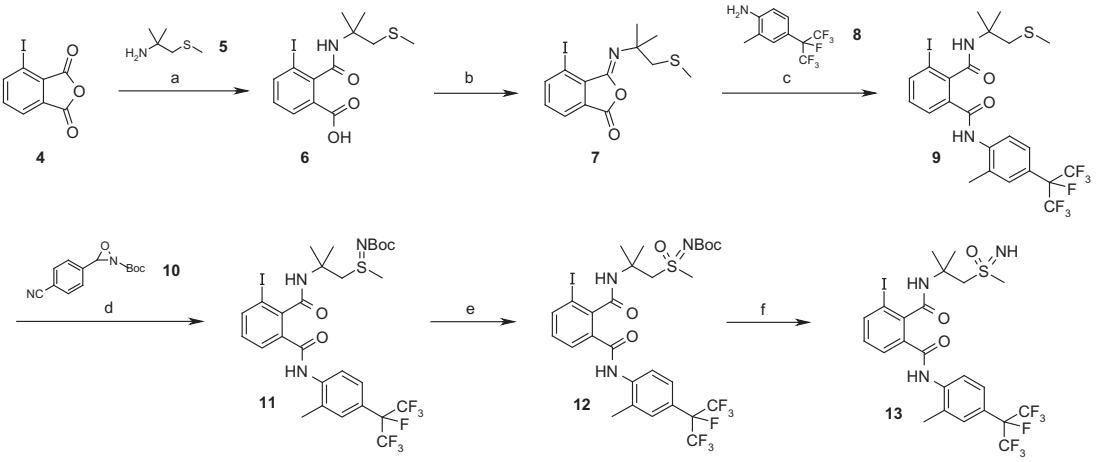
The Cu and Rh catalyzed iminations of sulfides or sulfoxides represent probably the most versatile and useful methods to date for use on the laboratory scale. Of special note here is the seminal paper by Bolm's group,[12] describing the easy imination of sulfoxides or sulfides to give sulfoximines or 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.

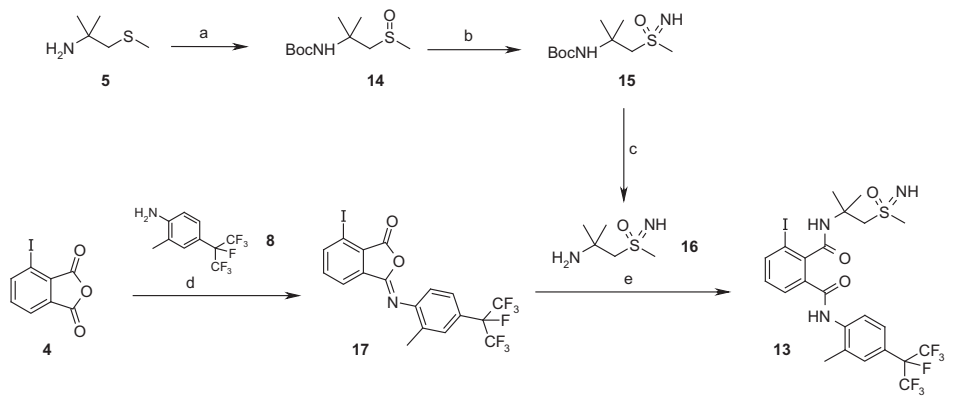
The sulfoximine analogue **13** of flubendiamide **1** was easily prepared by imination of the known sulfide **9**[3] using *N*-Boc-oxaziridine **10** in trifluoroethanol[10] (Scheme 1). The sulfilimine **11** was obtained in 57% yield together with 10% of the corresponding sulfoxide. Oxidation of **11** 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).

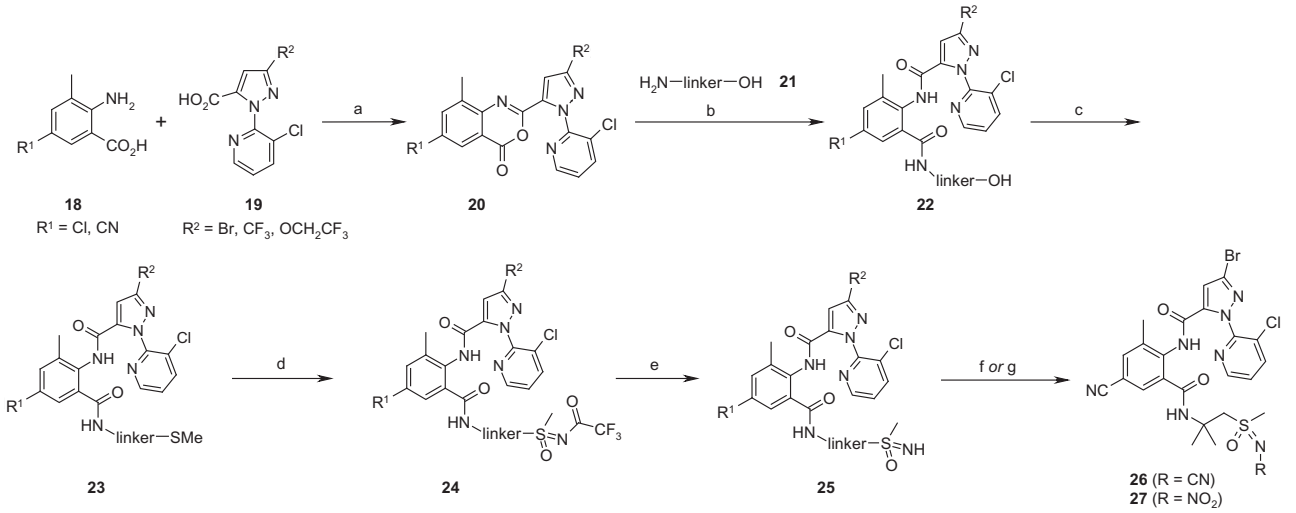
The sulfonimidamide building block **33** was made in 7 steps from racemic alaninol **21** in multigram quantities, as depicted in Scheme 4. The sulfur functionality[19] was introduced by a Mitsunobu reaction as described above. Initial oxidation with 2 equiv of SO_2Cl_2[17,20], gave the sulfinyl chloride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



Scheme 3. Synthesis of anthranilamide derivatives incorporating a sulfoximine motif. Reagents and conditions: (a) MsCl, pyridine, CH_3CN; (b) **21**, THF; (c) (i) BocN = NBoc, PPh_3, AcSH, THF, 0 °C; (ii) MeI, NaOH, MeOH; (d) (i) *m*-CPBA, CH_2Cl_2; (ii) CF_3CONH_2, $PhI(OAc)_2$, $Rh_2(OAc)_4$, MgO, CH_2Cl_2; (e) K_2CO_3, MeOH; (f) BrCN, DMAP, CH_2Cl_2, 97%; (g) HNO_3, H_2SO_4, Ac_2O, CH_2Cl_2, 50%.

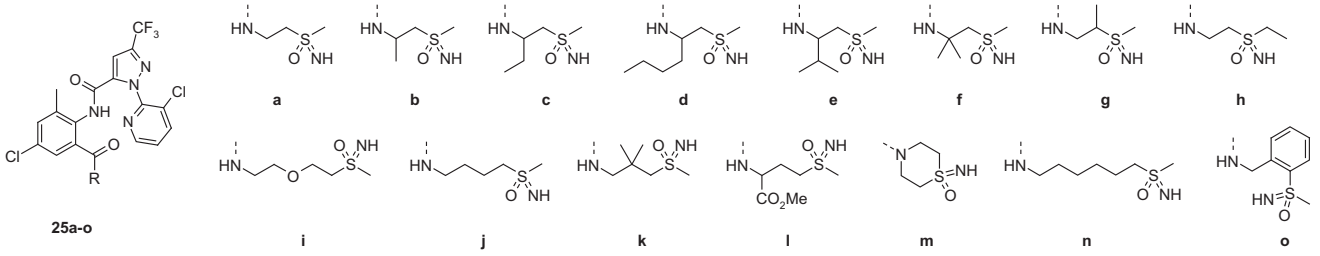
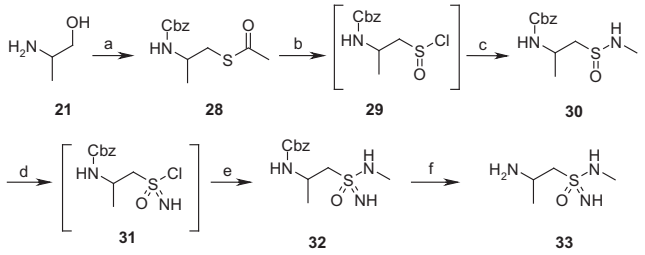
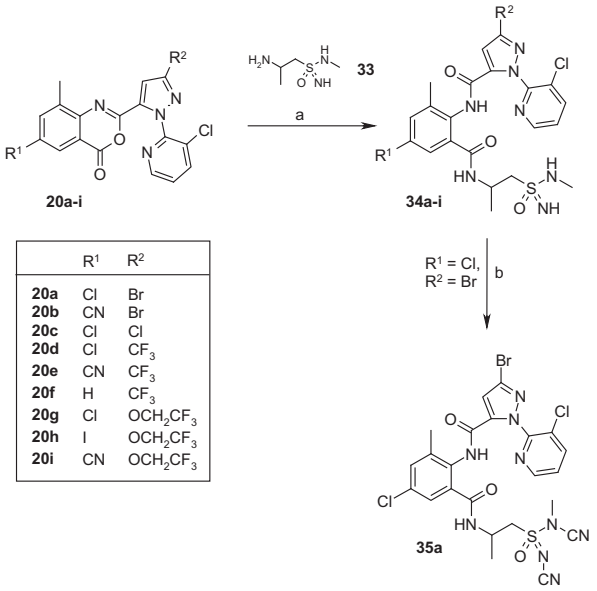


Figure 3. Anthranilamide derivatives with various sulfoximine moieties.



Scheme 4. Synthesis of the sulfonimidamide building block **33**. Reagents and conditions: (a) (i) CbzCl, NEt_3, THF; (ii) diisopropyl azodicarboxylate, PPh_3, AcSH, THF, 46%; (b) SO_2Cl_2, Ac_2O, CH_2Cl_2; (c) H_2NMe, 60% (two steps); (d) *N*-chlorobenzotriazole, THF; (e) NH_3, THF, 0 °C, 63% (two steps); (f) H_2, $Pd(OH)_2$, THF, quant.

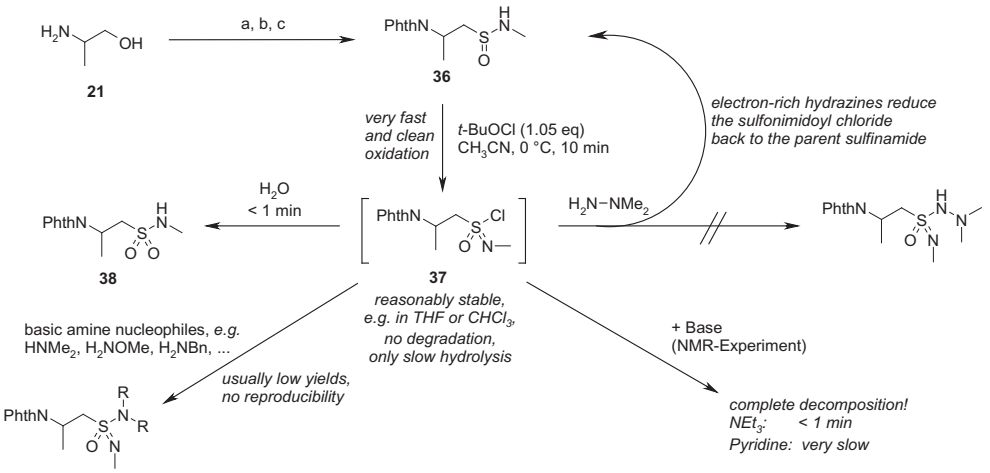
not isolated but directly reacted with methylamine to give the sulfinamide **30**. A second oxidation with *N*-chlorobenzotriazole[21] gave the moisture-sensitive sulfonimidoyl chloride **31** which again was directly reacted with ammonia to give the sulfonimidamide **32** in 63% yield over two steps. Removing the Cbz protecting group by hydrogenolysis using $Pd(OH)_2$ gave the free amino sulfonimidamide **33** which was reacted with different benzoxazinones **20a–i** to give a range of anthranilamide compounds **34a–i** (Scheme 5). The derivative **34a** was further derivatized with BrCN to give the bis-cyano derivative **35a**.



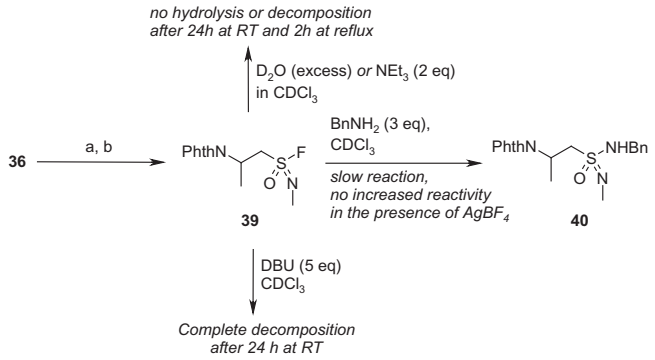
	R^1	R^2
20a	Cl	Br
20b	CN	Br
20c	Cl	Cl
20d	Cl	CF_3
20e	CN	CF_3
20f	H	CF_3
20g	Cl	OCH_2CF_3
20h	I	OCH_2CF_3
20i	CN	OCH_2CF_3

Scheme 5. Anthranilamides incorporating a sulfonimidamide motif. Reagents and conditions: (a) **33**, THF; (b) BrCN, DMAP, CH_2Cl_2, 30%.

Next, we wanted to extend our work to other sulfonimidoyl amide derivatives derived from racemic alaninol **21**, such as sulfonimidoyl hydroxylamides or hydrazides. Preliminary experiments with Cbz as an amino protecting group quickly revealed that its selective removal was not possible without cleaving the N–O bond of the sulfonimidoyl hydroxylamides and therefore, the phthalimide protected sulfinamide **36** was prepared in analogy to **30** (Scheme 6).



Scheme 6. Investigation of the chemical stability of sulfonimidoyl chloride **37**. Reagents and conditions: (a) phthalic anhydride, PhMe, quant.; (b) PPh_3, AcSH, BocN = NBoc, THF, 82%; (c) (i) Ac_2O, SO_2Cl_2, CH_2Cl_2; (ii) H_2NMe, CH_2Cl_2, 83%.



Scheme 7. Synthesis and reactivity of sulfonimidoyl fluoride **39**. Reagents and conditions: (a) *t*-BuOCl, CH_3CN, 0 °C, 10 min; (b) KF, 18-crown-6, CH_3CN, 0 °C to RT, 1 h, 91% (two steps).

The base promoted sulfonylation of amines with sulfonyl chlorides is accepted to proceed through 1,2-elimination of HCl and subsequent addition of the amine on the electrophilic sulfur of the intermediate sulfene.[22] In case of iminosulfenes however, the α-carbon can be more electrophilic and can therefore be preferentially attacked, even by such a weak nucleophile as the chloride ion.

Accordingly, we found that substitution of the sulfonimidoyl chloride **37** with amines, such as dimethylamine, methoxylamine or benzylamine was difficult, irreproducible and led to very low yields of the sulfonimidoyl amide, usually together with large amounts of the sulfonamide **38** (Scheme 6). We decided to investigate the oxidation of sulfinamide **36** with *tert*-butyl hypochlorite[23] by ^{1}H NMR spectroscopy and found it to be a very clean and fast reaction (<2 min). The sulfonimidoyl chloride **37** was stable in $CDCl_3$ or deuterated THF and only slow hydrolysis to the sulfonamide **38** was observed over several hours. Upon addition of water, hydrolysis was complete instantly.

The key experiment was to study the stability of the sulfonimidoyl chloride **37** towards bases. As a solution in $CDCl_3$, the chloride **37** was stable against deuterated pyridine (2 equiv) for several days, however, when treated with the stronger base NEt_3 (1 equiv), it decomposed very rapidly (<1 min). Due to the instability of the sulfonimidoyl chloride **37** under basic conditions, it is not a suitable intermediate for a general synthesis of sulfonimidoyl amides. Moreover, the sulfonimidoyl chloride **37** was found to be reduced

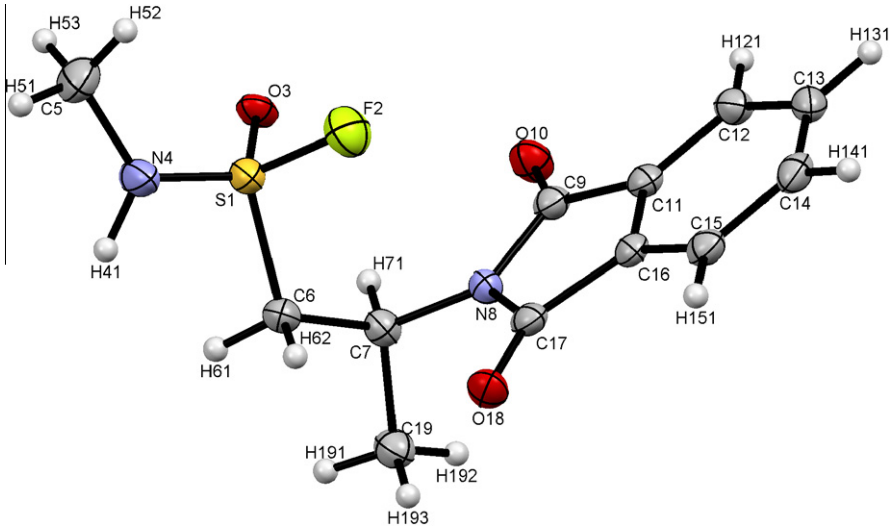
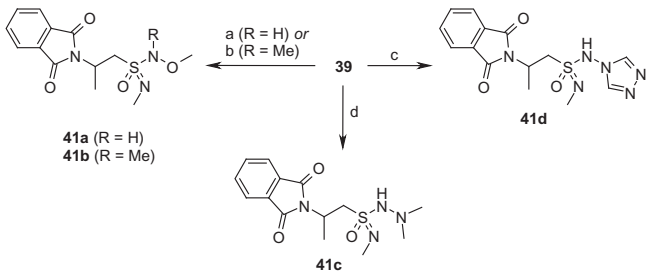
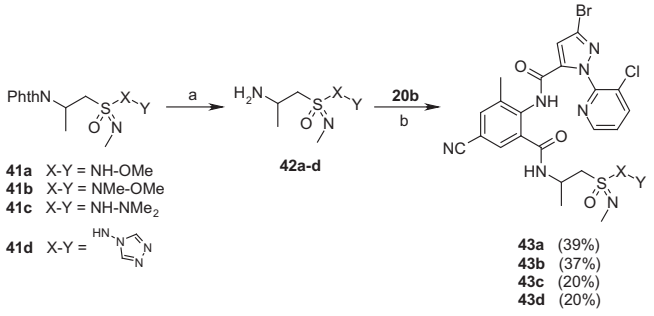


Figure 4. X-ray structure of the sulfonimidoyl fluoride **39** with displacement ellipsoids drawn at the 50% probability level.



Scheme 8. Synthesis of novel sulfonimidoyl derivatives. Reagents and conditions: (a) $MeONH_3Cl$, DBU, DMF, 100 °C, 81%; (b) $MeON(Me)H_2Cl$, DBU, DMF, 100 °C, 83%; (c) 4-amino-4*H*-1,2,4-triazole, DMF, 120 °C, 27%; (d) Me_2NNH_2, DMF, 120 °C, 39%.



Scheme 9. Synthesis of anthranilamides with novel sulfonimidoyl motifs. Reagents and conditions: (a) H_2NNH_2, EtOH, reflux; (b) **20b**, THF, RT.

by hydrazines to give back the parent sulfinamide **36** instead of the desired sulfonimidoyl hydrazide.

As an alternative to the sulfonimidoyl chloride, the corresponding sulfonimidoyl fluorides have been reported to be more stable against hydrolysis and also against reducing agents, such as organolithium reagents.[24] Thus, the sulfonimidoyl fluoride **39**[25] was prepared in a one pot procedure analogous to the literature in 91% yield, as depicted in Scheme 7.[24,26] Compound **39** was obtained as a colorless solid (1:1 mixture of diastereomers) which, after recrystallisation (cyclohexane/ethyl acetate 1:1) gave single crystals suitable for X-ray analysis (Fig. 4).[27] The relative configuration of the racemic diastereomer in the analyzed crystals was shown to be like, that is, a 1:1 mixture of the (*R*,*R*)- and the (*S*,*S*)-enantiomer.[28]

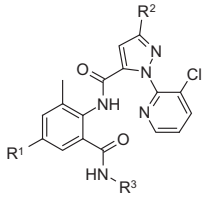
The stability and reactivity of the sulfonimidoyl fluoride **39** was studied by ^1H NMR spectroscopy. It was stable in $CDCl_3$ in the presence of an excess of D_2O or triethylamine (2 equiv) for at least 24 h at room temperature and 2 h at reflux. In contrast, complete decomposition was observed in the presence of 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) in $CDCl_3$ after 24 h. The reaction with benzylamine to give compound **40** was slow at room temperature and the reactivity was not increased by addition of a silver salt such as $AgBF_4$.

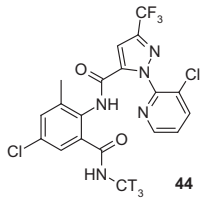
The sulfonimidoyl fluoride **39** reacted smoothly with methoxylamine hydrochloride (10 equiv) or *N*,*O*-dimethyl hydroxylamine hydrochloride (10 equiv) and DBU (8 equiv) in DMF at 120 °C to give the desired sulfonimidoyl hydroxylamide derivatives **41a** and **41b**[25] in 81% and 82% yield, respectively (Scheme 8). The choice of DBU as a base was crucial, due to its solubility properties and its high basicity.

Reactions with hydrazine derivatives were not general. 1,1-Dimethylhydrazine and 4-amino-4*H*-1,2,4-triazole added at 120 °C in DMF to give **41c** and **41d** in 39% and 27% yield.[25] Our attempts to use other hydrazine derivatives were unsuccessful, either because of insufficient stability of the products, as in case of acetyl hydrazide, or because of low reactivity as with *tert*-butyl hydrazine carboxylate or 3-amino-2-oxazolidinone.

Finally, the phthalimide protecting group of the sulfonimidoyl derivatives **41a–d** was removed (H_2NNH_2, EtOH, reflux) and the crude free amines **42a–d** were reacted with the benzoxazinone **20b** to give potential insecticidal diamides **43a–d** (Scheme 9).

Table 1
Selected results from greenhouse tests and binding assays (displacement of **44**)





Entry	R^1	R^2	R^3	Compound	Greenhouse[a] EC_{80} (ppm)			Binding assays[a] IC_{50} (ppm)		Physical properties	
					Spo	Plu	Myzus	Spo	Myzus	log*P*[b]	aq sol.[c] (ppm)
1	Cl	CF_3	$C(CH_3)_2CH_2S(O)(NH)CH_3$	**25f**	0.8	0.8	50.0	nd[d]	nd	2.4	196
2	Cl	OCH_2CF_3	$C(CH_3)_2CH_2S(O)(NH)CH_3$	**45**	0.8	0.2	12.5	nd	nd	2.4	295
3	CN	OCH_2CF_3	$C(CH_3)_2CH_2S(O)(NH)CH_3$	**46**	0.8	0.2	3.1	19	nd	1.6	361
4	Cl	CF_3	$C(CH_3)_2CH_2S(O)(N\text{-}CN)CH_3$	**47**	0.8	0.8	200	5	3	2.9	14
5	CN	Br	$C(CH_3)_2CH_2S(O)(NH)CH_3$	**48**	0.8	0.8	12.5	14	11	1.1	42
6	CN	Br	$C(CH_3)_2CH_2S(O)(N\text{-}CN)CH_3$	**26**	50.0	0.8	200	4	5	1.7	59
7	CN	Br	$C(CH_3)_2CH_2S(O)(N\text{-}NO_2)CH_3$	**27**	12.5	0.8	200	8	nd	1.9	29
8	CN	Br	$CH(CH_3)CH_2S(O)(NH)NHCH_3$	**34b**	50.0	12.5	200	5	nd	1.1	96
9	Cl	Br	$CH(CH_3)CH_2S(O)(NH)NHCH_3$	**34a**	12.5	3.1	200	4	nd	2.0	95
10	CN	Br	$CH(CH_3)CH_2S(O)(NCH_3)NHN(CH_3)_2$	**43c**	50.0	12.5	12.5	nd	nd	2.1	48
11	CN	Br	$CH(CH_3)CH_2S(O)(NCH_3)NHOCH_3$	**43a**	50.0	3.1	>200	57	nd	1.8	17
12	Chlorantraniliprole			**2**	0.8	0.8	50.0	3	2	2.8	1
13	Cyantraniliprole			**3**	3.1	0.8	12.5	5	1	1.9	14
14	Flubendiamide			**1**	3.1	3.1	>200	10	57	4.2	0.3

[a] Spo: *Spodoptera littoralis*, Plu: *Plutella xylostella*, Myzus: *Myzus persicae*.
[b] Measured according to Ref. 30.
[c] aq sol.: aqueous solubility (pH 7).
[d] nd: not determined.

The new diamides presented here were tested against a selection of phytophagous insects which cause damage in different cultures of high commercial relevance, such as lepidopteran chewing pests (*Spodoptera littoralis* (Egyptian cotton leafworm), *Heliothis virescens* (tobacco budworm) and *Plutella xylostella* (diamondback moth)), hemipteran sucking pests (*Myzus persicae* (green peach aphid), *Thrips tabaci* (onion thrips) or coleopteran pest (*Diabrotica virgifera* (western corn rootworm)).

The intrinsic activity of these compounds as modulators of the insect ryanodine receptors was quantified in two binding assays developed in a lepidopteran (*S. littoralis*) and a hemipteran species (*M. persicae*, Table 1; for a description of the assay, see the Supplementary data). The best sulfoximine and sulfonimidamide derivatives displaced the tritiated derivative **44** with IC_{50} values of 3–10 nM, comparable to the best compounds of the diamide class.

Selected results from greenhouse tests and binding assays as well as selected physical properties are summarized in Table 1. The high aqueous solubilities observed for the sulfoximines are not always well reflected by the log*P* values, which may be due to crystal packing effects.[29] Remarkable greenhouse activity against lepidopteran pests and interesting activity against aphids was observed for sulfoximine analogues (entries 1–5) as compared to diamide standards (entries 12–14). Interesting activity against corn rootworm and thrips was also detected for some analogues (data not shown). The interesting *Myzus* activity of some of the sulfoximines (entries 2, 3 and 5) may be explained by a better bioavailability profile (high aqueous solubility and relatively low log*P*), as compared to standards **2** and **1** (entries 12 and 14). Reduced activity of **25f** and **47** (entries 1 and 4) against *Myzus* is more difficult to rationalize.

Even though the sulfonimidamides (entries 8 and 9) had in vitro values comparable to the standards against *Spodoptera*, they were generally weakly active in the greenhouse (lepidoptera and hemiptera). The sulfonimidoyl hydroxylamides or hydrazides were much weaker in vitro as well as in vivo (entries 10 and 11).

Selected compounds were tested in the field following seed treatment application (Fig. 5; for a description of the tests, see the Supplementary data). High control of pests was observed for at least 20 days after planting. The consistent high activity of sulfoximines **25f** and **45** (Table 1, entries 1 and 2) is thought to be due to their high water solubility and relatively low log*P*, leading to systemicity in the plant and good distribution in the soil.

In conclusion, novel insecticidal diamides were prepared, having a sulfoximine, a sulfonimidamide or a sulfonimidoyl hydrazide or hydroxylamide moiety. The reported sulfonimidoyl functional groups have scarcely been reported in the literature. High activity against a range of insects in the greenhouse was detected and binding assays revealed high affinity for the ryanodine receptor in the nM range for some analogues. Seed treatment trials conducted under field conditions demonstrated the excellent soil movement and plant systemicity of some analogues.

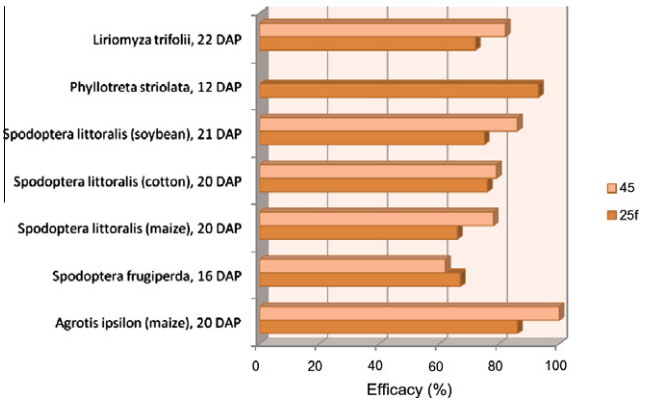


Figure 5. Seed treatment field trials with **25f** and **45** (Table 1, entries 1 and 2). Seed loading is 1 mg AI/seed. DAP: day after planting.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.03.106.

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