Synthesis and Properties of Thiamethoxam and Related Compounds*

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The neonicotinoids are the most successful chemical class of insecticides reaching sales of more than $1 billion in 2003, mainly due to the excellent market performance of imidacloprid and thiamethoxam. This paper describes the discovery, the synthesis and the insecticidal activity of thiamethoxam and related compounds and reports the hydrolytic stability and the degradation pathways of thiamethoxam together with the synthesis of the degradation products.

Key words: Neonicotinoids, Thiamethoxam, Clothianidin, 4-Nitroimino-1,3,5-oxadiazinanes, Insecticidal Activity

Introduction

An important milestone in the history of modern insect control is marked by the discovery of the neonicotinoid insecticides [1]. As the first representative of this chemical class, imidacloprid **1** was introduced to the market in 1991, and since then, a series of analogues (compounds **2 – 7**) have been launched (Table 1). The neonicotinoids are the fastest growing chemical class of insecticides, now exceeding 15% of the total insecticide market. This tremendous success is based on their unique chemical and biological properties, such as broad-spectrum insecticidal activity, low application rates, excellent systemic characteristics, favourable safety profile, and a new mode of action.

Neonicotinoids bind selectively to insect nicotinic acetylcholine receptors (nAChRs) with nanomolar affinity to act as potent insecticides. However, they do not act as a homogenous class of insecticides. Recent findings suggest that thiamethoxam binds, compared to the other neonicotinoid sales products, in a different way, possibly to a different site of the receptor in aphids [3].

Our own research in this area resulted in the discovery of thiamethoxam (**4**) [4]. This compound is a second-generation neonicotinoid and belongs to the thianicotinyl subclass. It was first synthesized in 1991

Table 1. Neonicotinoid sales products [2].

Common Name	Company	Year of Market Introduction	Sales 2003 Mio $[a]
Imidacloprid (**1**)	Bayer	1991	665
Nitenpyram (**2**)	Takeda	1995	45
Acetamiprid (**3**)	Nippon Soda	1996	60
Thiamethoxam (**4**)	Syngenta	1998	215/298[b]
Thiacloprid (**5**)	Bayer	2000	< 30
Clothianidin (**6**)	Takeda, Bayer	2002	< 30
Dinotefuran (**7**)	Mitsui Chemicals	2002	< 30

[a] Data from Phillips McDougall; [b] sales 2004, data from Syngenta Annual Report 2004.
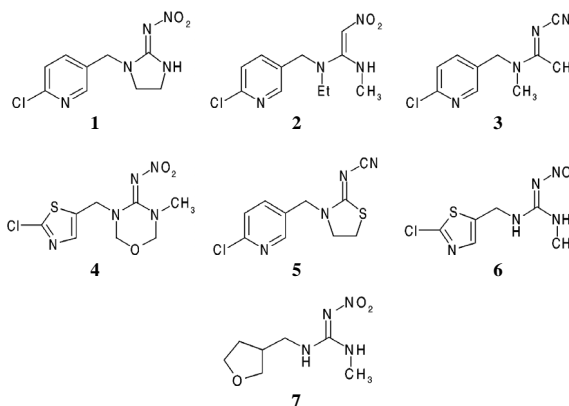
and is now developed worldwide for use in more than 100 crops. Thiamethoxam is marketed since 1998 under the trademarks Actara® for foliar and soil treatment and Cruiser® for seed treatment. In all these usages, thiamethoxam provides excellent control of a broad range of commercially important pests, such
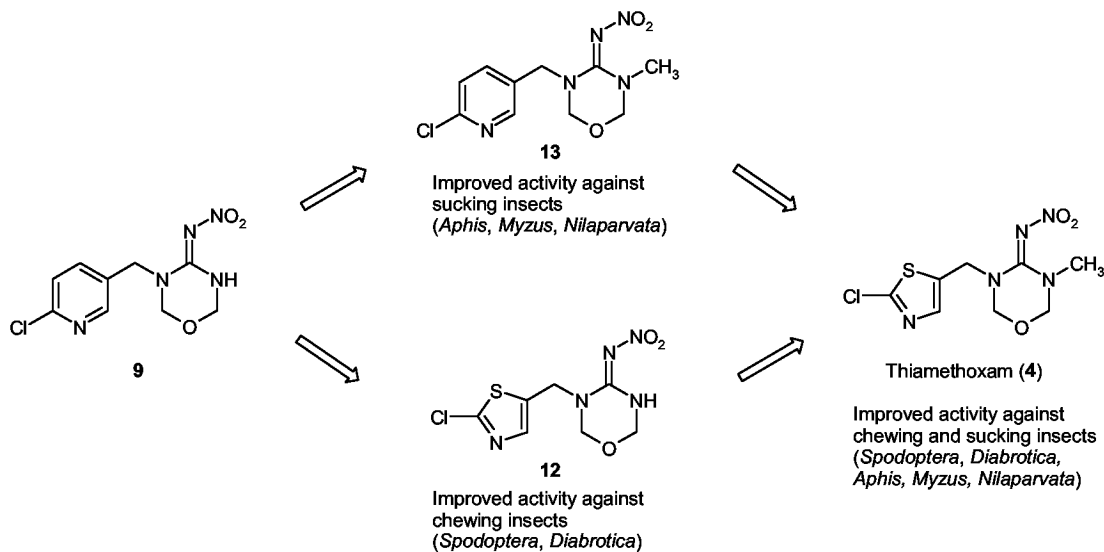
Scheme 1. Optimization of the lead structure **9**.

as aphids, whiteflies, thrips, rice hoppers, Colorado potato beetle, flea beetles, wireworms, leaf miners as well as some lepidopterous species [5]. Low use rates, flexible application methods, excellent efficacy, and the favourable safety profile make this new insecticide well suited for modern integrated pest management programs in many cropping systems.

Discovery of Thiamethoxam

As part of our program on neonicotinoid chemistry we have investigated novel variations of the nitroimino-heterocycle of imidacloprid, which resulted in the synthesis of compounds **8**, **9**, and **10** [4a].
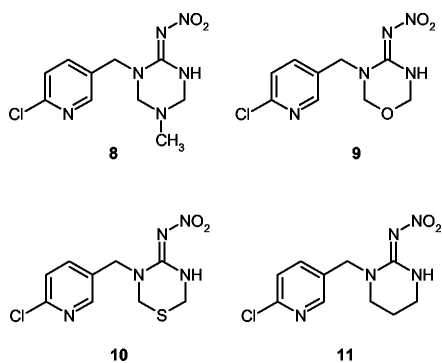
Bioassays revealed that among these compounds, the 4-nitroimino-1,3,5-oxadiazinane **9** exhibits clearly better insecticidal activity than the 2-nitroimino-hexa-
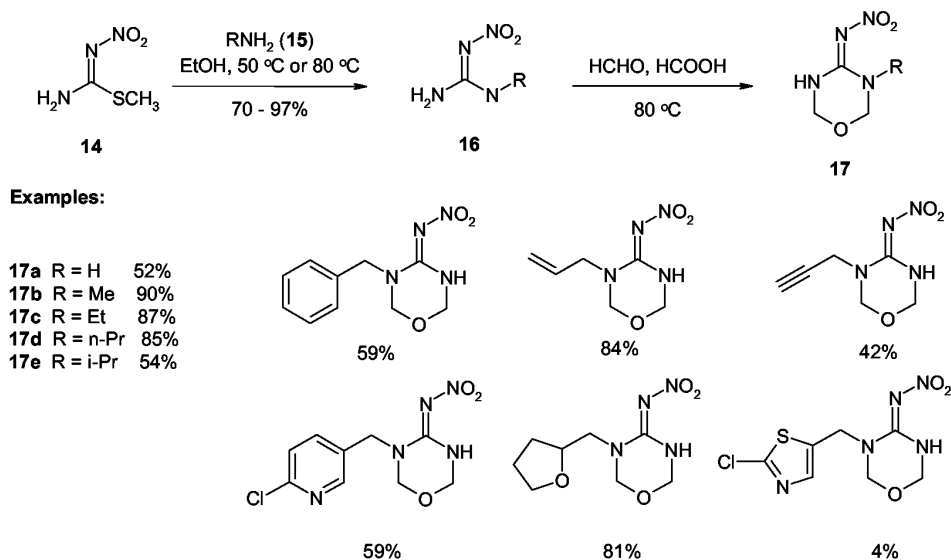
Table 2. Insecticidal activity of compounds **8 – 10** in comparison to imidacloprid **1** and its six-ring analogue **11**.

Compound	Structure Type	LC80 [mg AI liter^{-1}]		
		Aphis craccivora m. p. Pea, foliar spray	*Myzus persicae* m. p. Pea, into water	*Diabrotica balteata* L2 Filter paper, spray
8	Triazinane	> 200	3	200
9	Oxadiazinane	50	0.05	3
10	Thiadiazinane	200	0.8	12
11	Hexahydro-pyrimidine	12	0.2	3
1		12	0.05	0.8
4	Oxadiazinane	12	0.05 – 0.2	0.8

hydro-1,3,5-triazine **8** and the 4-nitroimino-1,3,5-thiadiazinane **10** and that its potency is close to imidacloprid and its six-ring analogue **11**, respectively (Table 2).

Chemical and biological exploration of the lead structure **9** showed that replacement of the 6-chloro-3-pyridyl group by a 2-chloro-5-thiazolyl moiety (→ compound **12**) resulted in a strong increase of the activity against chewing insects, whereas the introduction of a methyl group as pharmacophore substituent (→ compound **13**) increased the activity against sucking pests (Scheme 1). The combination of these two favourable modifications led to thiamethoxam (**4**). This compound was clearly the most active 4-nitroimino-1,3,5-oxadiazinane, and its performance in our greenhouse screening was comparable or better than that of the standard imidacloprid **1** [4a].
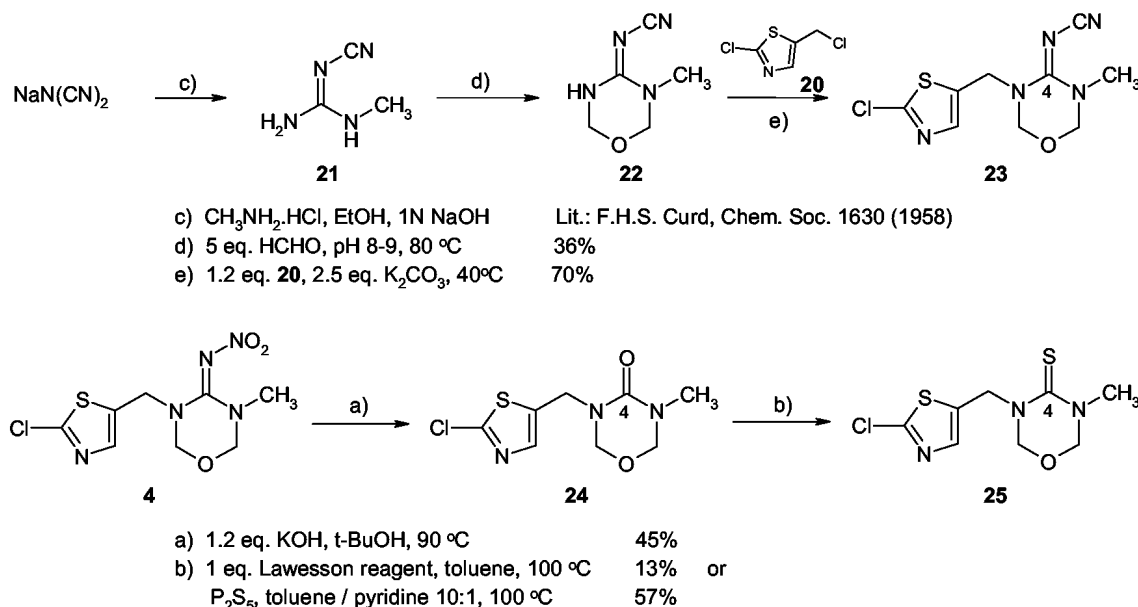
Method	Reaction conditions	Yield
A	5 eq. HCHO, pH = 9, 90 °C	traces
B	4 eq. $(CH_2O)_n$, 1 eq. Et_3N, toluene/1,4-dioxane 1:1, 110 °C	21%
C	3 eq. $(CH_2O)_n$, cat. HCl , toluene / 1,4-dioxane 1:1, 110 °C	21%
D	2 eq. $(CH_2O)_n$, CF_3COOH, $ClCH_2CH_2Cl$, r. t.	0% (dec.)
E	HCHO, 1.1 eq. p-TsOH, 90 °C	47%
F	HCHO, 1.1 eq. CF_3COOH, 90 °C	61%
G	HCHO / CH_3COOH 1:1, 90 °C	28%
H	HCHO / HCOOH 1:1, 90 °C	71 – 90%

Table 3. Mannich type cyclization of N-methyl nitroguanidine to 4-nitroimino-1,3,5-oxadiazinane **17b**.

Examples:

17a R = H   52%
17b R = Me   90%
17c R = Et   87%
17d R = n-Pr 85%
17e R = i-Pr   54%

59%   84%   42%

59%   81%   4%

Scheme 2. Synthesis of monosubstituted-4-nitroimino-1,3,5-oxadiazinanes **17**.
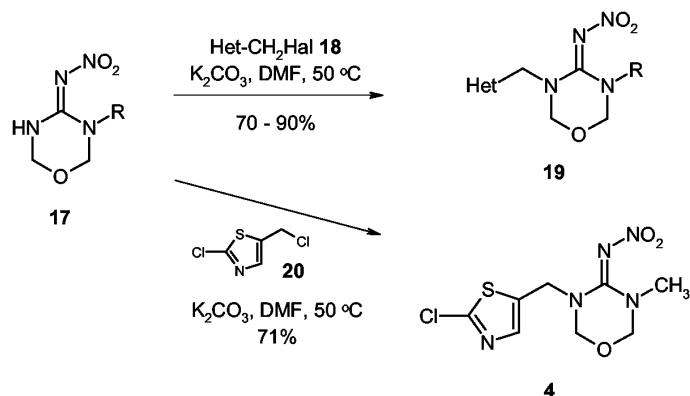
Scheme 3. Synthesis of thiamethoxam (**4**) and other disubstituted 4-nitroimino-1,3,5-oxadiazinanes **19**.

Synthesis of Thiamethoxam

At the start of our research, no practical synthetic route for the preparation of 4-nitroimino-1,3,5-oxadiazinanes was known. After much experimentation, we discovered a broadly applicable method for the synthesis of monosubstituted 4-nitroimino-1,3,5-oxadiazinanes **17** (Scheme 2). Thus, treatment of *S*-methyl-*N*-nitro-isothiourea (**14**) with amines **15** in eth-

anol at 50 °C or 80 °C afforded *N*-monosubstituted-*N'*-nitroguanidines **16**. Heating of compounds **16** in a 1:1 mixture of formaldehyde and formic acid for several hours at 80 – 90 °C provided the 4-nitroimino-1,3,5-oxadiazinanes **17** in good to excellent yields. Key step in this synthesis is the Mannich type cyclisation reaction. Many different reaction conditions were investigated; some examples are shown in Table 3. Among the many acids tested only formic acid gave good re-

c) CH$_3$NH$_2$.HCl, EtOH, 1N NaOH　　Lit.: F.H.S. Curd, Chem. Soc. 1630 (1958)
d) 5 eq. HCHO, pH 8-9, 80 °C　　　　36%
e) 1.2 eq. **20**, 2.5 eq. K$_2$CO$_3$, 40°C　　70%

a) 1.2 eq. KOH, t-BuOH, 90 °C　　　　　45%
b) 1 eq. Lawesson reagent, toluene, 100 °C　13%　or
　　P$_2$S$_5$, toluene / pyridine 10:1, 100 °C　57%

Scheme 4. Pharmacophore modifications – synthesis of compounds **23** – **25**.

sults. Other acids such as acetic acid, trifluoroacetic acid and HCl strongly decreased the yields.

Compounds **17** could be coupled with heterocyclyl-methyl halides **18** to afford the disubstituted 4-nitro-imino-1,3,5-oxadiazinanes **19** (Scheme 3). Optimal yields for these alkylation reactions were obtained using 2.5 equivalents of potassium carbonate as a base and dimethylformamide as solvent. Following the methodologies described above, thiamethoxam (**4**) has been synthesised in three steps from *S*-methyl-*N*-nitro-isothiourea (**14**) in an overall-yield of 62%.

Variation of the Pharmacophore

Several variations of the pharmacophore (N-C(N)=N-NO$_2$) have been carried out. The cyanoimino derivative **23** was prepared starting from *N*-methyl-*N'*-cyanoguanidine **21**, which was obtained in 56% from sodium dicyanamide and methylamine (Scheme 4). The conversion of **21** to 3-methyl-4-cyanoimino-1,3,5-oxadiazinane (**22**) was not achieved under the reaction conditions applied for the preparation of the 4-nitroimino-1,3,5-oxadiazinanes **17**. However, treatment of **21** with a large excess of aqueous formaldehyde at pH 8 gave compound **22** in moderate yield. Alkylation of **22** with the chloride **20** afforded the cyanoimino-analogue **23**.

The urea **24** and the thiourea **25** were prepared starting from thiamethoxam **4**. Treatment of **4** with potas-

sium hydroxide in *tert*-butanol provided the urea **24**, which was reacted with Lawesson's reagent to yield the thiourea **25** in only 13% yield. Replacement of Lawesson's reagent by phosphorus pentasulfide resulted in much better yields (57%) in the sulfuration reaction.

The biological evaluation of these compounds revealed that the potency is highly dependent on the pharmacophore. Replacement of the nitroimino group by a cyanoimino moiety (compound **23**) clearly diminished the activity, while compounds like the urea **24** (X = O) and the thiourea **25** (X = S) were not active at the highest concentration tested (100 ppm). These differences in the biological activities seem to be clearly related to the electronic properties of the pharmacophore moiety. Activity is only found if the functional group at C-4 is strongly electron-withdrawing and has a hydrogen accepting head like in N-NO$_2$ and in N-CN.

Variation of the Pharmacophore Substituent

A wide range of modifications of the pharmacophore substituent has been carried out as shown in Scheme 5. The key intermediate **12** was prepared by Mannich type cyclisation of nitroguanidine (**26**) followed by selective monoalkylation with the chloride **20**. Under optimized reaction conditions (1.2 eq. **20**, 1.0 eq. KOC(CH$_3$)$_3$, DMF-pyridine 4:1, −5 °C to r. t.)
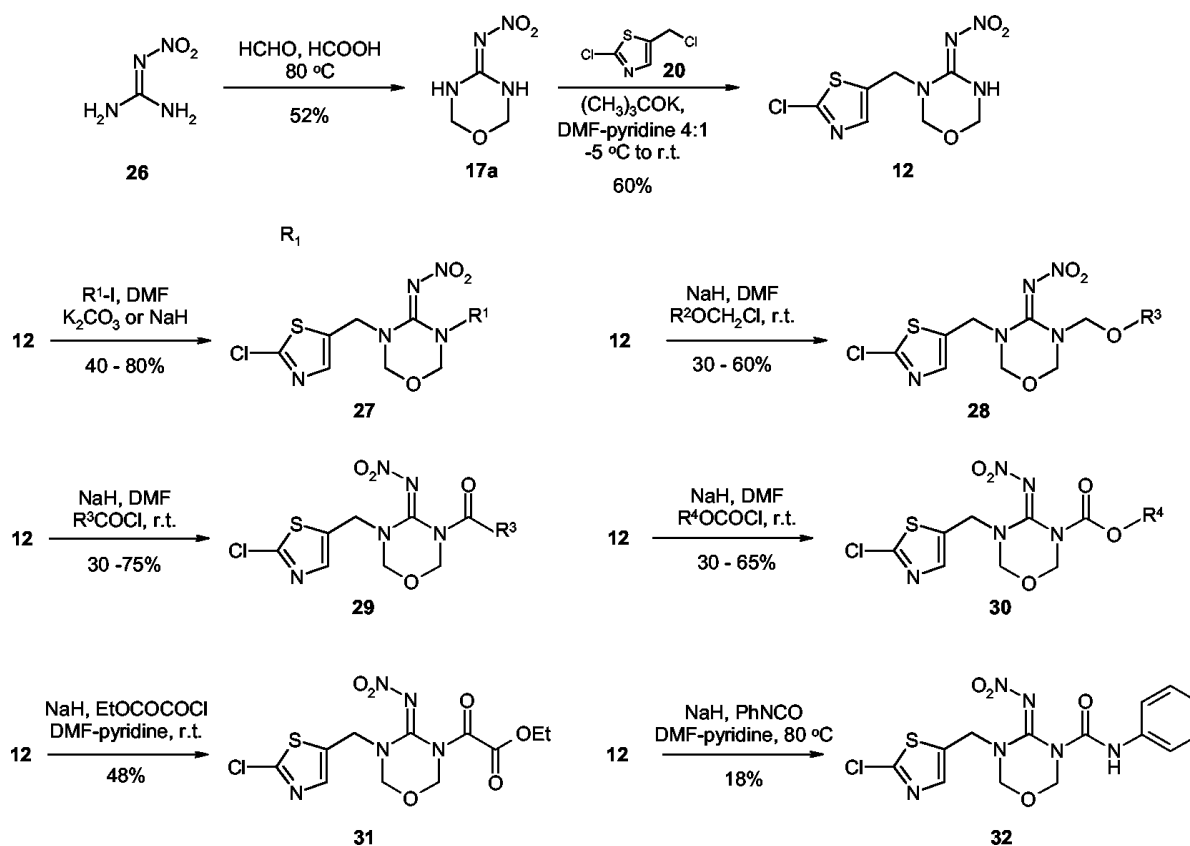
Scheme 5. Variation of the pharmacophore substituent: synthesis of compounds **27 – 32**.

and a special work-up procedure (crude dissolved in CH$_2$Cl$_2$, extracted with 2N NaOH, after acidification of the aqueous phase with HCl to pH = 4, the product separates as pale brown solid), compound **12** was obtained in 60% yield from **17a**.

Compounds of type **27**–**30** and **32** showed moderate to good insecticidal activity, whereas the oxalic acid derivative **31** was found to be inactive. However, none of these new compounds exhibited the potency and the broad-spectrum insecticidal activity of thiamethoxam **4**. Best activity was observed for compounds with the pharmacophore substituent being H, Et, allyl, propargyloxymethyl and ethylcarbonyl. Steric as well as electronic factors seem to have an important influence on the biological activity. When the pharmacophore substituent is an alkyl group, the activity decreases with the chain length and the steric bulk (Me >Et>*n*-Pr ≫ *i*-Pr, *n*-Bu). Somewhat surprisingly, the methyl-substituted compound **4** is clearly more active than the unsubstituted compound **12**. This is in contrast to the imidacloprid series where the activity

Table 4. Kinetic data of the hydrolytic degradation of thiamethoxam (**4**).

pH	T [°C]	Rate constant [h^{-1}]	Half-life [h]	Estimated half-life at 25°C [days]
5	70	2.55×10^{-4}	2718	6990
7	70	1.18×10^{-2}	59	152
9	25	4.72×10^{-3}	147	6.1

drops significantly when a methyl group is introduced as pharmocophore substituent.

Hydrolytic Degradation of Thiamethoxam

The hydrolytic degradation of thiamethoxam **4** was investigated in the pH range from 5 to 9 and was found to follow pseudo-first order kinetics (Table 4) [6].

Two major degradation pathways were observed in the pH range from 5 to 9. The first pathway led to the corresponding 1,3,5-oxadiazinan-4-one **24** and the second pathway to the ring opened *N*-nitro-urea **33** and to the 2-chloro-5-aminomethyl-thiazole (**34**), respectively (Scheme 6).
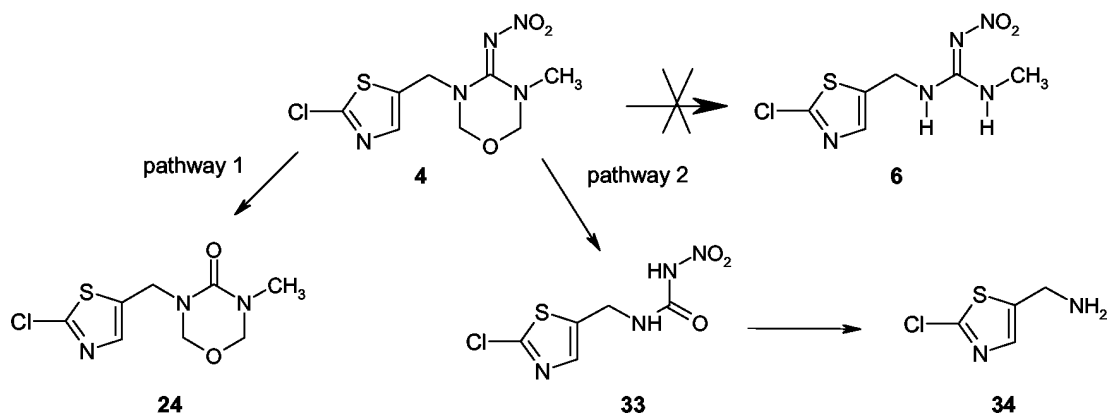
Scheme 6. Hydrolytic degradation pathways of thiamethoxam (**4**).

Cleavage of thiamethoxam under acidic conditions:
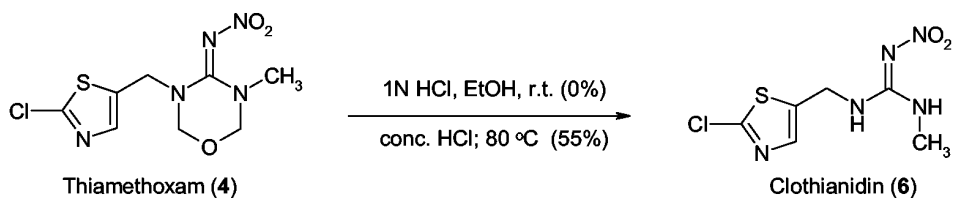
For comparison: Cleavage of the triazinane **35**
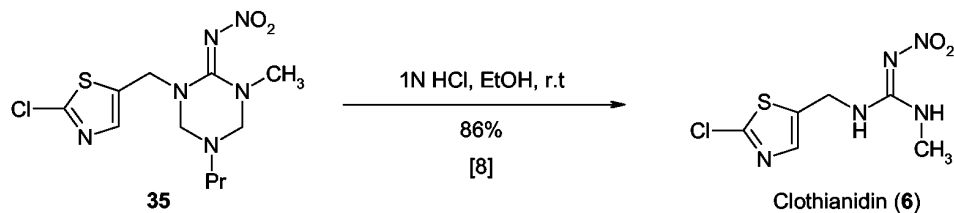
Cleavage of thiamethoxam under basic conditions:
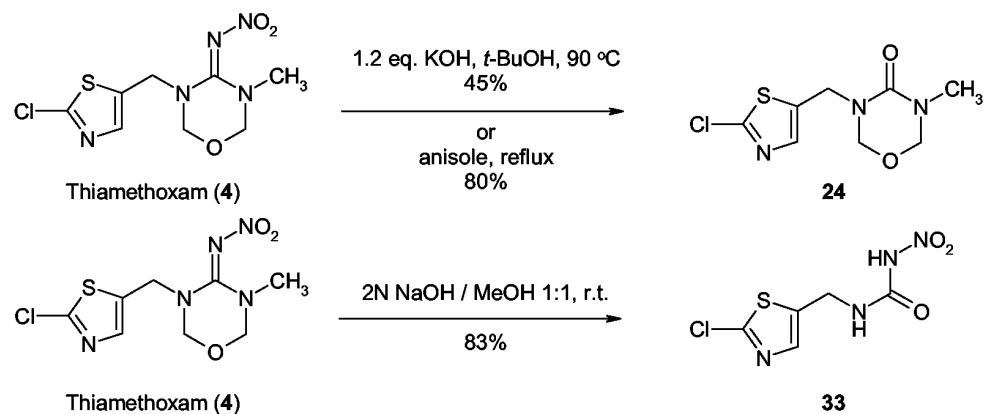
Scheme 7. Cleavage of thiamethoxam (**4**) under acidic and basic conditions.

The product distribution was also pH-dependent. The formation of the N-nitro-urea **33** at higher concentrations was only observed at pH 9. This intermediate was not observed (or only at very low concentrations) at pH 5 and pH 7 due to the further rapid hydrolytic degradation to the corresponding amine **34**. The cleavage of the 1,3,5-oxadiazinane ring to the corresponding acyclic nitroguanidine **6** (clothianidin) was not observed (for synthesis of clothianidin see lit. [7]). Under more drastic conditions very similar results were obtained as shown in Scheme 6. Our studies have shown that thiamathoxam (**4**) is only converted to clothianidin (**6**) under very drastic conditions such as heating to 80 °C for several hours in conc. HCl.

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