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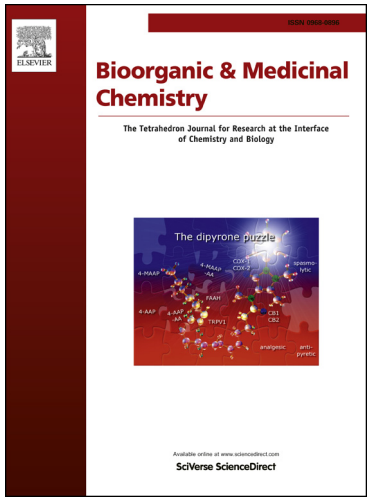

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PII: S0968-0896(15)30182-6
DOI: http://dx.doi.org/10.1016/j.bmc.2015.12.014
Reference: BMC 12707

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 1 October 2015
Revised Date: 2 December 2015
Accepted Date: 7 December 2015

Please cite this article as: Jeanmart, S., Edmunds, A.J.F., Lamberth, C., Pouliot, M., Synthetic approaches to the 2010-2014 new agrochemicals, *Bioorganic & Medicinal Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bmc.2015.12.014

Synthetic approaches to the 2010-2014 new agrochemicals

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Abstract

In this review, the synthesis of 30 agrochemicals that received an international standardization organization (ISO) name during the last five years (January 2010 to December 2014) is described. The aim is to showcase the range and scope of chemistries used to discover or produce the latest active ingredients addressing the crop protection industry's needs.

Abbreviations: Ac, acetyl; ALS, acetolactate synthase; aq., aqueous; BzCl, benzoyl chloride; cat., catalytic; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA, diisopropylethylamine; DMA, dimethylacetamide; DME, dimethoxyethane; DMF, dimethylformamide; eq., equivalent; FRAC, fungicide resistance action committee; GABA, gamma-aminobutyric acid; HPPD, 4-hydroxyphenylpyruvate dioxygenase; IRAC, insecticide resistance action committee; ISK, Ishihara Sangyo Kaisha; ISO, international standardization organization; MsCl, methanesulfonyl chloride; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NMP, *N*-methyl-2-pyrrolidone; PKS, polyketide synthase enzyme; PPO, protoporphyrinogen oxidase; rt, room temperature; SDHI, succinate dehydrogenase inhibitor; TBME, *tert*-butyl methyl ether; THF, tetrahydrofuran; TMEDA, tetramethylethylenediamine.

Keywords: Synthesis; Agrochemicals; Crop Protection; Fungicides; Herbicides; Insecticides; Nematicides

1. Introduction

This review article aims to present the synthetic methods for the agrochemicals that received an international standardization organization (ISO) name during the last five years (January 2010 to

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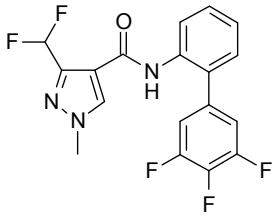
December 2014).[1] This is in line with the popular review articles highlighting the synthetic methods towards the yearly launched pharmaceuticals.[2-13] From a total of 47 molecules that received an ISO name in that period,[14] this review focuses on the synthesis of 30 of them (Figure 1). We have selected the molecules based on chemical diversity or representatives of the different classes of modern agrochemicals across all indications.



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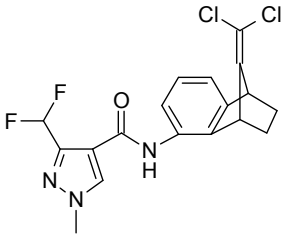

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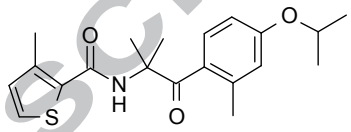

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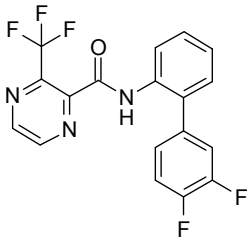
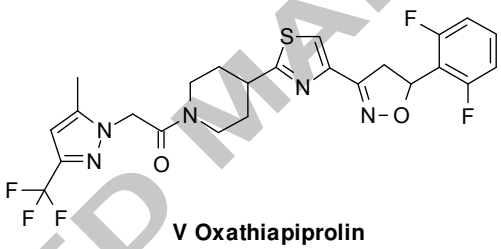


IV Pyraziflumid



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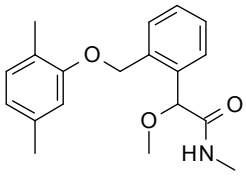

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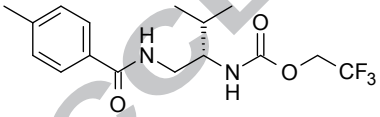

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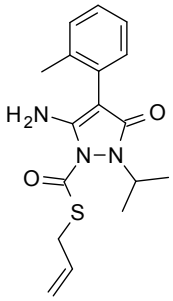

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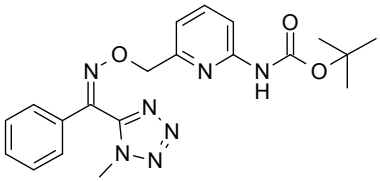

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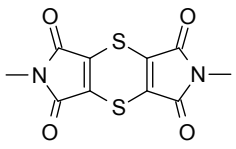
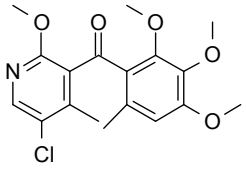
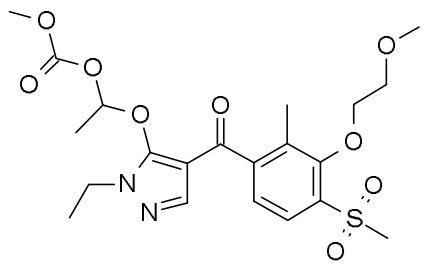


X Dipymetitrone



XI Pyriofenone

Figure 1. Structure of the 30 agrochemicals featured in this review (fungicides).



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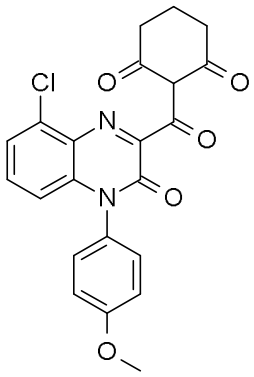

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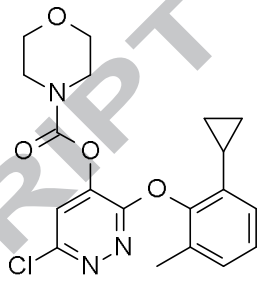

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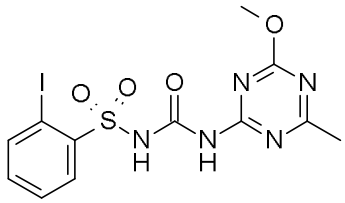
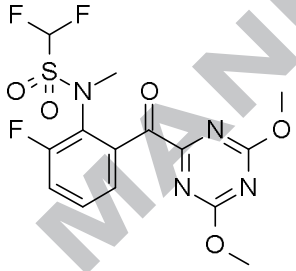
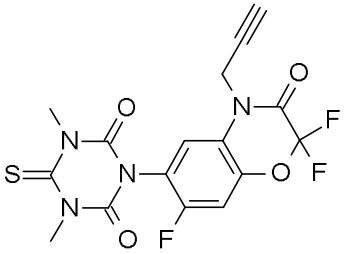


XV Iofensulfuron



XVI Triafamone



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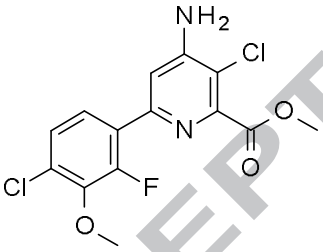
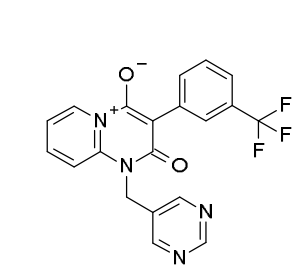


XVIII Halauxifen-methyl

Figure 1. Continued (herbicides)



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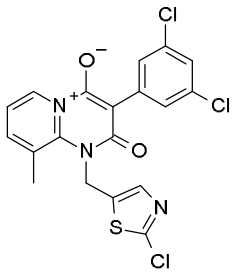

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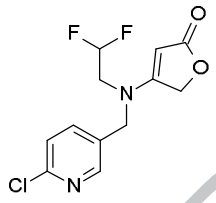

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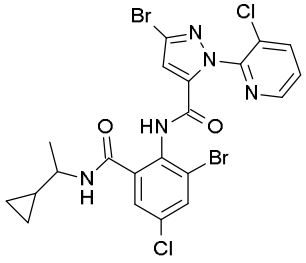

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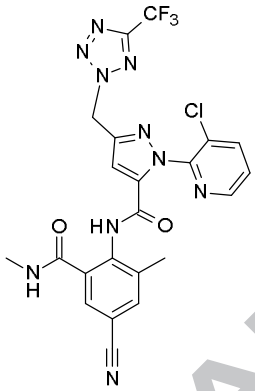

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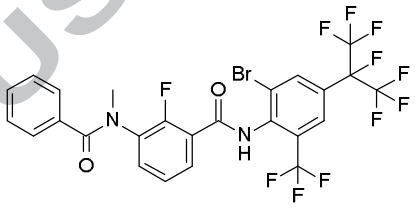

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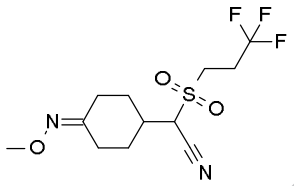
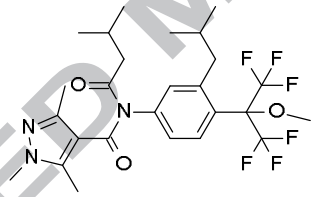
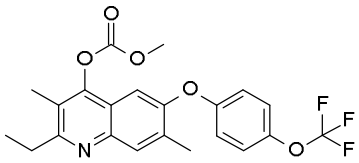


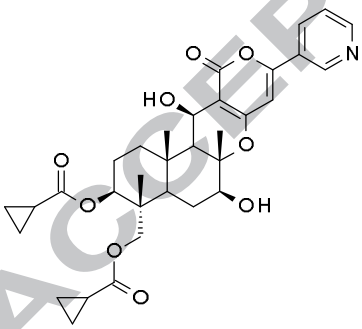
XXV Fluhexafon



XXVI Pyflubumide



XXVII Flometoquin



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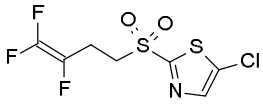
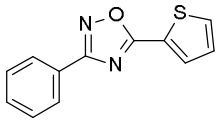


XXIX Fluensulfone



XXX Tioxazafen

Figure 1. Continued (insecticides and nematicides)

In most cases, the synthetic routes reported herein have been extracted from published process patent applications and published literature, however, the exact manufacturing route for an agrochemical is often not fully disclosed. Consequently, the routes described might be close to the manufacturing routes, undoubtedly scalable, but will unlikely be the exact production routes. Nevertheless, this review intends to show the scope and the range of chemistries likely to be used for the production of the latest active ingredients addressing the crop protection industry's needs.

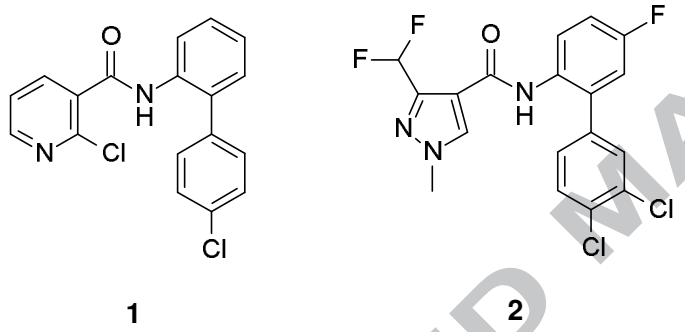
This review is organized in four sections; fungicides, herbicides, insecticides and nematicides. Where possible, the molecules have been further grouped by their mode of action within these sections.

2. Fungicides

2.1. Fluxapyroxad (I)

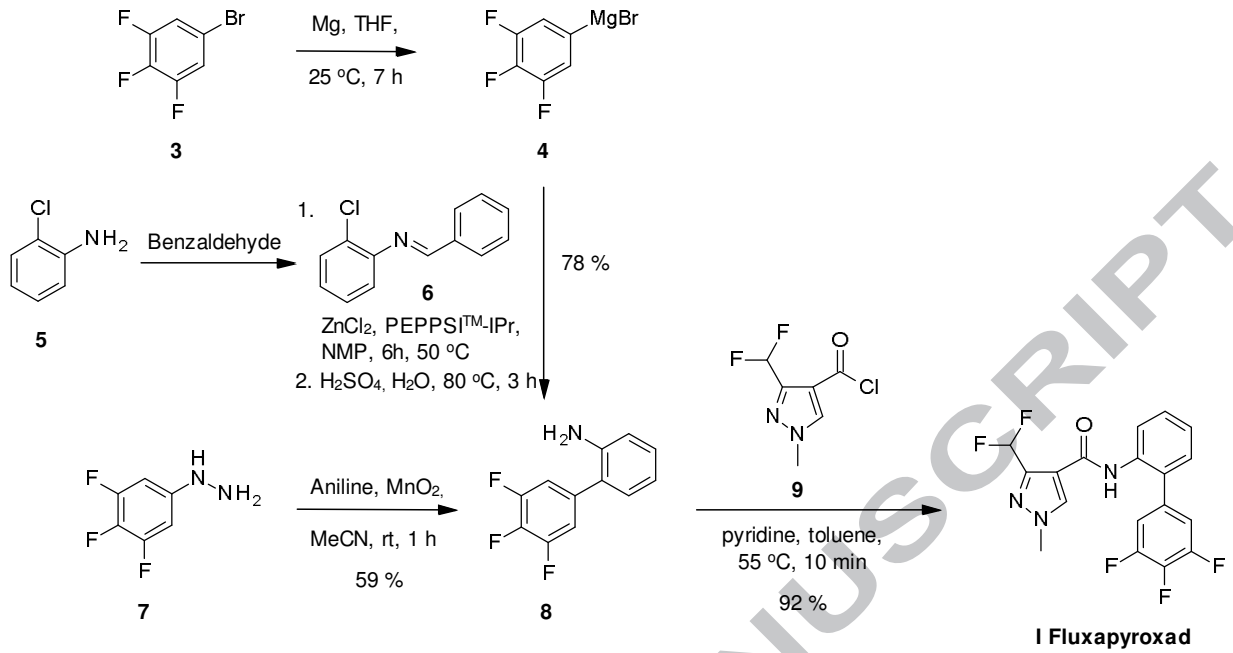
Fluxapyroxad (**I**) was presented to the public by BASF in 2010.[15] This active ingredient belongs, like the other new fungicides benzovindiflupyr (**II**), isofetamid (**III**) and pyraziflumid (**IV**), to the class of succinate dehydrogenase inhibitors (SDHI), a group of modern and important fungicides blocking the complex II election transport of the respiratory chain.[16,17] Its biphenylaniline moiety is very similar to the aniline part of two other SDHI, namely boscalid (**1**)[18] and bixafen (**2**)[19] (Figure 2), and further shares with the latter the 3-difluoromethyl-1-methylpyrazole-4-carboxylic acid motif. As with many other SDHI, fluxapyroxad (**I**) can be applied in different crops to prevent a broad range of fungal plant diseases, and is especially efficacious against leaf spot diseases caused by *Ascomycetes* species.[20] Several different methods can be envisaged for the construction of the trifluorinated biphenyl aniline moiety of fluxapyroxad (**I**). A preparation of fluxapyroxad (**I**) is likely to involve a metal catalyzed cross coupling reaction to produce the key aniline intermediate **8**. Such reactions have precedence in the agrochemical community as demonstrated by both the manufacturing of boscalid's 2-(4-chlorophenyl)aniline which involves the world's largest production volume palladium-catalyzed Suzuki-Miyaura coupling,[17,21] and the preparation of the 3',4'-dichloro-5-fluorobiphenyl-2-amine of bixafen (**2**) *via* a Goossen-type Pd/Cu-catalyzed decarboxylative cross-coupling.[16,22] In

principal, both of those transition metal-catalyzed C-C coupling methods could be applied to the synthesis of fluxapyroxad (**I**). However, the alternative Negishi cross-coupling of a trifluorophenylzinc species generated *in situ* from its corresponding Grignard **4**, with the 2-chloroaniline Schiff base **6**, offers an additional approach that seems perfectly suited for the synthesis of fluxapyroxad's 2-(3,4,5,-trifluorophenyl)aniline (**8**) (Scheme 1).[23] Additional synthetic methods for the synthesis of aniline **8** could involve a manganese dioxide mediated Gomberg-Bachmann-type regioselective radical arylation of aniline with 3,4,5-trifluorophenylhydrazine (**7**).[24,25] Whichever route is used, it is apparent that subsequent amidation of **8** with 3-difluoromethyl-1-methylpyrazole-4-carbonyl chloride (**9**) will yield fluxapyroxad (**I**).



1 **2**

Figure 2. Boscalid **1** and bixafen **2**.

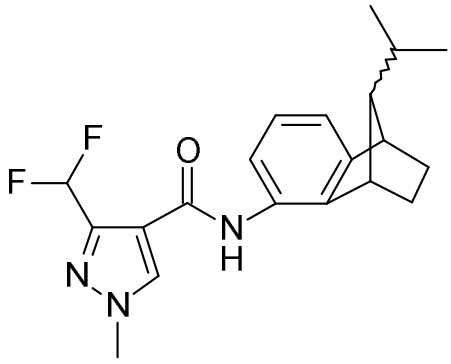


Scheme 1. Synthesis of fluxapyroxad (**I**).

2.2 Benzovindiflupyr (II)

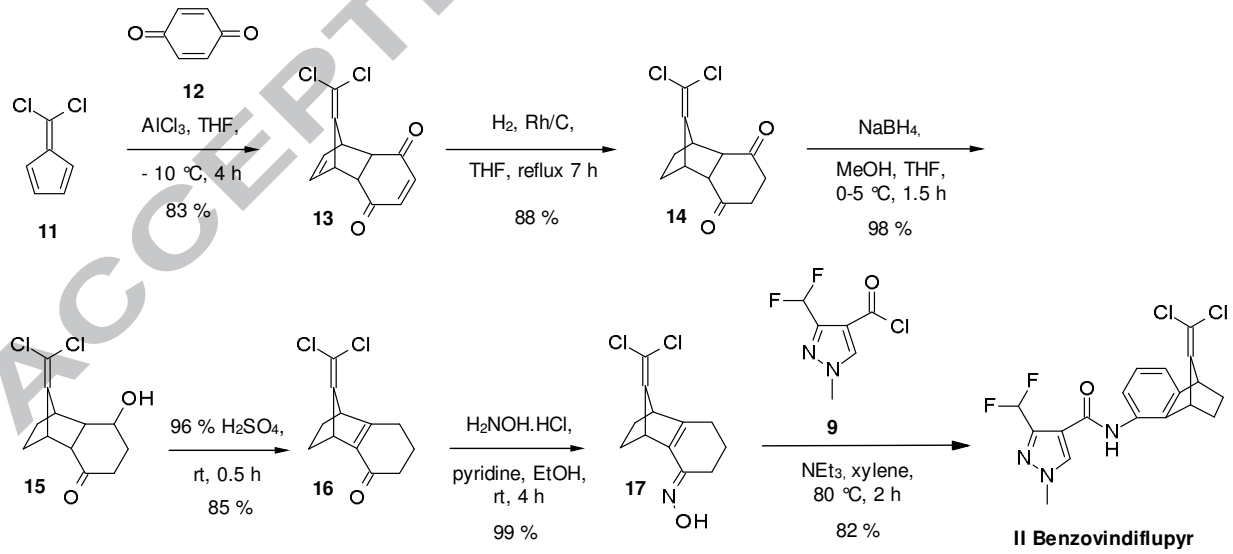
Benzovindiflupyr (**II**) was announced by Syngenta in 2011.[26] Within the SDHI,[16,17] benzovindiflupyr is, after isopyrazam (**10**)[27] (Figure 3), the second pyrazole carboxamide bearing a benzonorbornene aniline moiety. Benzovindiflupyr is a broad-spectrum fungicide with a special focus on rust diseases. Due to its outstanding efficacy, it is the unrivaled new standard for the control of *Phakopsora pachyrizi* (Asian soybean rust), a plant disease of immense economic importance, especially in Latin America.[28] In the first lab synthesis of benzovindiflupyr, the unique benzonorbornene ring system was formed by a Diels-Alder reaction of 6,6-dichlorofulvene (**11**) with a nitrobenzyne.[29] Safety considerations regarding this highly energy-rich and reactive intermediate were a major obstacle for the scale-up of this original synthesis pathway. Therefore, scientists at Syngenta searched for alternative routes, which would be more appropriate for large-scale manufacturing.[27,30] The result was that rather than utilizing a nitrobenzyne, 1,4-benzoquinone (**12**) was chosen as the dienophile for the Diels–Alder cycloaddition with 6,6-dichlorofulvene (**11**) . This chemistry yielded the tricyclic ketoenone **13**, which had to be converted to the final product. The first step toward this goal is the catalytic

hydrogenation of **13** with rhodium on charcoal, which selectively reduced both endocyclic C-C double bonds whilst preserving the exocyclic dichlorovinyl function to yield **14**. Regioselective ketone reduction and subsequent dehydration under acidic conditions afforded the enone **16**. Oxim ation of the carbonyl lead to **17**, which was directly transformed into benzovindiflupyr (**II**) in a Semmler-Wolff type aromatization using two equivalents of 3-difluoromethyl-1-methylpyrazole-4-carbonyl chloride (**9**) (Scheme 2).[16,27,30]



10

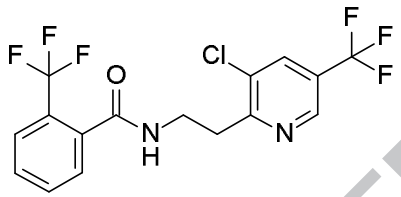
Figure 3. Isopyrazam (**10**).



Scheme 2. Synthesis of benzovindiflupyr (**II**).

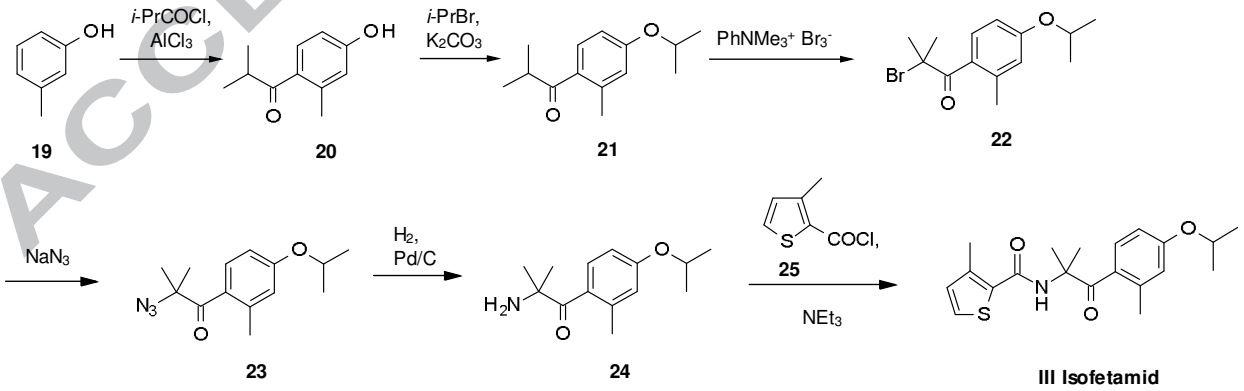
2.3. Isofetamid (III)

Isofetamid (**III**) was announced by Ishihara Sangyo Kaisha (ISK) in 2012.[31] After fluopyram **18** (Figure 4), [32] isofetamid (**III**) is the second compound of this class bearing a phenethylamide derivative,[33] all other SDHI,[16,17] including the new market entries benzovindiflupyr (**II**) and fluxapyroxad (**I**), having an anilide moiety.[17] Isofetamid (**III**) has been shown to be highly effective against *Botrytis cinerea* (grey mold) on grape.[34] It is registered for the control of different *Botrytis* and *Sclerotinia* spp. on grape, lettuce, rapeseed, low growing berry, and turfgrass on golf courses.[35] The phenethylamine moiety of isofetamid (**III**) is prepared in five steps starting from *m*-cresol (**19**) by Friedel-Crafts acylation to **20**, etherification of the phenol function to **21**, α-ketobromination to **22**, bromo-azido exchange to **23,** and azide reduction to the isofetamid amine **24**. This important intermediate is then converted to isofetamid (**III**) by amidation with 3-methylthiophene-2-carbonylchloride (**25**) (Scheme 3).[36]



18

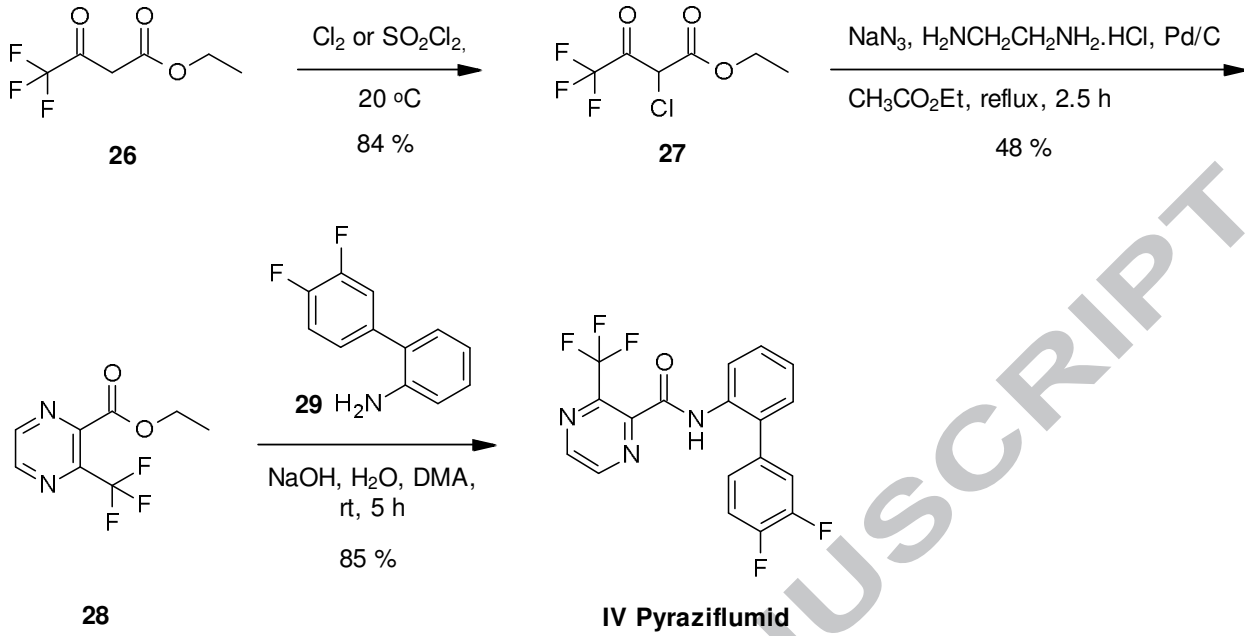
Figure 4. Fluopyram (**18**).



Scheme 3. Synthesis of isofetamid (**III**).

2.4. Pyraziflumid (IV)

Pyraziflumid (**IV**) is the fourth, and most recent, SDHI[16] presented to the public before 2015. It is currently under development at Nihon Nohyaku.[14] Pyraziflumid (**IV**) is another carboxamide with a biphenylaniline moiety making it closely related to the other SDHI's boscalid (**1**)[18], bixafen (**2**)[19] and fluxapyroxad (**II**). Therefore, its 2-(3,4-difluorophenyl)aniline can be easily prepared using the Suzuki-Miyaura methodology leading to boscalid's biphenylamine[17,21] or the Negishi coupling delivering the amine moiety of fluxapyroxad (**II**) as previously discussed.[37] With its unique 2-trifluoromethylpyrazine-3-carboxylic acid, pyraziflumid (**IV**) is only the second complex II inhibitor which contains a six-membered heterocyclic moiety as the carboxylic acid portion. The pyrazine building block **28** is prepared in just two steps from ethyl 4,4,4-trifluoro-3-oxobutanoate (**26**)[38] in a process which involves chlorination of the β-ketoester in position 2 with chlorine[39] or sulfuryl chloride,[40] followed by a subsequent one-pot transformation with sodium azide, 1,2-ethylenediamine and palladium on charcoal. Hereby the 2-chloroketoester **27** is converted by sodium azide into the corresponding 2-iminoketoester, which undergoes ring closure with 1,2-ethylenediamine to form a dihydropyrazine that is aromatized *in situ* by the palladium. The ester **28** thus formed can then directly be transformed into pyraziflumid (**IV**) with 2-(3,4-difluorophenyl)aniline (**29**) under basic conditions (Scheme 4).[38]

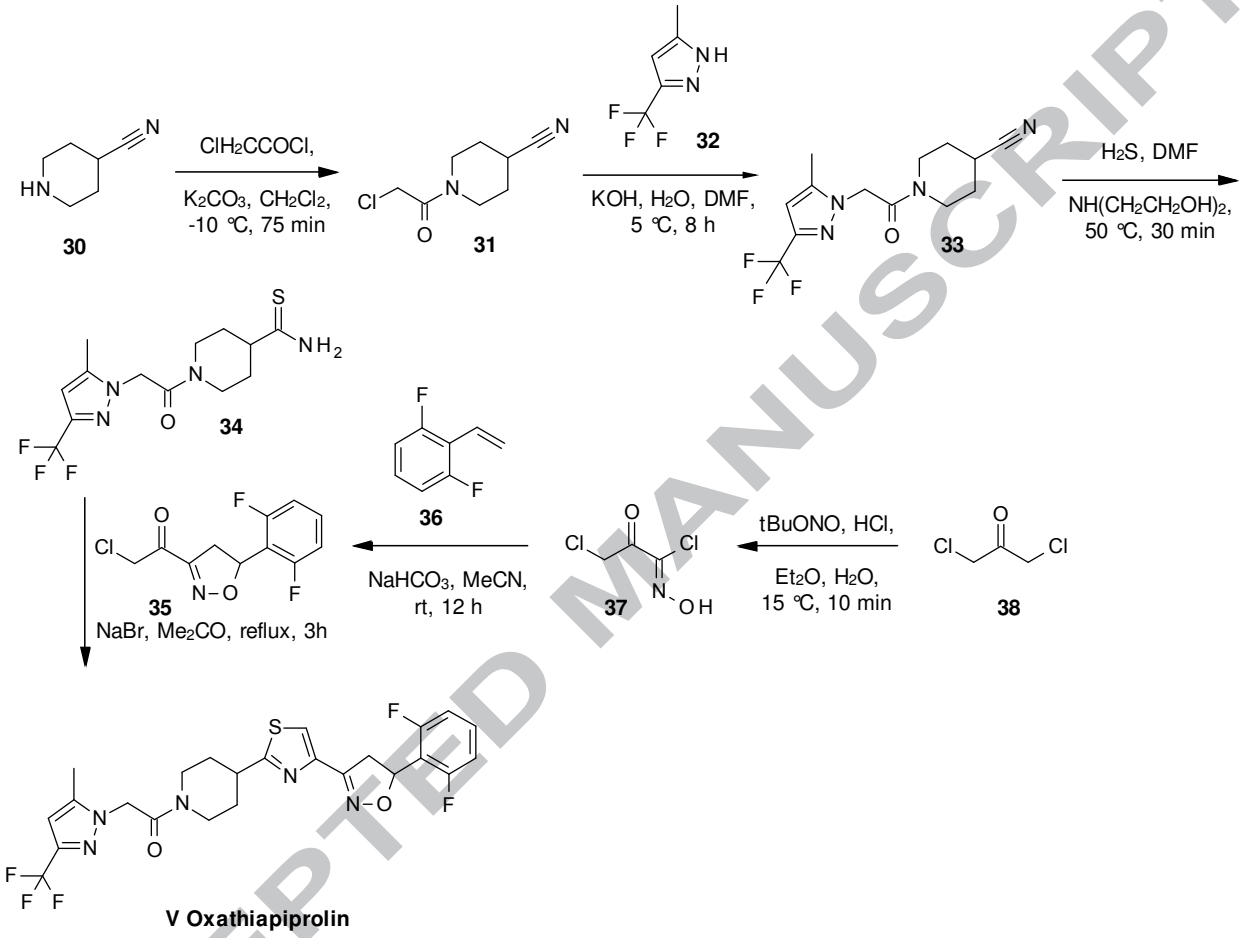


Scheme 4. Synthesis of pyraziflumid (**IV**).

2.5. Oxathiapiprolin (V)

Oxathiapiprolin (**V**) was announced by Du Pont in 2012.[41] This compound belongs to the new class of piperidinyl thiazole isoxazolines[42,43] and selectively controls plant pathogens of the *Oomycete* genus by inhibition of oxysterol-binding protein, a mode of action which doesn't exist amongst commercialized fungicides.[44] Whilst established market products need 100 g or more per hectare to efficiently control *Phytophthora infestans*, the causal agent of potato late blight, and *Plasmopara viticola*, responsible for grape downy mildew, oxathiapiprolin (**V**) achieves the same effect with 10 – 20 g/ha, a tenth of the typical use rate.[41] Therefore, the arrival of oxathiapiprolin (**V**) on the fungicide market will set a new standard in the control of downy mildew diseases. Oxathiapiprolin (**V**) has also been described to be efficacious against *Phytophthora capsici* in bell pepper[45] and against black shank in tobacco,[46] caused by *Phytophthora nicotianae*. The synthesis of oxathiapiprolin (**V**) begins with the acylation of 4-cyanopiperidine (**30**) to the chloroacetyl derivative **31**, which is then alkylated on the ring nitrogen of 5-methyl-3-trifluoromethylpyrazole (**32**) to yield the pyrazole acetamide **33**. The conversion of the nitrile function in **33** to a thioamide affords the important building block **34**,

which is then reacted with the chloroacetylisoxazoline derivative **35** to yield oxathiapiprolin (**V**). The required intermediate **35** is readily obtained in just two steps from 1,3-dichloroacetone (**38**) by oxymation to the carboximidoyl chloride **37** followed by 1,3-dipolar cycloaddition with 2,6-difluorostyrene (**36**) (Scheme 5).[42,47,48]

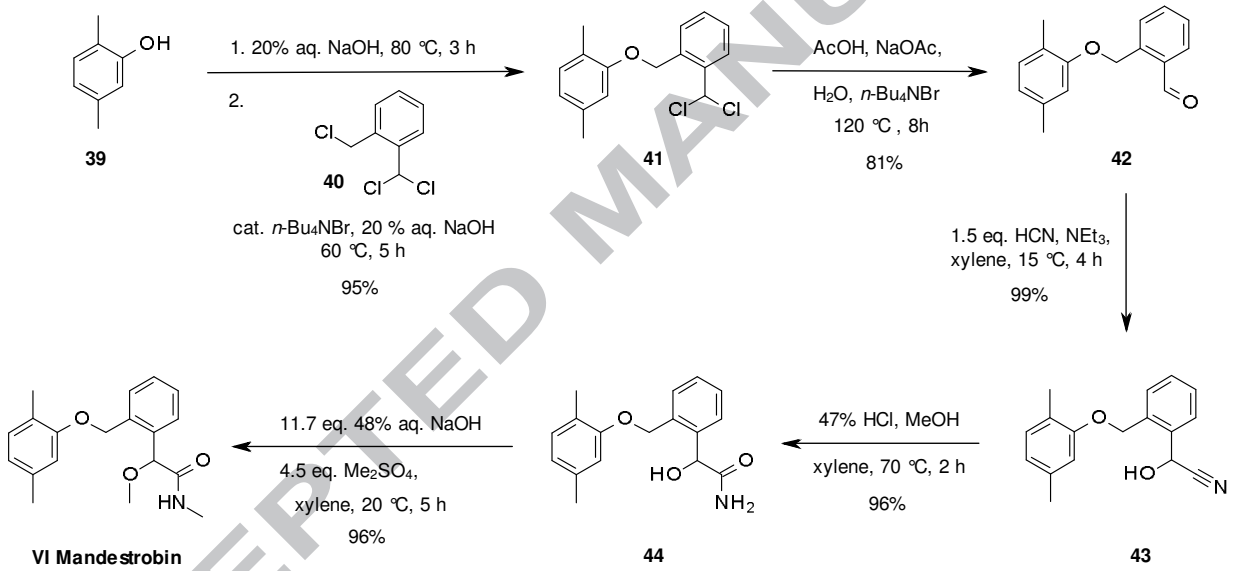


Scheme 5. Synthesis of oxathiapiprolin (**V**).

2.6. Mandestrobin (VI)

Mandestrobin (**VI**) is a new strobilurin registered by Sumitomo Chemical Company. The strobilurins are a very well-known class of fungicides.[49] They reached the market in the early 90's and major crop protection companies have several of them in their business portfolios as such compounds tend to have an extremely large spectrum of efficacy. Strobilurins act as antifungal agents by inhibiting the complex III of the respiration cycle at the Qo site.[49] There

have been several new strobilurins registered recently, but we are only discussing mandestrobin (**VI**) in this review as it possesses a new toxophore, a 2-methoxy-*N*-methyl-acetamide. The synthesis of mandestrobin (**VI**) begins with the alkylation of 2,5-dimethylphenol (**39**) with 2-(chloromethyl)benzal chloride (**40**), to give the intermediate **41**, which upon hydrolysis provides the aldehyde **42** (Scheme 6).[50] Aldehyde **42** is converted into the cyanohydrine **43** by reaction with cyanide.[51] Two process patents have been filed for this step; The latest one, not depicted in the scheme *vide infra* involves the following conditions: [HCN, *n*-Bu_4NBr, xylene, MeOH, H_2O, rt → 10°C then AcOH, H_2O, 0.5 h, 10 °C; 10 °C, pH 7.76; 10 °C, pH 7.37; 3 h, 10 °C].[52] Finally, mandestrobin (**VI**) is generated by hydrolysis of the nitrile group, followed by a bis-alkylation with methyl sulfate.[53]

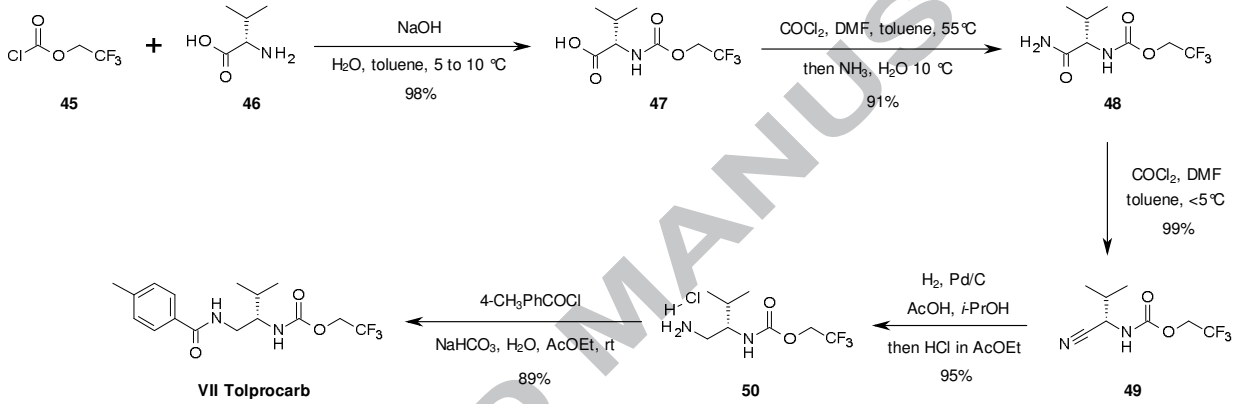


Scheme 6. Synthesis of mandestrobin (**VI**).

2.7. Tolprocarb (VII)

The valine carbamate fungicide tolprocarb (**VII**) was presented by Mitsui Chemicals in 2012.[14] It is being developed with a focus on the rice market, where it shows good control of *Magnaporthe grisea*, the causal agent of rice blast. Tolprocarb's (**VII**) fungicidal activity results from the inhibition of melanin biosynthesis, an essential step which allows the fungal *appressoria* to infect host plants. While other agrochemicals are known to inhibit reductase and dehydratase

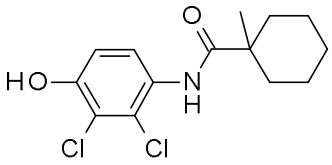
enzymes in the melanin biosynthesis pathway, tolprocarb (**VII**) is unique in that it inhibits the polyketide synthase enzyme (PKS).[54,55] The first step of the synthesis of tolprocarb (**VII**) is the carbamate coupling of valine (**46**) with trifluoroethyl chloroformate (**45**) in basic biphasic reaction conditions (Scheme 7).[56,57] The carbamate **47** thus obtained is then treated sequentially with phosgene and ammonia to yield carboxamide **48**, which is again reacted with phosgene to afford the nitrile intermediate **49**. Palladium catalyzed hydrogenation of **49**, followed by amidation of **50** with 4-methylbenzoic acid, yields tolprocarb (**VII**) in 6 synthetic steps and 75% overall yield.



Scheme 7. Synthesis of tolprocarb (**VII**).

2.8. Fenpyrazamine (VIII)

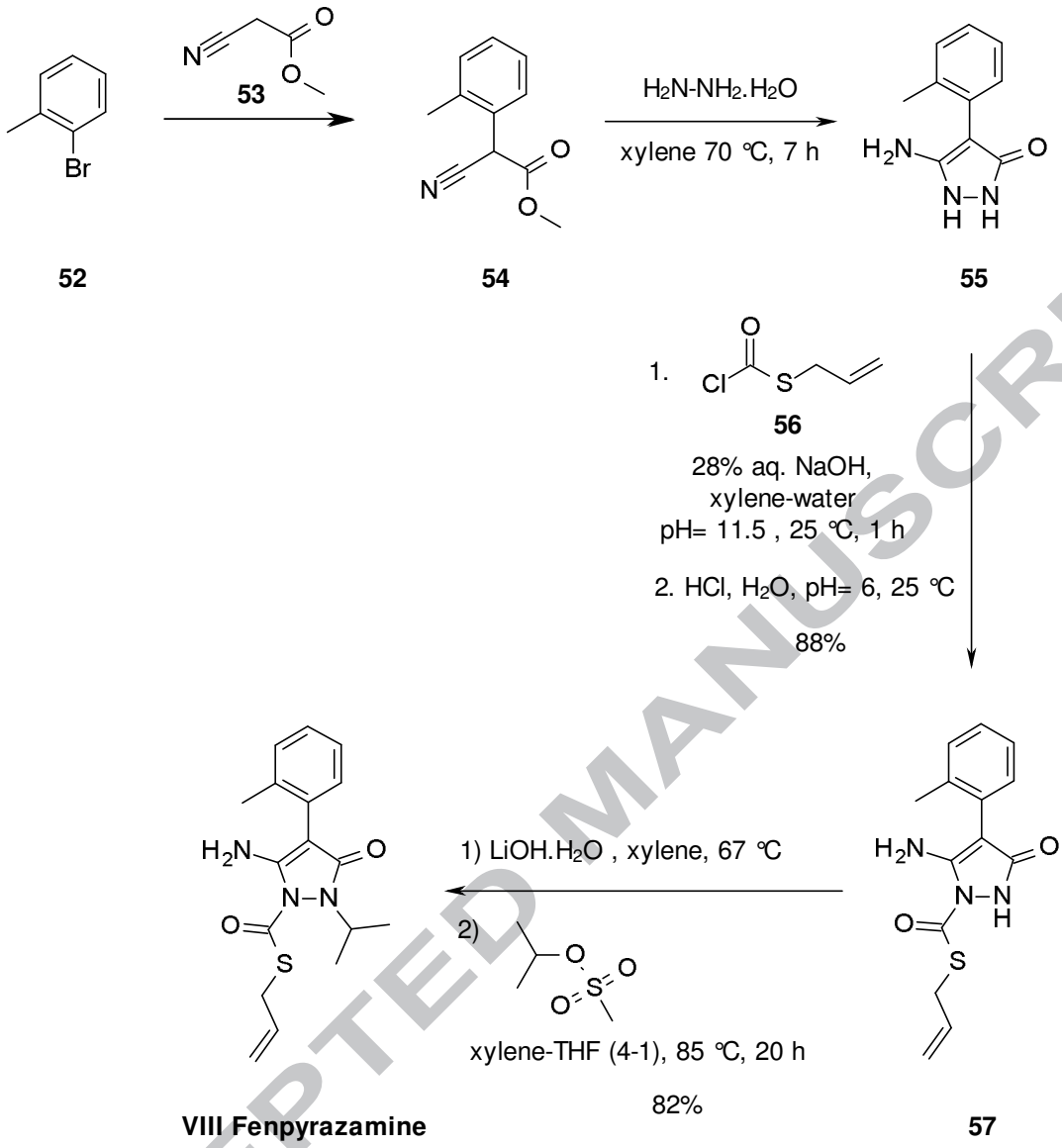
Fenpyrazamine (**VIII**) is a fungicide that was discovered and developed by Sumitomo Chemical Company. The molecule is particularly efficient against the *Sclerotiniaceae* family such as *B. cinerea* (grey mould), other *Botrytis spp.* and *Sclerotinia* spp.[58] Fenpyrazamine (**VIII**) exerts its antifungal activity by inhibiting the sterol biosynthesis, more particularly the 3-keto reductase of the enzymatic complex of the sterol C-4 demethylation.[58] This is the second molecule, after fenhexamide **51** (Figure 5),[59] reaching the crop protection market with this particular mode of action. The two molecules have completely different scaffolds. It is not yet known if the molecules are acting on the same active site or not.



51

Figure 5. Fenhexamide (**51**).

The synthesis of fenpyrazamine (**VIII**) starts with methyl 2-cyano-2-(o-tolyl)acetate (**54**). It has been reported in the literature that compounds **54** can be formed from the coupling of the bromo-tolyl **52** or the corresponding chloride and the cyano-acetate **53** by a metal catalysed coupling process.[60] The formation of the 5-amino-1,2-dihydropyrazol-3-one (**55**) is performed by condensation of hydrazine hydrate with the cyano acetate **54**, by an azeotropic distillation of water, followed by condensation.[61] The yield for this reaction has not been reported, but there is no doubt that this is high yielding reaction. *S*-allyl chloromethanethioate (**56**) is introduced with high regioselectively, as shown in scheme 8, yielding compound **57**, although there are potentially 2 other reactive nitrogens.[61] The choice of base and the mixture of water and xylene may play a major role in this selectivity. Finally, the addition of isopropyl methane sulphonate in the presence of lithium hydroxide provides fenpyrazamine (**VIII**) (Scheme 8).[61] The *S*-allyl chloromethanethioate **56** is prepared from the reaction of allyl mercaptan with phosgene in the presence of a catalytic amount of triethylamine in excellent yield [*S*-allylmercaptan, phosgene, cat NEt_3, xylene, 40 °C, 11 h]. All the reactions described are performed in xylene, suggesting good opportunities for telescoping in manufacturing and reducing costs.

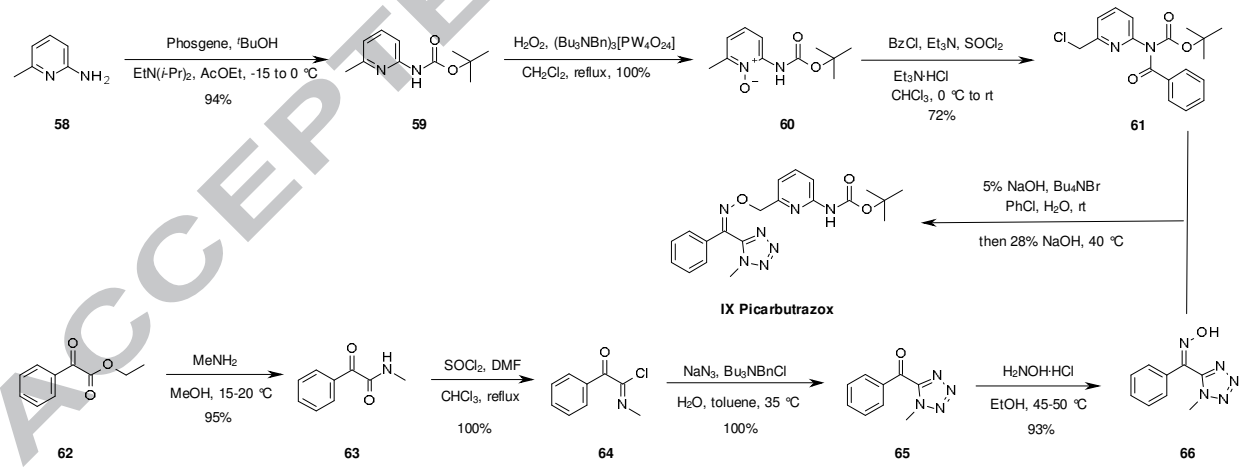


Scheme 8. Synthesis of fenpyrazamine (**VIII**).

2.9. Picarbutrazox (IX)

Nippon Soda presented picarbutrazox (**IX**) as a new oomycete specialist fungicide in 2013.[14] This new active ingredient belongs to an unprecedented class of tetrazolyloximes for which the mode of action is, as yet, unknown.[62] Picarbutrazox (**IX**) is active against *P. viticola* and *P. infestans*, and its spectrum also includes important *Pythium* species responsible for damping-off

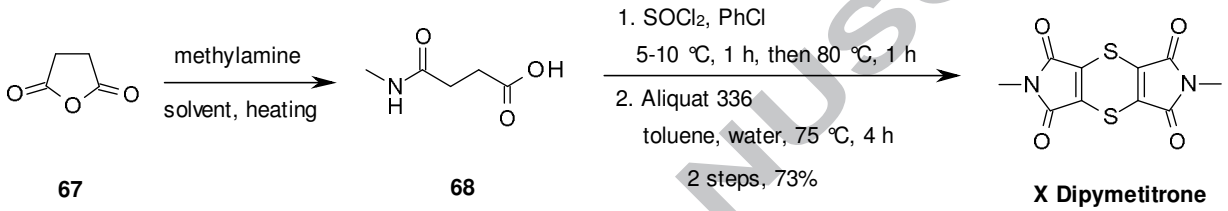
disease in many crops. Nippon Soda has investigated and patented many different routes for the synthesis of picarbutrazox (**IX**).[63] The synthesis shown below has been selected for its high convergence and the relatively low cost of the reagents. However, it is evident that some steps might prove challenging to apply safely on ton scale. The synthesis of picarbutrazox (**IX**) involves the late stage combination of two advanced building blocks, the pyridine carbamate **61** and the tetrazolyloxime **66** (Scheme 9). The key compounds required for this synthesis begin with reaction of 2-aminopyridine **58** with phosgene in the presence of *tert*-butanol to afford carbamate **59** in 94% yield.[63] The pyridine **59** is oxidized quantitatively to its pyridine *N*-oxide analogue **60,** followed by a nice one pot procedure involving chlorination of the methyl group of the pyridine and protection of its NH functionality, by the successive addition of benzoyl chloride and thionyl chloride to give **61** in 72% yield.[64] The second building block synthesis starts with the amidation of ethyl phenylglyoxylate (**62**) affording amide **63** in 95% yield. The tetrazole ring is prepared in two steps by chlorination of **63** with thionyl chloride, affording intermediate **64,** which is subsequently treated with sodium azide in the presence of a phase transfer catalyst to yield quantitatively **65**. The α-ketotetrazole is then oximated using hydroxylamine, yielding **66**.[65] The two advanced intermediates **61** and **66** are combined together in basic conditions to deliver, after debenzoylation, picarbutrazox (**IX**).[66]



Scheme 9. Synthesis of picarbutrazox (**IX**).

2.10. Dipymetitrone (X)

Dipymetitrone (**X**) has been presented by Bayer CropScience as a new fungicide in 2014.[14] The first synthesis dated back to 1967 when Draber reacted 3,4-dichloro-*N*-methylmaleimide and hydrogen sulfide in basic methanolic solution.[67] Bayer CropScience applied for a patent for its use as a fungicide in 2008.[68] The synthesis of dipymetitrone (**X**) could start from the reaction of methylamine and succinic anhydride (**67**) to afford **68**. Treatment of **68** with thionyl chloride and isomerization of the intermediate diisomaleimide-dithiine with water yields dipymetitrone (**X**) (Scheme 10).[69] The mechanism of this atypical reaction has been investigated by Valla.[70]

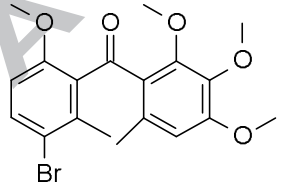


67 **68** **X Dipymetitrone**

Scheme 10. Synthesis of dipymetitrone (**X**).

2.11. Pyriofenone (XI)

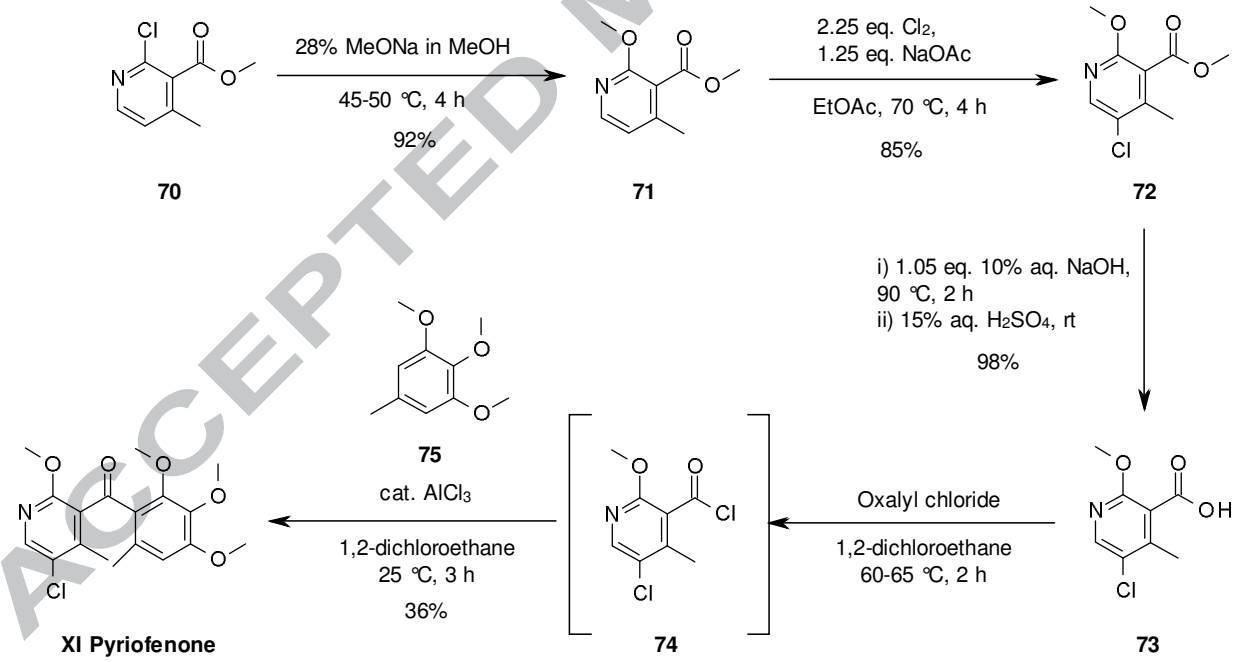
Pyriofenone (**XI**) is a new fungicide introduced by ISK to control powdery mildews in cereals, grapes and vegetables.[14] The mode of action is not known but it could be from the same group of fungicides as metrafenone **69** (Figure 6), since pathogens with cross-resistance to both compounds have been reported in the literature.[71] In addition, their chemical structures are very closely related so it is not unreasonable to assume that they share the same mode of action. It has been proposed that the molecules are exerting their antifungal effect by disruption of actin.[72]



69

Figure 6. Metrafenone (**69**).

There is no process yet published for the preparation of pyriofenone (**XI**). It is however possible to described a synthetic route from the active ingredient patent application and a process patent of the nicotinic acid derivate **73** published by ISK.[73,74] The synthesis starts with methyl 2-chloro-4-methyl nicotinate (**70**) which has not been reported by ISK, but for which several syntheses can be found in the literature.[75] An S_NAr reaction allows the introduction of the methoxy group, which followed by a selective chlorination of the pyridine ring, provides compound **72** in 85% yield. Hydrolysis to the corresponding acid **73**, and conversion to the acid chloride gives **74**, which is primed for Friedel-Crafts acylation with 3,4,5-trimethoxy-toluene (**75**) under Lewis acid catalysis (Scheme 11). The formation of the acid chloride and the Friedel-Crafts acylation have been reported as a one-pot procedure.[73] A similar Friedel-Crafts acylation has also been used by BASF scientists for the synthesis of metrafenone (**69**).[76] Other synthetic approaches to pyriofenone (**XI**) are reported in the original active ingredient patent.[73]

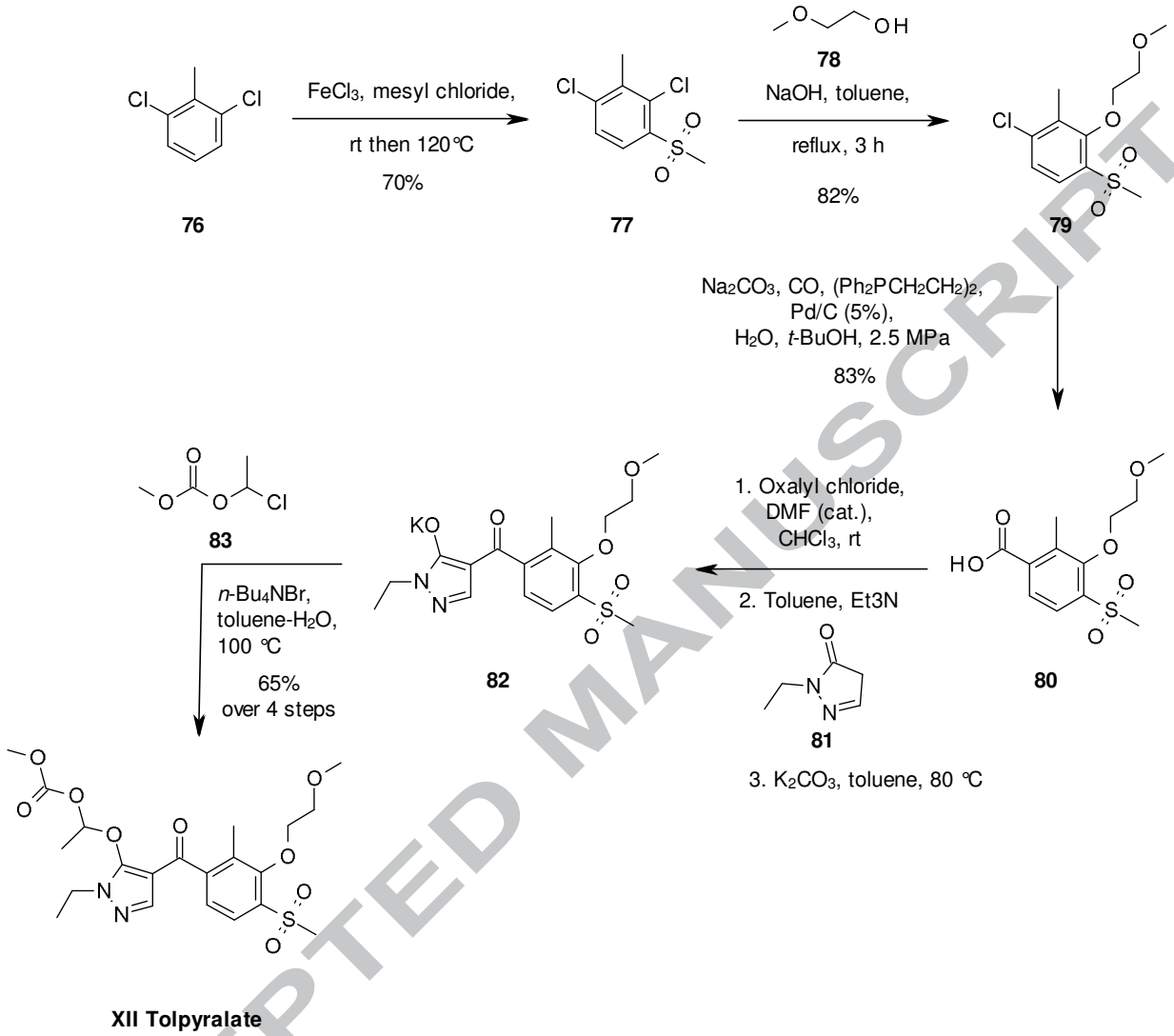


Scheme 11. Synthesis of pyriofenone (**XI**).

3. Herbicides

3.1. Tolpyralate (XII).

Tolpyralate (**XII**) is a new selective herbicide for weed control in corn, which was discovered by ISK.[77] Tolpyralate (**XII**) controls a wide range of grass and broadleaf weeds, with excellent selectivity in corn.[77] Tolpyralate (**XII**) is a procide, with the active species being the molecule **82,** in which the carbonate of **XII** has been cleaved. The active species was first published in 2007,[78] with this area of chemistry also being investigated by Dow AgroSciences and Nissan.[79] Similarly to other 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors, the synthesis (Scheme 12) involves the preparation of the required acid (in this case **80**) and then O-acylation with a dione, or in this case the pyrazolone (**81**),[80] followed by a O-acyl to C-acyl rearrangement to yield the pyrazole (**82**). The required acid **80**, is prepared from **76**, *via* a Friedel-Crafts reaction of **76** with mesyl chloride, followed by regioselective aromatic substitution reaction of the resultant **77** with **78** under basic conditions, and finally palladium catalyzed carbonylation of **79** under high pressure.[81] The rearrangement chemistry discussed above yields the sodium salt of pyrazole **82**, which is then alkylated with **83** under phase transfer conditions to give Tolpyralate (**XII**).[81,82]

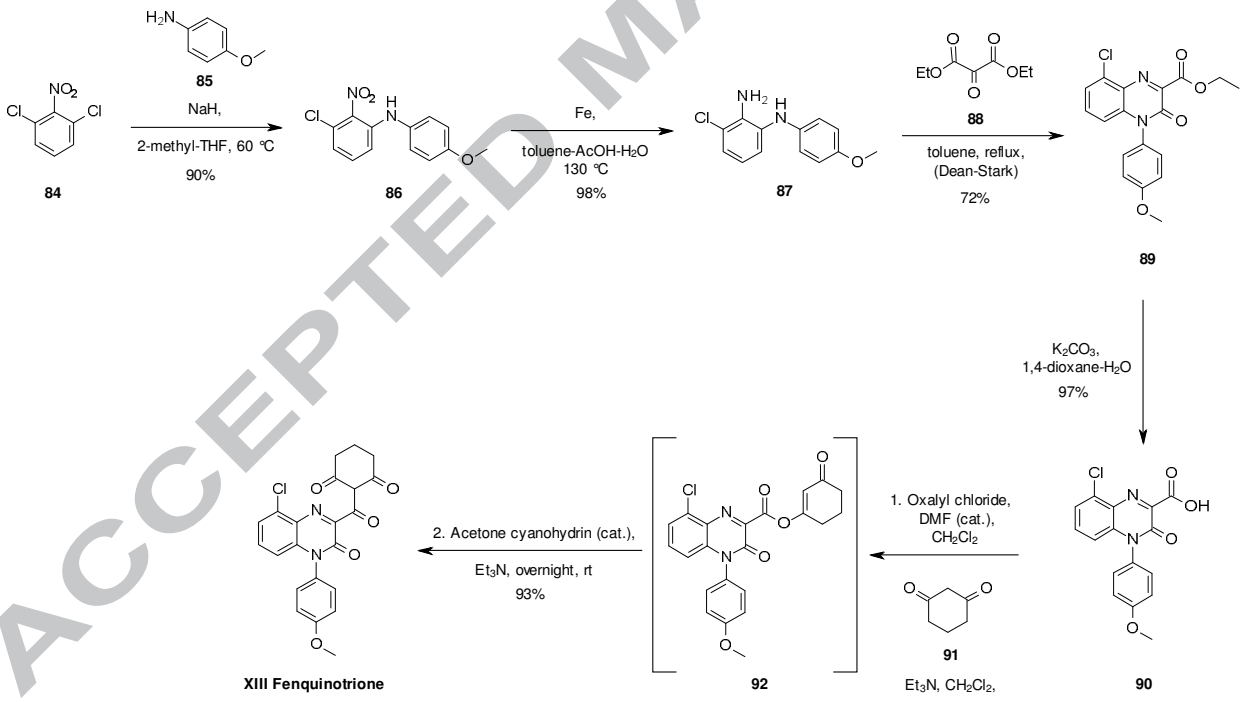


Scheme 12. Synthesis of Tolpyralate (**XII**).

3.2. Fenquinotrione (XIII).

Fenquinotrione (**XIII**) is a new herbicide developed by Kumiai Chemical Industry and Ihara Chemical Industry for use in rice and other crops.[83] Fenquinotrione (**XIII**) controls a wide range of sedges and broadleaf weeds with residual activity, and has excellent rice selectivity in any rice production system. Fenquinotrione (**XIII**) exerts its herbicidal effect through inhibition of

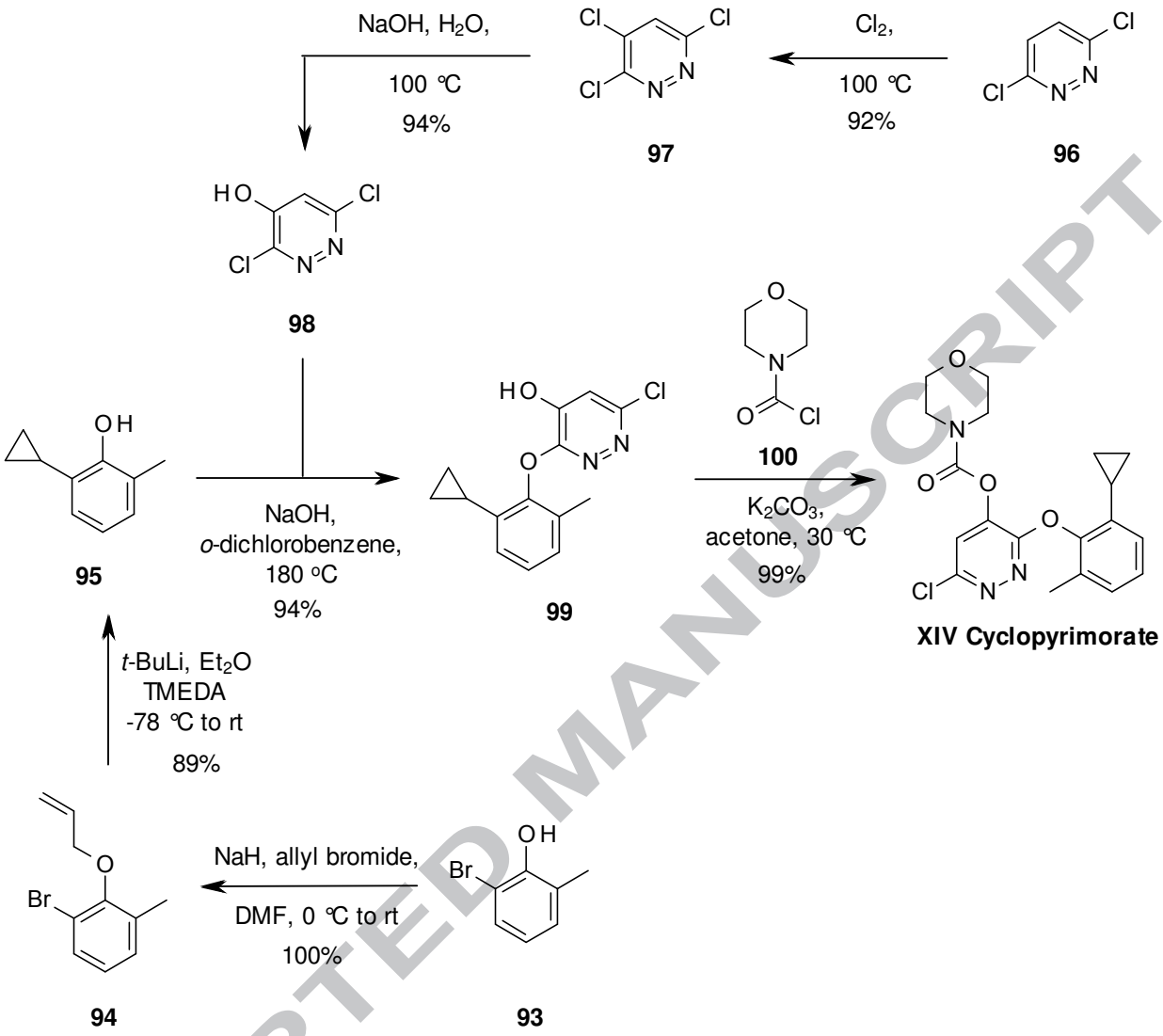
HPPD, and is effective on troublesome acetolactate synthase (ALS) resistant weeds, which are widely common in rice production areas.[83] The synthesis of fenquinotrione (**XIII**)[84] involves the now well established *O*-Acyl coupling of the acid **90** to cyclohexandione (**91**), followed by a cyanide catalyzed rearrangement (*via* the acyl cyanide) of **92** to the *C*-acylated product (Scheme 13).[85] The required acid **90** for this chemistry is synthesized by an aromatic substitution reaction of **84** with **85** to give **86**. Béchamp reduction of the nitro group, followed by a Dean-Stark condensation of **87** with diethyl ketomalonate (**88**) gives the ester **89**. The reaction is regioselective, with the primary aniline function of **87** attacking the keto function of **88**, with the secondary aniline function then attacking one of the ester carbonyls to close the ring. The isomer that would be obtained by the primary aniline **87** first attacking an ester functionality, and the secondary aniline then attacking the carbonyl, is not reported. Hydrolysis of the ester **89** with potassium carbonate and water gives the required acid **90** that can be converted to fenquinotrione (**XIII**) by the rearrangement chemistry previously mentioned.



Scheme 13. Synthesis of fenquinotrione (**XIII**).

3.3. Cyclopyrimorate (XIV).

Cyclopyrimorate (**XIV)** is a new pyridazine selective broad-spectrum rice herbicide discovered by Daiichi Sankyo (now Mitsui Chemicals Agro).[86] The mode of action of cyclopyrimorate is as yet unknown. The compound is a procide and the active ingredient patents claiming the cide (the substituted pyridazin-4-ol derivative **99**) have also been published.[87] A convergent synthesis is shown in scheme 14.[88] Alkylation of **93** under standard conditions leads to **94**, which undergoes an allowed 6-*exo*-dig cyclisation after anion generation, to the key cyclopropyl intermediate **95**.[89] The other key intermediate **98** can be prepared in excellent overall yield by chlorination of **96**, followed by selective hydrolysis.[90] The coupling of **98** with **95** was optimized to give **99** in excellent yield and with high chemoselectivity, in a procedure that involves preparing anhydrous NaOH in *o*-dichlorobenzene by azeotropic removal of water, and then adding **98** in *t*-BuOH, with continued azeotropic removal of *t*-BuOH during the reaction.[88] The synthesis is completed by acylation of **99** with **100** under standard conditions.[88]

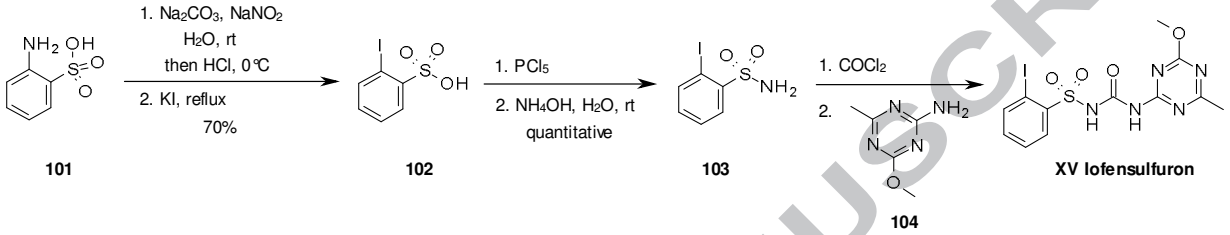


Scheme 14. Synthesis of cyclopyrimorate (**XIV**).

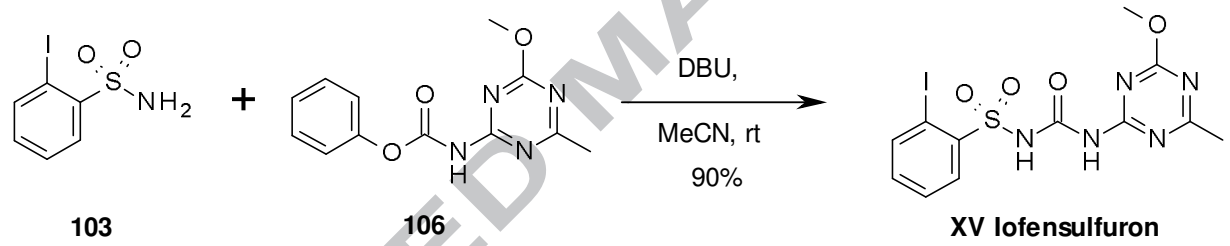
3.4. Iofensulfuron (XV).

Iofensulfuron (**XV**) received a common name from ISO in 2011, and it is known that Bayer CropScience plans to commercialize this compound as its sodium salt.[14] Iofensulfuron (**XV**) is a herbicide sulfonylurea and, as other active ingredients from this chemistry class, an inhibitor of ALS, an enzyme common to the biosynthesis of branched chain amino acids.[91] The first step in the synthesis of iofensulfuron (**XV**) involves a Sandmeyer iodination of 2-aminobenzenesulfonic acid (**101**) yielding 2-iodobenzenesulfonic acid (**102**). This can be readily transformed into its

sulfonamide analogue **103** *via* sequential treatment with phosphorous pentachloride and ammonium hydroxide.[92,93] It is likely that the last step of the manufacturing route of iofensulfuron (**XV**) would involve reaction of sulfonamide **103** with phosgene, and subsequent reaction with aminotriazine **104,** as depicted in scheme 15. However, the only synthesis of iofensulfuron reported by Bayer CropScience involves the reaction of sulfonamide **103** with carbamate **106** (Scheme 16).[94]



Scheme 15. Synthesis of iofensulfuron (**XV**).

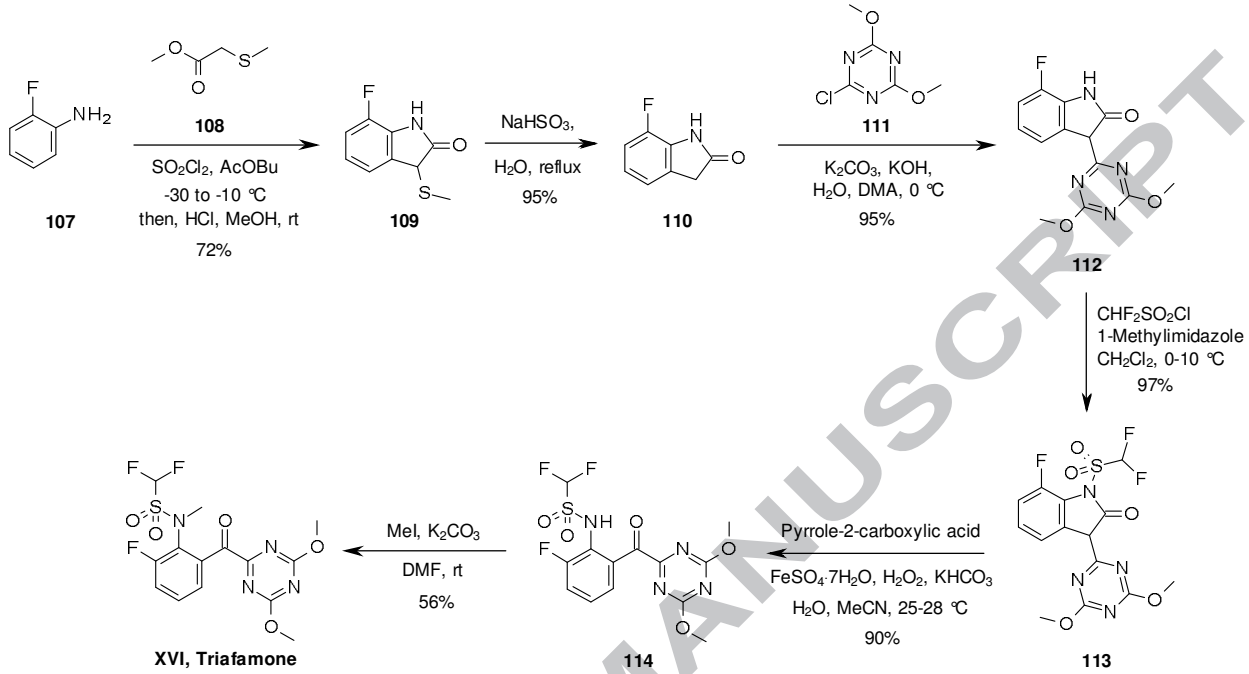


Scheme 16. Alternatvie synthesiss of iofensulfuron (**XV**) based on the active ingredient patent.

3.5 Triafamone (XVI)

Triafamone (**XVI**) was announced by Bayer CropScience in 2010. It exerts its herbicidal activity by blocking the biosynthesis of branched chain amino acids by inhibiting the ALS enzyme.[14] The synthesis of triafamone (**XVI**) begins by the reaction of aniline **107** and methyl 2-methylthioacetate (**108**) in the presence of sulfuryl chloride, which yields indolone **109**.[95] Reductive cleavage of the methylthiol group, followed by S_NAr reaction of intermediate **110** with triazine **111** under basic conditions delivers indolone **112**.[96,97] The sulfonamide **113** is easily obtained by treating **112** with difluorosulfonyl chloride in the presence of 1-methylimidazole.[98] The benzophenone motif of triafamone (**XVI**) is finally revealed by the oxidation of the indolone

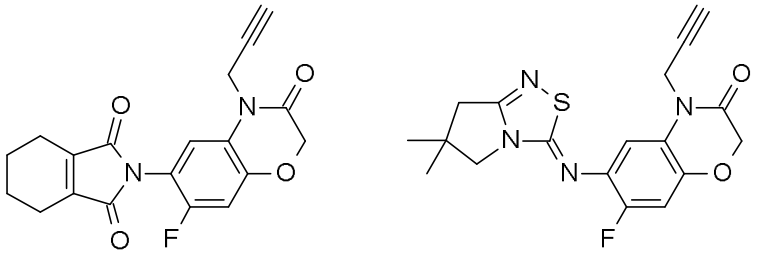
113 using an iron sulfate and hydrogen peroxide mixture,[99] and its synthesis completed after methylation of the advanced intermediate **114** (Scheme 17).[100]



Scheme 17. Synthesis of triafamone (**XVI**).

3.6. Trifludimoxazin (XVII)

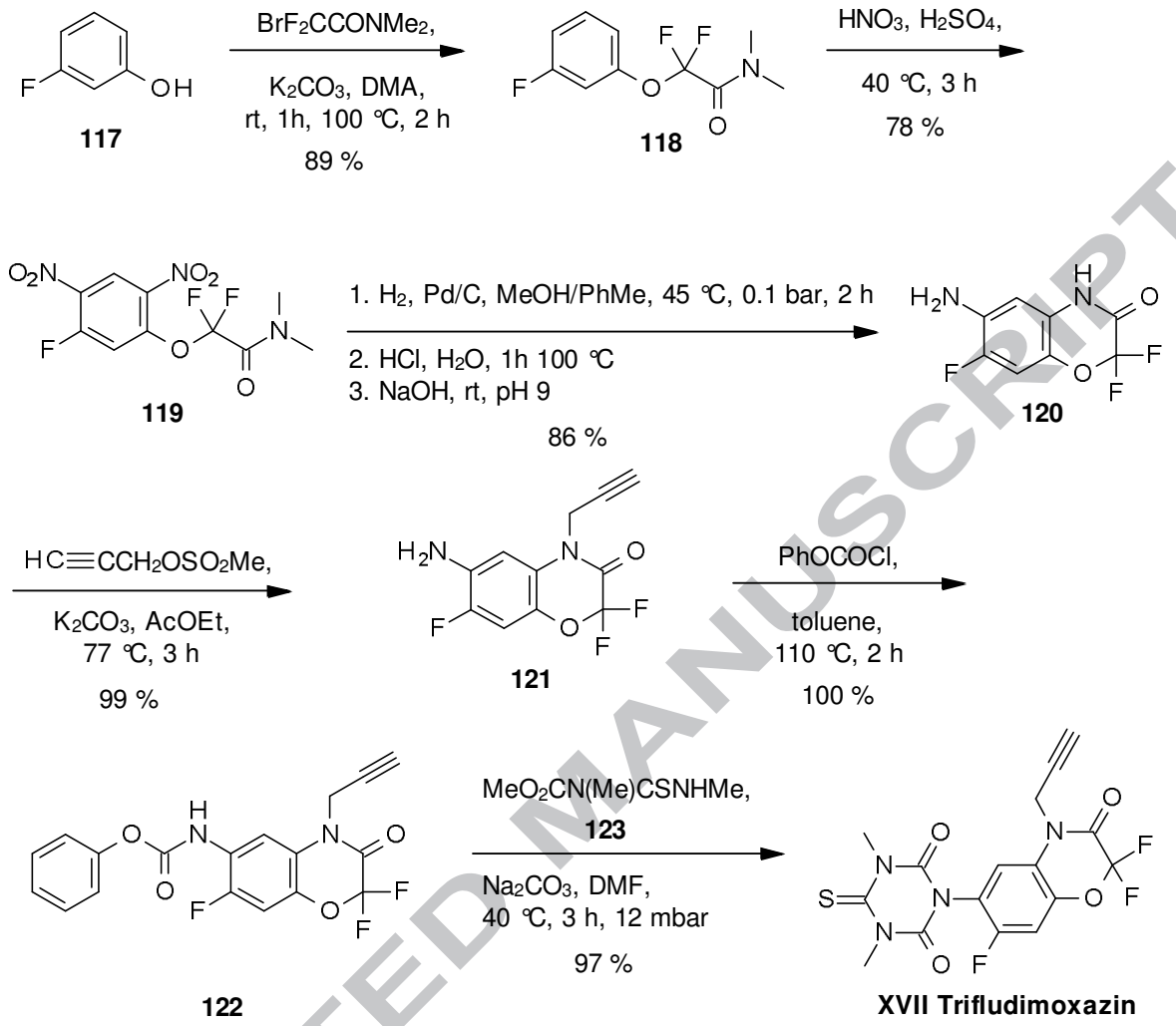
The triazinone herbicide trifludimoxazin (**XVII**) was reported by BASF in 2014.[14] After flumioxazin (**115**)[101] and thidiazimin (**116**)[102] (Figure 7), it will be the third benzoxazinone derivative amongst the group of protoporphyrinogen oxidase (PPO) inhibitors. However, in contrast to this new compound, the two aforementioned established market products neither contain trifludimoxazin's dimethylated thiocyanuric acid moiety nor bear the *gem*-difluoro substitution within its oxazinone ring.



115 **116**

Figure 7. Flumioxazin (**115**) and thidiazimin (**116**).

The synthesis of trifludimoxazin (**XVII**) starts with the alkylation of 3-fluorophenol (**117**) with bromodifluorodimethylacetamid. The resulting aryloxyacetamide **118,** is nitrated to the tetrasubstitited phenyl derivative **119**. After reduction of the nitro groups, the benzoxazinone derivative **120** is formed, bearing three different fluoro substituents, two of which are located in the oxazinone ring and the third one in the phenyl ring. Propargylation of the ring nitrogen, with subsequent protection of the amino function as a phenyl carbamate yields the intermediate **122**. This can be directly cyclized to trifludimoxazin (**XVII**) with *N*-methoxycarbonyl-*N*,*N*-dimethylthiourea (**123**) under basic conditions (Scheme 18).[103]

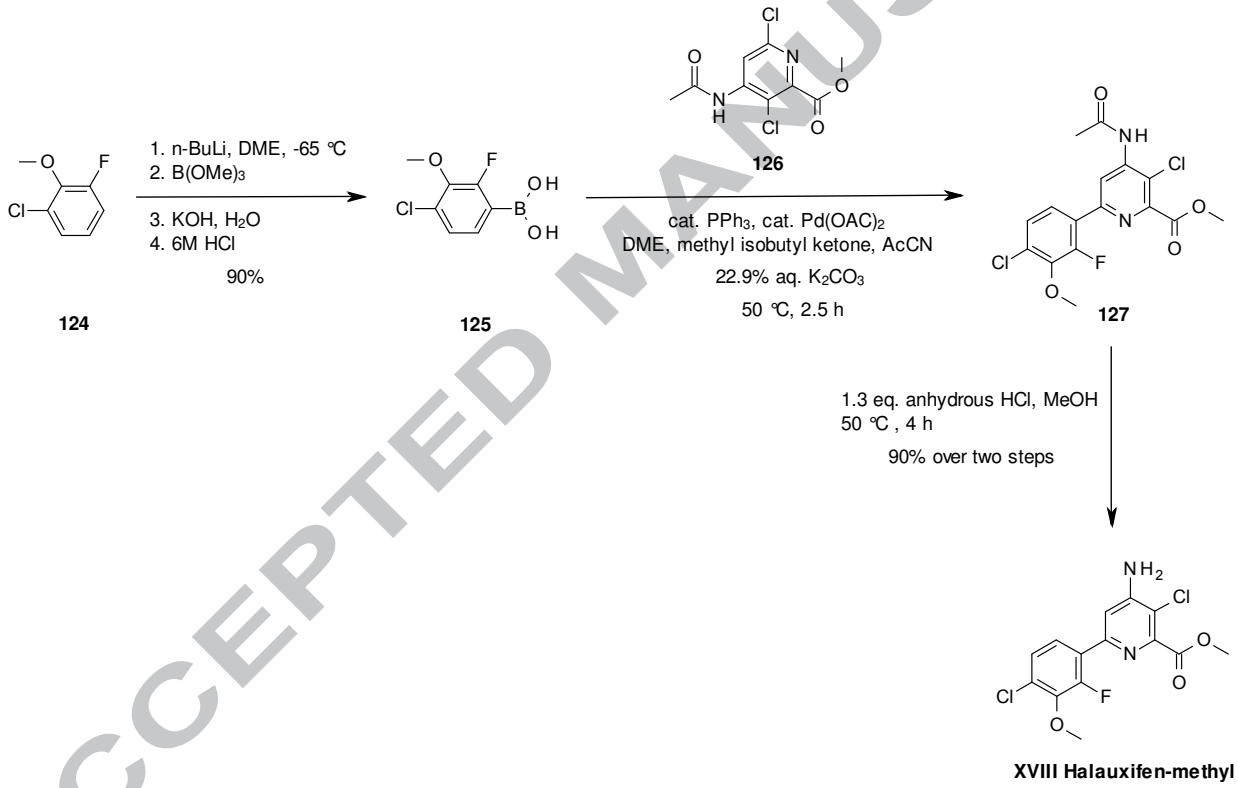


Scheme 18. Synthesis of trifludimoxazin (**XVII**).

3.7. Halauxifen-methyl (XVIII)

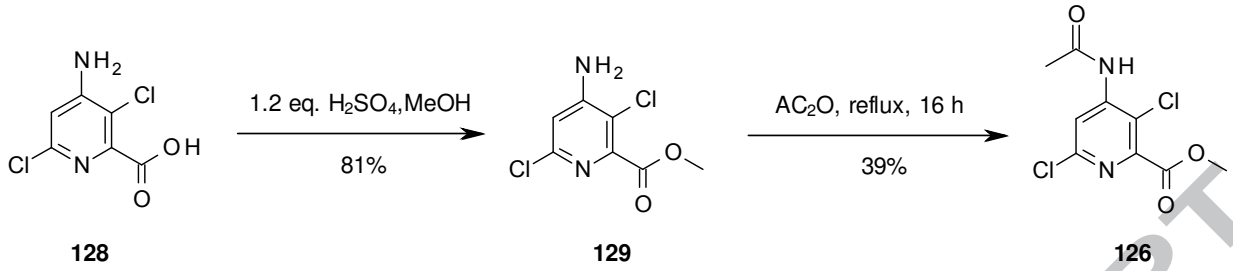
Halauxifen-methyl (**XVIII**) is a new herbicide launched as Arylex™ by Dow AgroSciences.[104] Halauxifen-methyl (**XVIII**) is the first member of the new phenyl aminopyralid class of synthetic auxin herbicides. The compound is cleaved *in planta* to the carboxylate which is the active ingredient. Halauxifen provides a step change in the control of broadleaf weeds as it is active at much lower rates than classical auxin herbicides.[104]

Two types of synthetic routes have been reported in process patents from Dow AgroSciences:[105,106] One of these involves the *de novo* synthesis of the pyridine ring,[105] while the other utilizes a cross-coupling reaction to generate the biaryl system.[106] The later was chosen to be reported in this review as the scale described in process patents, and the number of process patents published suggests this is the favored route. Following the cross coupling strategy (Scheme 19), halauxifen-methyl (**XVIII**) is prepared from the 2-chloro-6-fluoroanisole **124** by metallation, and borylation to yield boronic acid **125**. Suzuki reaction of **125** with **126** yields **127** which is subsequently deprotected, to the title product. The two last steps are reported to give an overall yield of 90%.[106]



Scheme 19. Synthesis of halauxifen-methyl (**XVIII**).

Compound **126** is easily prepared form the commercial herbicide aminopyralid (**128**), which has been described in WO2001051684,[104] in a process involving esterification to **129**, followed by acylation of the aniline function (Scheme 20).[104]



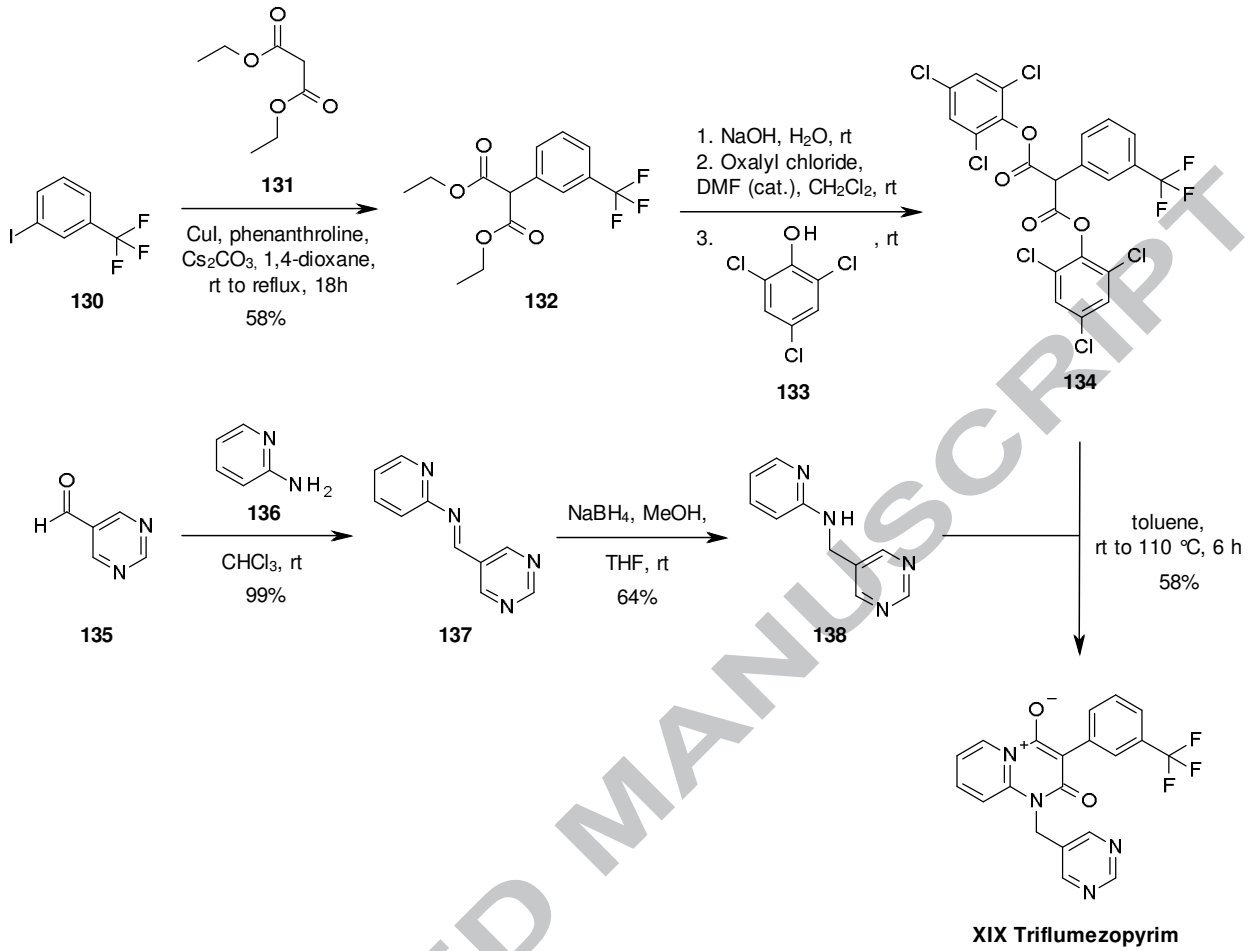
128 **129** **126**

Scheme 20. Synthesis of intermediate **126**.

4. Insecticides

4.1. Triflumezopyrim (XIX)

Triflumezopyrim (**XIX**)[108] is a new rice insecticide which targets the insect acetylcholine receptor.[109] Triflumezopyrim (**XIX**) is a potent hopper (brown plant hopper/leaf hopper) specialist with good residual activity in rice. The compound also has a very favorable environmental profile.[108] Triflumezopyrim (**XIX**), has a unique mesoionic core and can be synthesized as shown in scheme 21.[110] The synthesis involves a copper catalyzed addition of diethyl malonate (**131**) to **130**, followed by ester hydrolysis of the intermediate **132**. The resultant di-acid is activated as a trichlorophenoxy ester (**134**),[111] which is condensed with the intermediate **138** (which in turn had been prepared by reductive amination of the pyrimidine aldehyde **135** with **136**) to complete the synthesis.[110]

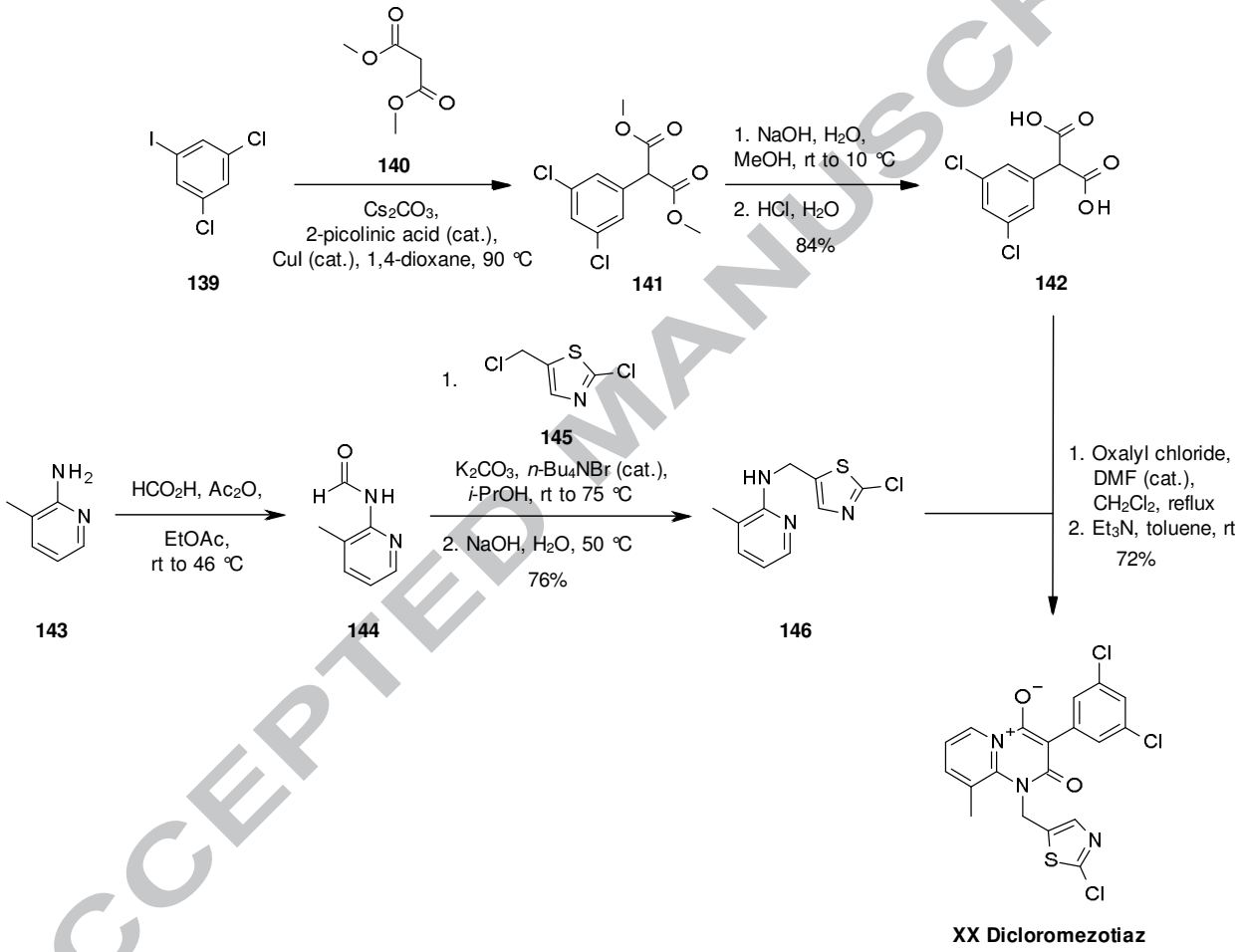


Scheme 21. Synthesis of triflumezopyrim (**XIX**)

4.2. Dicloromezotiaz (XX)

Dicloromezotiaz (**XX**)[112] is the second mesoionic insecticide from DuPont, which has the same mode of action as triflumezopyrim (**XIX**, see section 4.1.).[109] The compound is structurally very similar to triflumezopyrim (**XIX**), having a mesoionic central core, a *meta*-substituted aromatic (in this case a dichloro benzene) and a methylene heteroaryl substituent on the nitrogen. The only other difference is the additional methyl substituent on the amino pyridyl moiety (Figure 1). Whilst triflumezopyrim (**XIX**) is a hopper specialist, dicloromezotiaz (**XX**) has good activity on a range of *Lepidopteran* species.[112] The synthesis of dicloromezotiaz (**XX**) is similar to that of triflumezopyrim (**XIX**), and is shown in scheme 22. The convergent synthesis begins with a copper catalyzed coupling of dimethyl malonate **140** with the iodide **139**. The crude product **141**

is directly hydrolysed to the diacid **142** in overall yield of 84% for the two steps. The required coupling partner **146** is prepared efficiently by formamide protection of **143**, followed by phase transfer catalyzed alkylation of **144** with 2-chloro-5-(chloromethyl)thiazole (**145**), followed by *in situ* deprotection, to yield **146** in 76% yield. To complete the synthesis, the diacid is activated as the diacid chloride and treated with **146** in toluene in the presence of triethyl amine. This gives diclorom ezotiaz (**XX**) in 72% yield as a single crystal polymorph.[113]

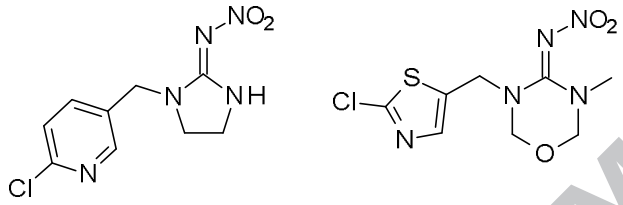


Scheme 22. Synthesis of diclorom ezotiaz (**XX**).

4.3. Flupyradifurone (XXI)

Flupyradifurone (**XXI**, Bayer CropScience), is proposed as an alternative insecticide for controlling sucking pest species. Foliar applications, and soil drenches of the end-use product,

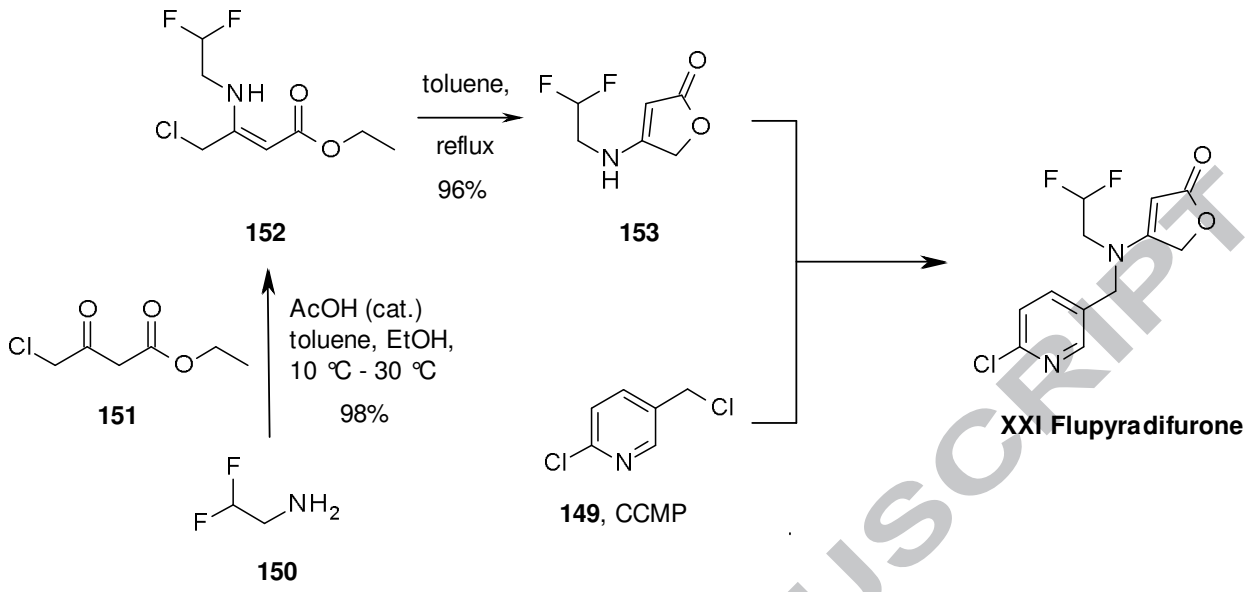
Sivanto™ 200 SL, are approved for use on a large number of crops, including fruits and vegetables.[114] Flupyradifurone (**XXI**) acts on insect nicotinic acetylcholine receptors as has been shown in radioligand binding studies conducted with tritiated imidacloprid (**147**).[114] Whilst imidacloprid (**147**) and thiamethoxam (**148**) are nicotinic acetylcholine receptor competive modulators,[114,115] belonging to the IRAC class group 4A, flupyradifurone (**XXI**) in contrast belongs to the butenolide sub-group 4D.[114,115] Technical synthesis of flupyradifurone (**XXI**) might involve 6-chloro-3-chloromethyl-pyridine (**149**, CCMP) as a key intermediate, as this is also a key intermediate of Bayer CropScience's imidachloprid (**147**).[116] There are two possible technical syntheses of **XXI**, both of which have been described by Bayer CropScience. The first of these is illustrated in scheme 23.



147 **148**

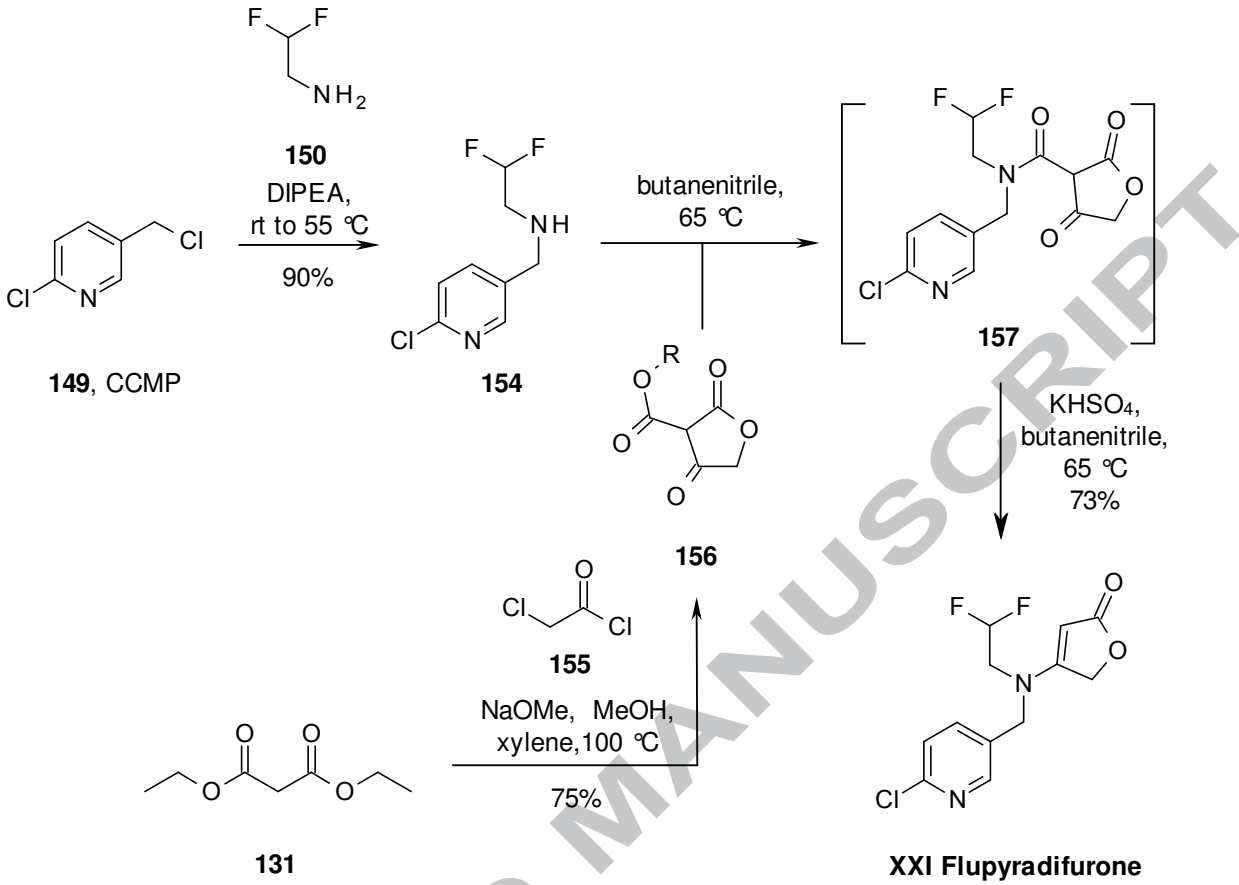
Figure 8. Imidacloprid (**147**) and thiamethoxam (**148**).

As shown in scheme 23, reaction of 2,2-difluoroethanamine (**150**) with ethyl 4-chloro-3-oxo-butanoate (**151**) under acidic catalysis leads to **152** in excellent yield.[117] Subsequent heating of **152** in toluene leads to the furanone **153**.[117] Alkylation of **153** with CCMP (**149**) would in principle provide flupyradifurone (**XXI**). This actual alkylation is not described but very similar chemistry has been reported by Bayer CropScience chemists.[117,118]



Scheme 23. Synthesis of flupyradifurone (**XXI**).

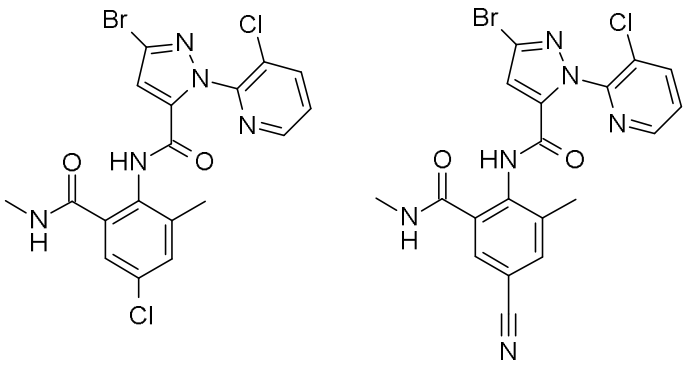
Alternatively, flupyradifurone (**XXI**) can be synthesized as shown in scheme 24. Condensation of diethyl malonate (**131**) and chloroacetyl chloride (**155**) under basic conditions leads to tetronic acid derivative **156** as a mixture of methyl and ethyl esters.[119] This is coupled with **154**, which was prepared by reaction of CCMP (**149**) with 2,2-difluoroethanamine (**150**),[120] to give the amide **157**. This can be isolated, but is most likely rearranged to flupyradifurone (**XXI**) by heating in butyronitrile by a ring opening-ring closing mechanism followed by decarboxylation in good yield.[120] The key intermediate amine **150** required for both of these synthesis can be prepared from 2-chloro-1,1-difluoro-ethane either directly by treatment with ammonia under high pressure conditions,[121] or by alkylation of 2-chloro-1,1-difluoro-ethane with a protected amine, followed by deprotection.[122,123]



Scheme 24. Synthesis of flupyradifurone (**XXI**) by an amide rearrangement pathway.

4.4. Cyclaniliprole (XXII)

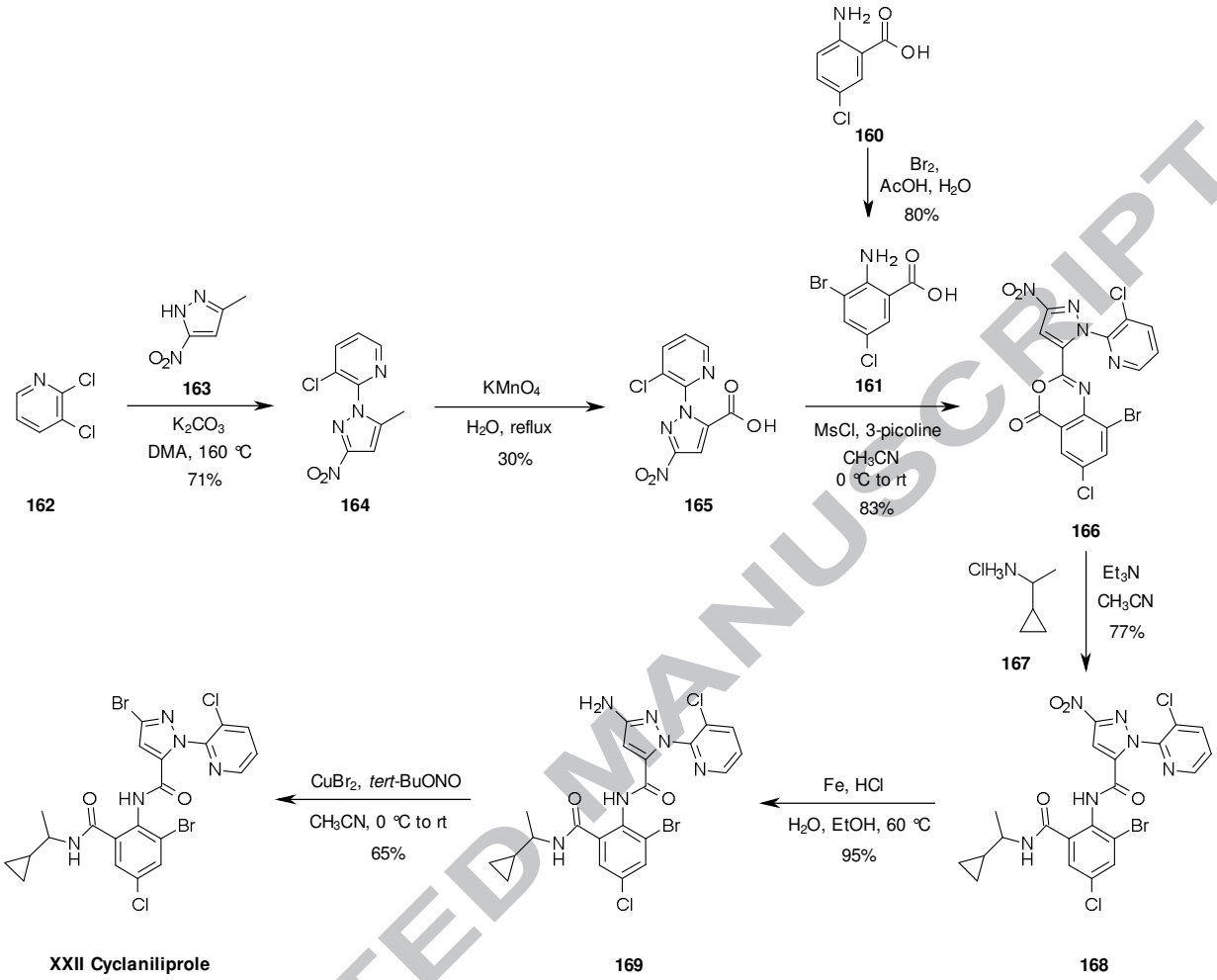
ISK has presented cyclaniliprole (**XXII**) as a new anthranilic diamide insecticide in 2013.[14] It is related to DuPont's commercial products chlorantraniliprole (**158**) and cyantraniliprole (**159**) (Figure 9),[124,125] both structurally and by its mode of action as all three are classified as ryanodine receptor modulators. Each of these active ingredients bears the 5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamid moiety, differing from one another solely by substitution on the anthranillic acid portion of the molecules.



158 **159**

Figure 9. Chlorantraniliprole (**158**) and cyantraniliprole (**159**).

One convergent route explored by ISK for the synthesis of cyclaniliprole involves the coupling of anthranilic acid **161** and pyrazole carboxylic acid **165** (Scheme 25).[126] The anthranilic acid **161** in turn was synthesized by bromination of **160**.[127] The first step toward the synthesis of **165** involves reaction of pyrazole **163** and pyridine **162** in the presence of potassium carbonate at 160 °C, which affords the pyrazolylpyridine **164**.[128] Oxidation of **164** then yields the key intermediate **165** which is reacted together with **161** in the presence of methanesulfonyl chloride and 3-picoline to yield benzoxazinone **166**. Reaction of **166** with amine **167** yields the anthranilic diamide functionality of **168**.[129] Béchamp reduction of **168** gives the aminopyrazole **169**, the aniline function of which is converted to the bromine by Sandmeyer reaction to give cyclaniliprole (**XXII**).

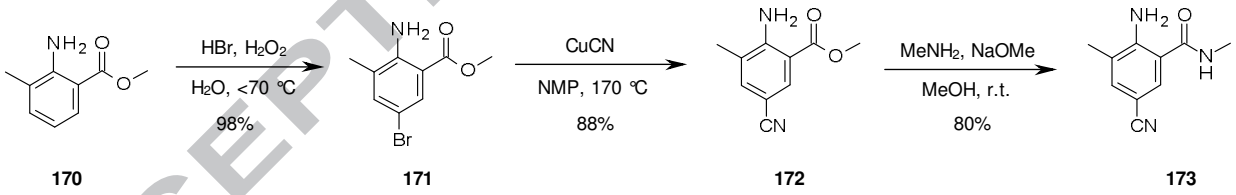


Scheme 25. Synthesis of Cyclaniliprole (**XXII**).

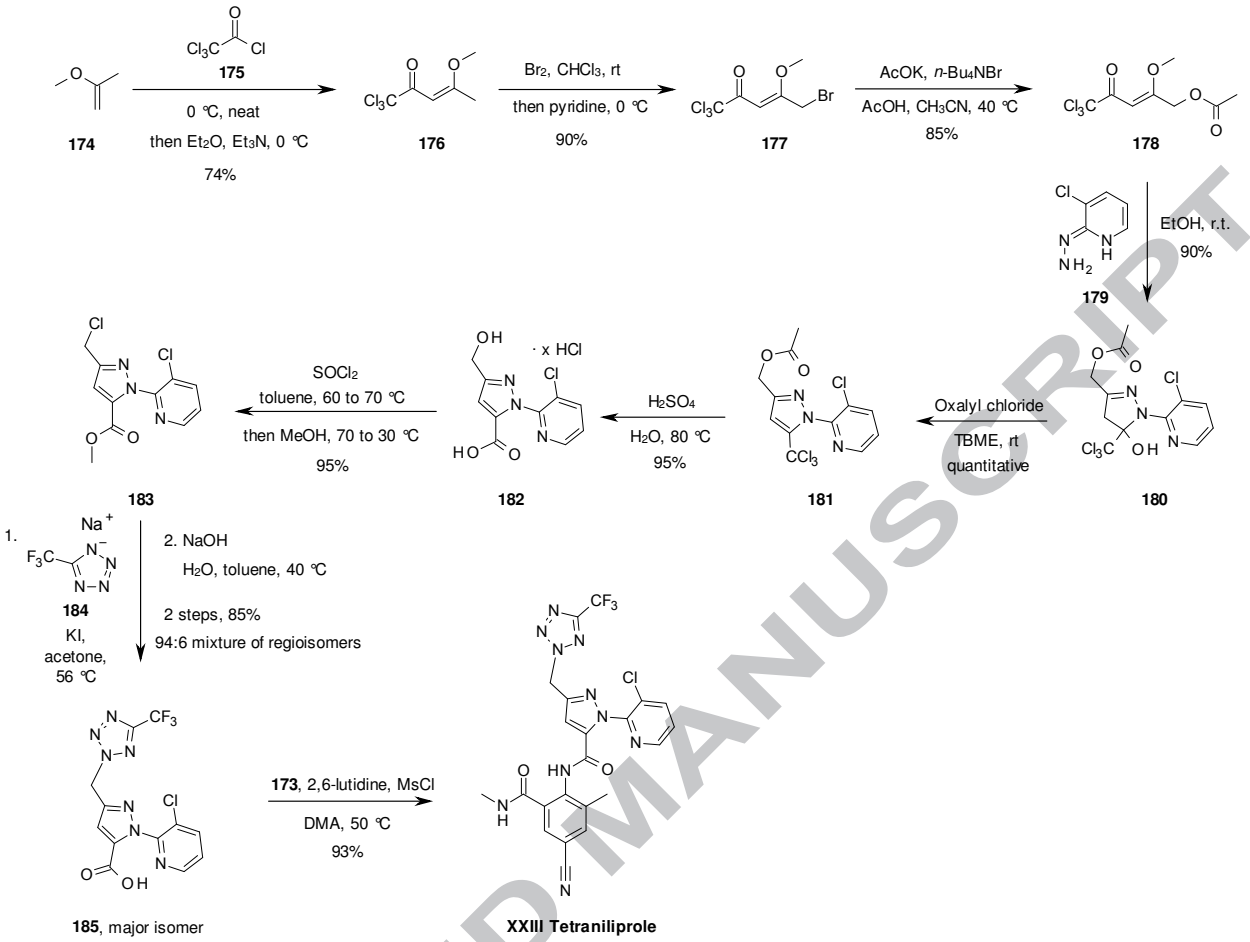
4.5. Tetraniliprole (XXIII)

Tetraniliprole (**XXIII**) was announced by Bayer CropScience in 2014,[14] as a new diamide insecticide. As with other anthranilic diamides, it acts as a ryanodine receptor modulator, but structurally differentiates itself from chlorantraniliprole (**158**) and cyantraniliprole (**159**) as the pyrazole moiety is substituted by a tetrazolylmethyl group rather than a bromide (Figure 1 and 9). A plausible synthetic route to tetraniliprole (**XXIII**) involves the coupling of anthranilic amide **173** with the advanced intermediate pyrazole carboxylic acid **185**. Bayer CropScience has filed a patent application for the synthesis of **173** from 2-amino-3-methylbenzoate **170** (Scheme

26).[130] This involves bromination of **170** using hydrobromic acid and hydrogen peroxide, and further reaction of the resulting bromide **171** with copper cyanide to provide anthranilate **172**. Reaction of **172** with methylamine in a basic methanol/sodium methanolate media affords anthranilamide **173** with an overall 69% yield. Synthesis of the more complex intermediate **185** begins with electrophilic acylation of the vinyl ether **174** with trichloroacetyl chloride (**175**), to afford enone **176** (Scheme 27).[131] Treatment of **176** with bromine,[132] followed by displacement of the resulting bromide of **177** with potassium acetate yields **178**, which upon reaction with hydrazine **179**, leads to dihydropyrazole **180** which is then dehydrated to pyrazole **181** by treatment with oxalyl chloride. Hydrolysis of pyrazole **181** under acidic simultaneously hydrolyses both the CCl_3 and acetate moieties to give the pyrazole carboxylic acid **182.** Treatment of **182** with thionyl chloride followed by methanol quench leads to **183**,[133] which contains now the required methylene chloride side chain for nucleophilic substitution. This is executed by treatment of **183** with the tetrazole sodium salt **184** in the presence of potassium iodide to give the advanced intermediate **185** as the main component of a 94 to 6 regioisomeric mixture. In the final step of the synthesis of tetraniliprole (**XXIII**), the second amide bond is obtained by reacting acid **185** and aniline **173** in the presence of methanesulfonyl chloride and 2,6-lutidine.[134] The latter step proceeds through an intermediate benzoxazinone as previously discussed for cyclaniliprole (**XXII**) in scheme 25.



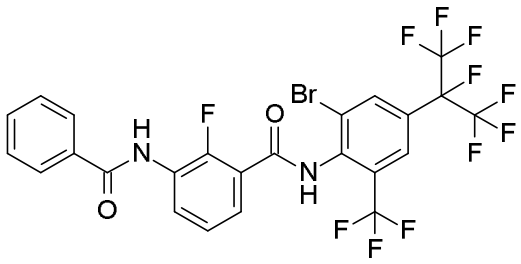
Scheme 26. Synthesis of intermediate **170**.



Scheme 27. Synthesis of tetraniliprole (**XXIII**).

4.6. Broflanilide (XXIV)

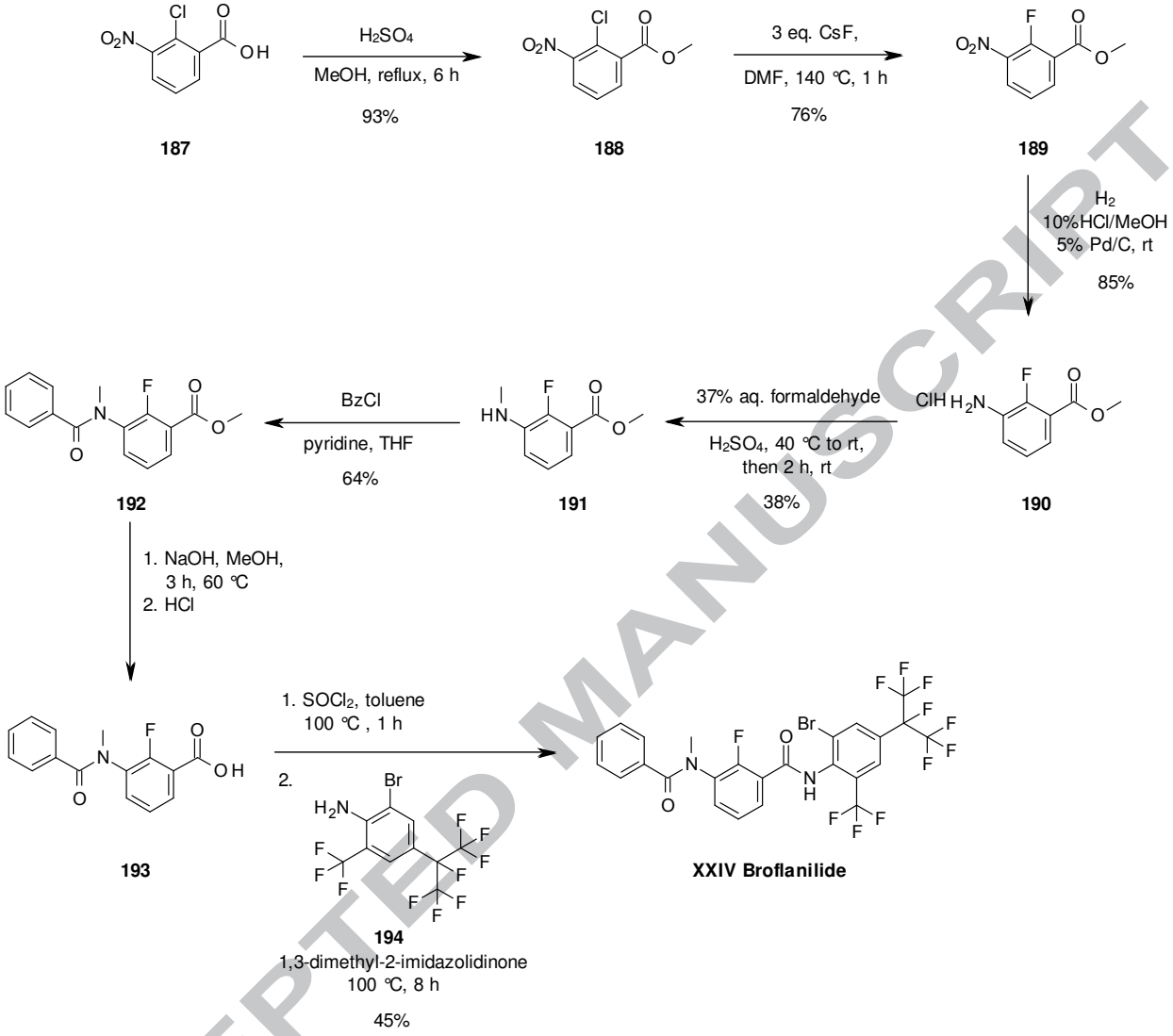
Broflanilide **(XXIV)** is a new insecticide belonging to the *meta*-diamide class disclosed by Mitsui.[135] Broflanilide (**XXIV**) exhibits larvicidal activity against *Spodoptera litura*. Broflanilide is, in fact, a procide where the methyl of the amide functionality is metabolized to liberate the desmethyl-broflanilide (**186**) (Figure 10). The molecule **186** is reported to be a non-competivite gamma-aminobutyric acid (GABA) receptor antagonist,[135] but distinct from that of conventional non-competitive antagonists such as fipronil, picrotoxin, lindane, dieldrin, and α-endosulfan.[135] It has been postulated that the binding mode of desmethyl-broflanilide is different from other compounds binding at the GABA receptor, and thus it is expected to be useful against pests resistant to cyclodienes and fipronil.[135]



186

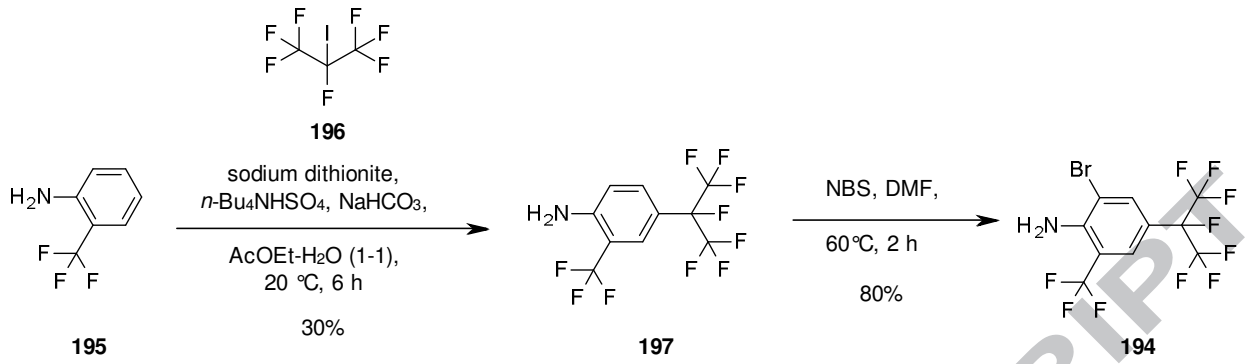
Figure 10. Desmethyl-broflanilide (**186**).

The reported synthesis begins with protection of the acid function of 2-chloro-3-nitrobenzoic acid (**187**), as its methyl ester, followed by S_NAr reaction of the chlorine in **188** with fluorine using cesium fluoride. This sequence potentially allows the introduction of a cheap source of fluoride like potassium fluoride. After reduction of the nitro group in **189**, the amino group of molecule **190** is methylated through a variant of the Eschweiler-Clarke Reaction and subsequently condensed with benzoyl chloride to produce compound **192**. Deprotection of the acid function, formation of the acid chloride followed by coupling with the aniline **194** provides broflanilide (**XXIV**) (Scheme 28).[136]



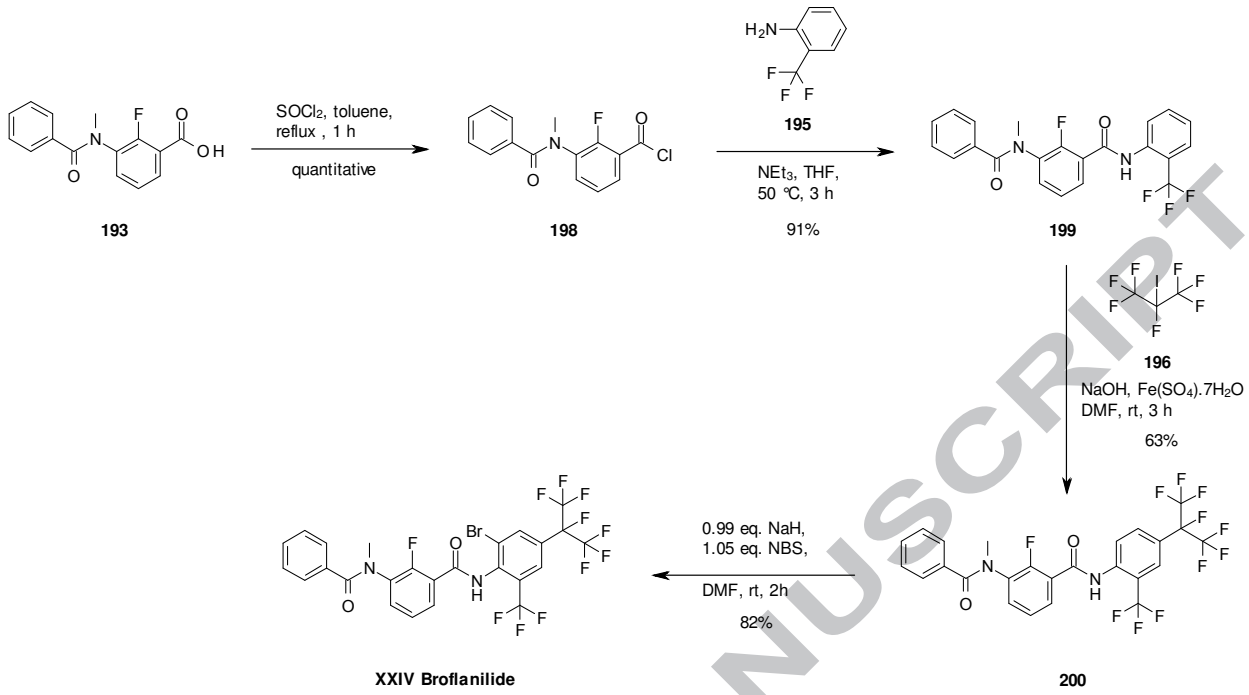
Scheme 28. Synthesis of broflanilide (**XXIV**).

The aniline required (**194**) is prepared according to scheme 29 starting from 2-trifluoromethyl aniline (**195**), radical condensation with heptafluoroisopropyl iodide (**196**), and subsequent bromination with *N*-bromosuccinimide (NBS).[137]



Scheme 29. Synthesis of aniline **194**.

The last step in the synthetic scheme 28 is reported with low yield (45%).[136] This is most likely due to the fact that the aniline **194** is substituted with electron withdrawing groups and thus not very reactive. An alternative approach, which adds the perfluorinated *iso*-propyl group unit at a later stage and on a higher molecular weight intermediate is reported in scheme 30.[138] Compound **193** is activated as its acid chloride **198** and then coupled 2-trifluoromethyl aniline (**195**) to yield the advanced intermediate **199**. Introduction of the perfluorinated *iso*-propyl group under the radical conditions previously noted leads to **200**, which is selectively brominated at the 2 position of the aromatic containing the perfluorinated *iso*-propyl group to give broflanilide (**XXIV**).

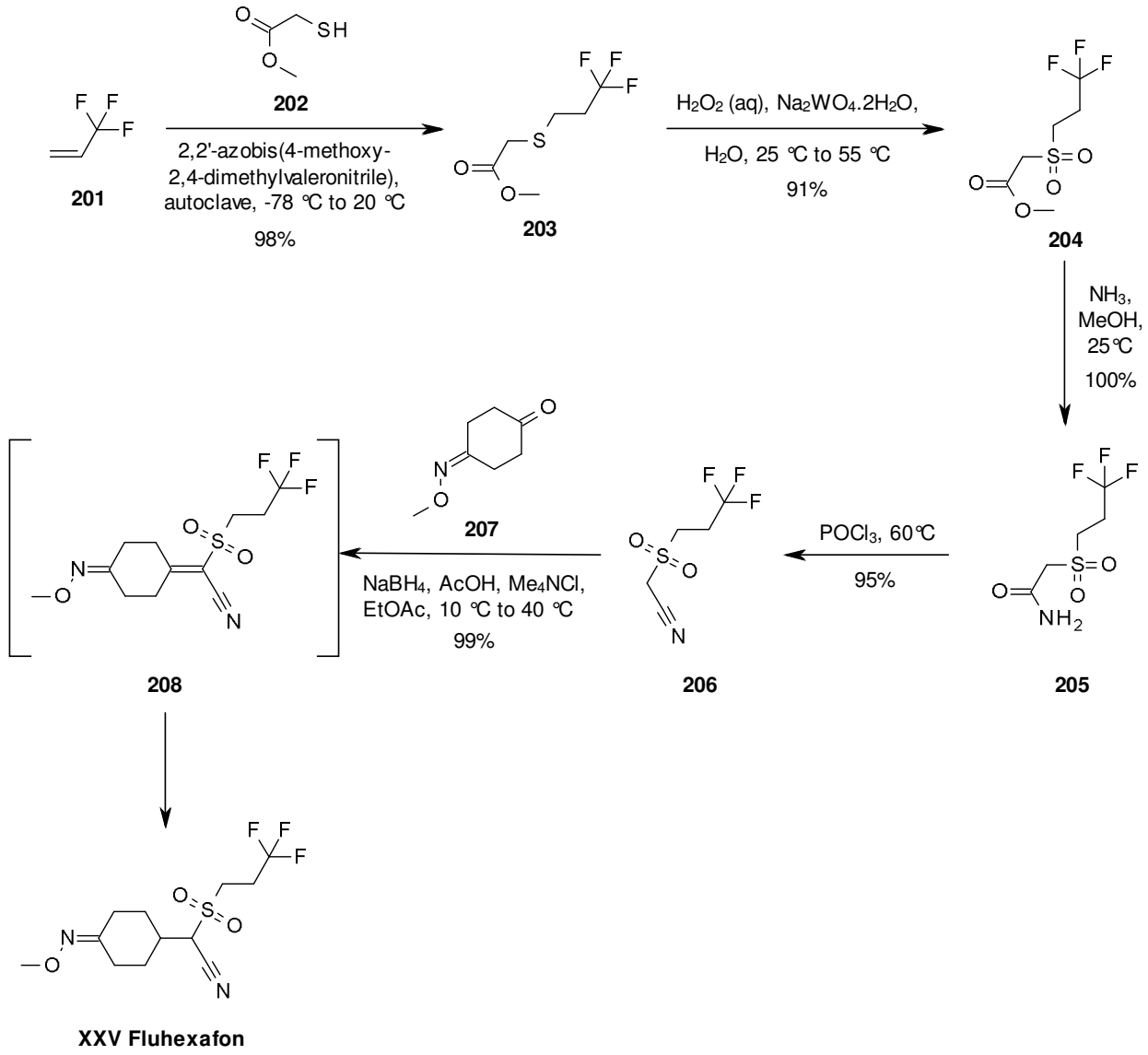


Scheme 30. Alternative synthesis of broflanilide (**XXIV**).

4.7. Fluhexafon (XXV)

Fluhexafon (**XXV**) is a new insecticide from Sumitomo.[139] It has reported uses on aphids and hoppers,[139] but is also reported to have uses in animal health (activity on ectoparasites)[140,141] and public health, with activity on cockroaches,[142] house flies,[139] and mosquitoes.[139] The mode of action has not yet been reported for this chemistry, and is thus classified as unknown.[143] A likely convergent technical synthesis is shown in scheme 31.[144,145] The key for a scalable synthesis of fluhexafon (**XXV**) was to find a cheap source of CF_3 that could be incorporated into the final product. Sumitomo scientists achieved this by a radical addition of thioglycolate (**202**) to 3,3,3-trifluoropropene (**201**). This radical addition yields **203** in excellent yield and selectivity. Tungstate catalyzed oxidation of the sulphide **203** gives the sulphone **204**, which can be converted to the primary amide 2**05**, and then dehydrated to the required molecule **206** with high efficiency. The sulphone **206** is then condensed and reduced in a single step with the oxime **207** to give fluhexafon (**XXV**), using *in situ* prepared triacetoxyborohydrides. The synthesis of **207** is

not described, but selective preparation of mono oximes from cyclohexane-1,4-dione is described in the literature and occurs in high yields.[146]

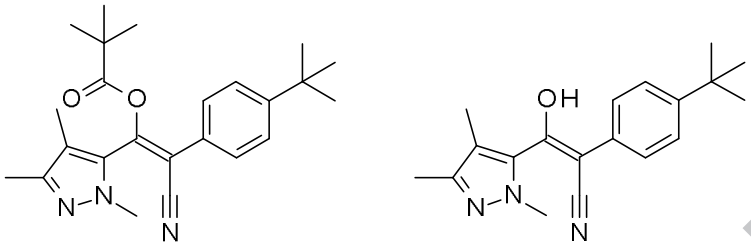


Scheme 31. Synthesis of fluhexafon (**XXV**).

4.8. Pyflubumide (XXVI)

Pyflubumide (**XXVI**) is a novel acaricidal compound that has been developed by the Nihon Nohyaku Company. Pyflubumide (**XXVI**) is in fact a procide, with the active ingredient being the free N-H molecule which is obtained by *in vivo* cleavage of the acyl group (molecule **216** in scheme 32).[147] The metabolite (free N-H) **213** contains similar features to the carboxamide

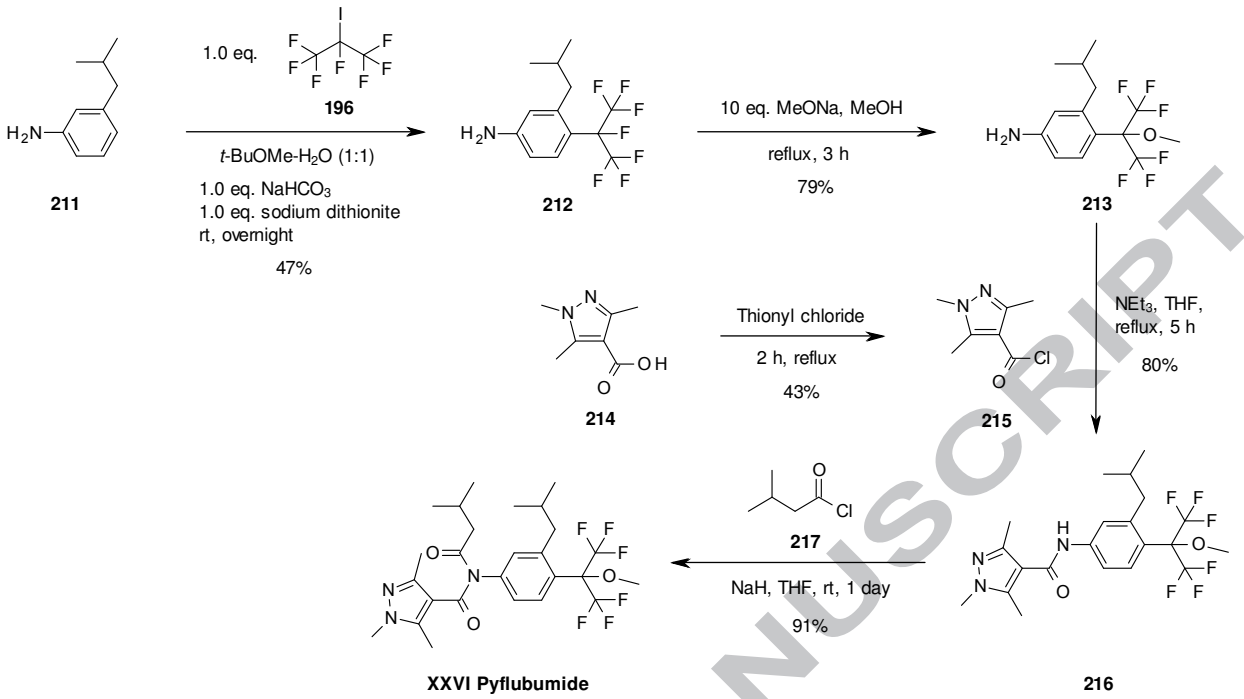
fungicides known to be succinate-dehydrogenase inhibitor (SDHI, see section 2.1. to 2.4. of this review). It was therefore postulated, and indeed verified, that the deacetylated form of pyflubumide (**XXVI**) is a mitochondrial complex II inhibitor.[147] A double-inhibitor titration assay suggested that the metabolite of pyflubumide (**213)** may bind in a different mode at a different site than another known complex II acaricide, namely the metabolite of cyenopyrafen **210** (Figure 11).[147,148]



209 **210**

Figure 11. Cyenopyrafen (**209**) and its active metabolite generated *in vivo* **210**

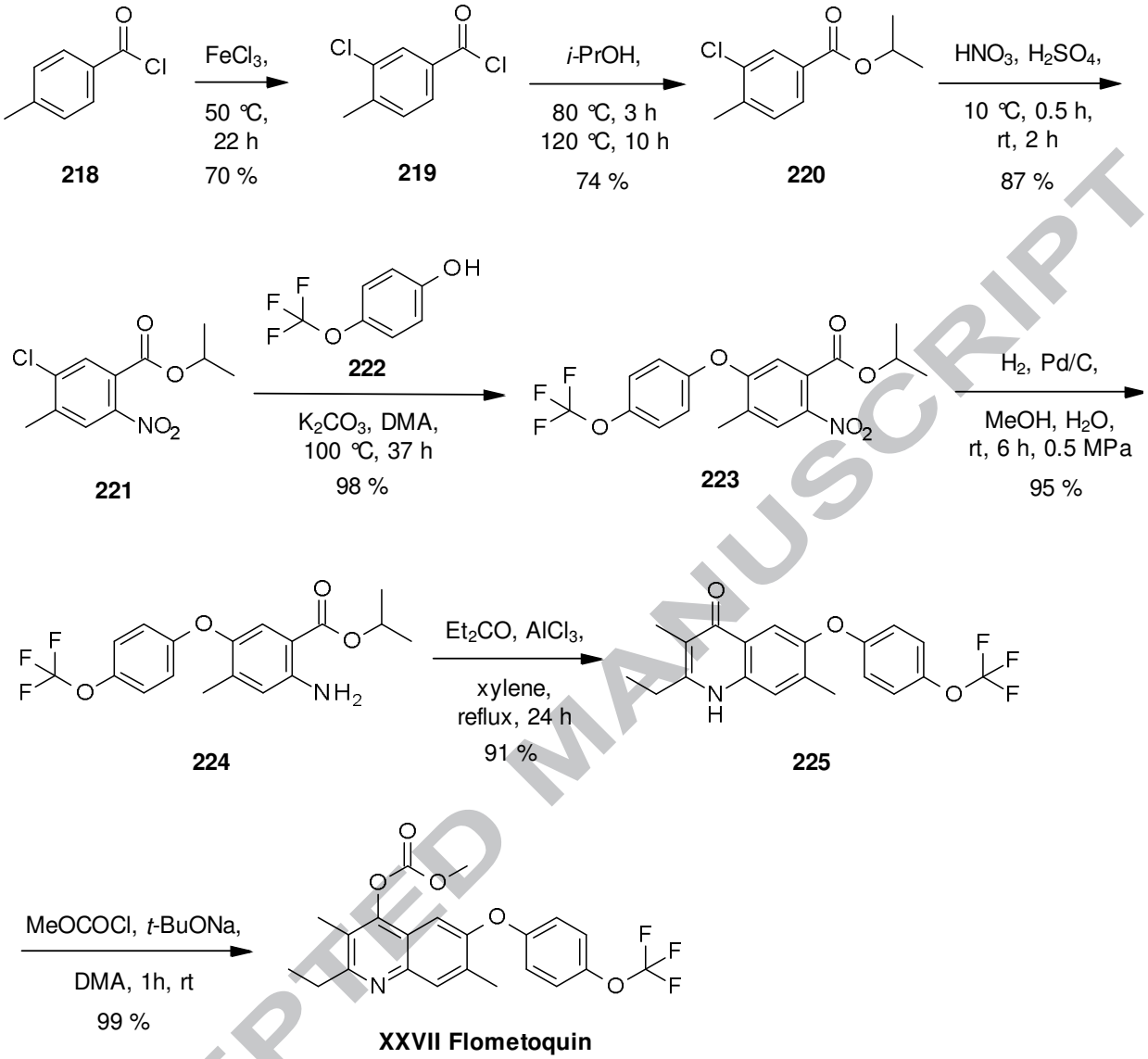
No process patent application could be found for the synthesis of pyflubumide (**XXVI**). However, a synthetic scheme could be deduced from the active ingredient patent applicaton.[149] The synthesis from Nihon Nohyaku starts from 3-isobutylaniline (**211**), which is reacted with heptafluoroisopropyl iodide (**196**) *via* a radical reaction (as discussed for broflanilide (**XXIV**), section 4.6.) to generate compound **209**. The fluoride in the 2-position of the isopropyl heptafluoridemoiety is displaced in a nucleophilic reaction by treatment with sodium methoxide in methanol. The aniline **213** is subsequently coupled with two acid chlorides as depicted in scheme 32 (initialy with the 1,3,5-trimethylpyrazole-4-carbonyl chloride **215** and then with isobutyl carbonyl chloride (**217**) to give pyflubumide (**XXVI**).[149] The 1,3,5-trimethylpyrazole-4-carbonyl chloride **215** is prepared from the corresponding acid **214** with thionyl chloride at reflux for 2 hours.[150]



Scheme 32. Synthesis of pyflubumide (**XXVI**).

4.9. Flometoquin (XXVII)

Flometoquin (**XXVII**) has been presented by Nippon Kayaku as a new insecticide, which is active on thrips, white flies and some *lepidoptora* spp.[151] Flometoquin (**XXVII**) is a procide and the active ingredient is the molecule **225** depicted in the scheme 33. Flometoquin (**XXVII**) is efficiently prepared in a seven-step synthesis starting from *p*-toluoyl chloride (**218**).[152,153] Regioselective chlorination in the *meta*-position of **218** is followed by the conversion of the acid chloride into an isopropyl ester, to yield compound **220**. Nitration of **220** occurs at the less sterically demanding *ortho*-position of this molecule to yield the tetrasubstituted benzene derivative **221.** This is coupled by an S_NAr reaction with 4-(trifluoromethoxy)phenol (**222**) to the yield **223** in almost quantitative yield. After the catalytic reduction of the nitro group, the resulting anthranilic ester **224** undergoes ring closure with diethyl ketone to yield quinolinone **225**. The pyridine ring of the latter intermediate is then aromatized in the final step by *O*-acylation with methyl chloroformate to deliver flometoquin (**XXVII**).[152,153]

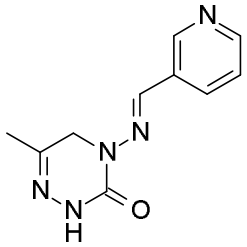


Scheme 33. Synthesis of flometoquin (**XXVII**).

4.10. Afidopyropen (XXVIII)

Afidopyropen (**XXVIII**) is a new, natural product derived insecticide with an unknown mode of action. It is reported to be active against sucking insects, such as pea aphids (*acyrthosiphon pisum*).[154] The molecule is based on the natural product pyripyropne A (**228)** that was isolated by the group of Ōmura from the fungi *Aspergillus fumigatus*.[155] In their original articles, Ōmura *et al.* already reported that pyripyropene A is active on the acyl-coenzyme A cholesterol acyl

transferase (ACAT) with an IC50 value of 58 nM.[155] The group of Gloer subsequently reported not only on the isolation of pyripyropene A (**228)** from the fungi *Eupenicilium crustaceum,* but also on its insecticidal properties.[156] A collaboration between the Ōmura group and Meiji Seika Pharma also confirmed pyripyropene A **228** to be a potent insecticide, which was the starting point for the discovery of afidopyropen (**XXVIII**). The molecule **XXVIII** is now under development through collaboration between Japan's Meiji Seika Pharma and BASF.[157] The Insecticide Resistance Action Committee (IRAC) proposed selective homopteran feeding blockers as a mode of action. This is the group encompassing pymetrozine **226** and flonicamid **227** (Figure 12).[154] Apart from a common 3-substituted pyridine ring, the three molecules do not appear to be closely related. In a recent paper, Scott *et al.* concluded it is possible that pymetrozine (**226**) and afidopyropen (**XXVIII**) indeed share the same mode of action as both have identical insecticidal spectrum and have similar symptomology on crayfish.[154]



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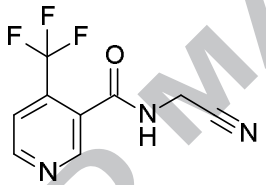
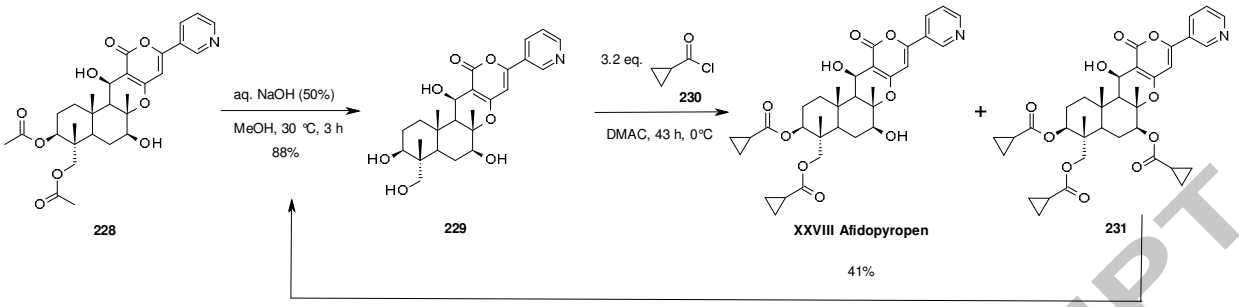


227

Figure 12. Pymetrozine **226** and flonicamid **227**.

The semi-synthesis of afidopyropen (**XXVIII**) is shown in the scheme 34 below and is based on a process patent application published by BASF.[158] The semi-synthesis begins from the natural product pyripyropne A **228,** which is hydrolysed under basic condition to afford **229**. The free hydroxyl groups of **229** are then acylated with cyclopropane carbonyl chloride (**230**). Some selectivity is observed and afidopyropen (**XXVIII**) can be obtained in 41% yield, together with the tri-acylated product (**231**). The latter can be easily recycled to **229**.

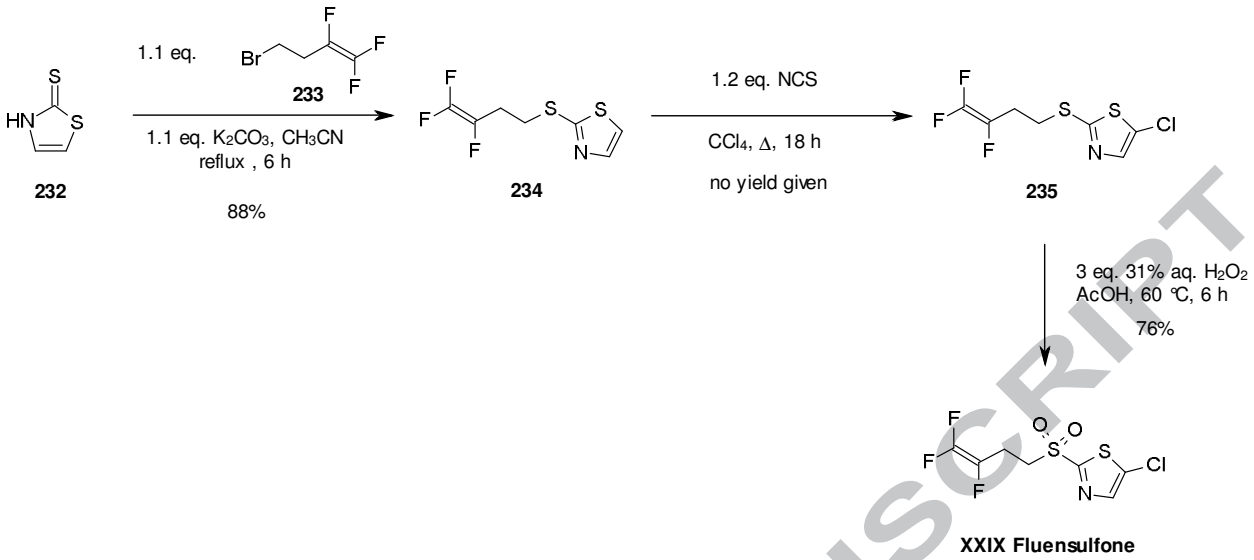


Scheme 34. Hemi-synthesis of afidopyropen (**XXVIII**).

5. Nematicides

5.1. Fluensulfone (XXIX)

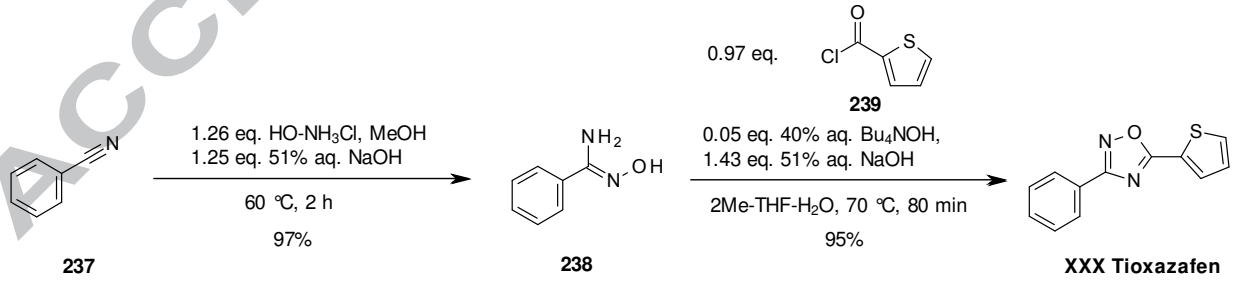
Fluensulfone (**XXIX**) is a new nematicide introduced to the market by ADAMA, although originally discovered at Bayer CropScience.[159] It is reported to be effective on plant parasitic nematodes including various species of *Meloidogyne*.[160] Fluensulfone (**XXIX**) exerts its action by affecting the mobility and the body posture of nematodes.[160] Those effects are similar to the other well-known insecticide classes such as the organophosphates, carbamates, and the avermectins. However, it has been shown that the mode of action of fluensulfone **(XXIX)** is distinct from these acetylcholine esterase inhibitors and allosteric modulators of glutamate gated chloride channels of nematodes.[160] Thus, the mode of action remains unknown, although it has been postulated that it may be related to the inhibition of medium-chain acyl-coenzyme A dehydrogenases.[161] A synthesis of fluensulfone (**XXIX**) has been described in the original active ingredient patent from Bayer CropScience.[162] The synthesis starts with the alklylation of the 2-mercaptothiazole (**232**) by 4-bromo-1,1,2-trifluorobutene (**233**). The thiazole **234** obtained is subsequently chlorinated, and the sulfide function oxidized to the sulphone by hydrogen peroxide in the presence of acetic acid (Scheme 35). In 2002, Bayer CropScience filed a patent for the oxidation of the thioether into the sulphone using Oxone as an oxidant [1.16 eq. Oxone, MeOH-H_2O, 20 °C, 2 h (formation of the sulfoxide) then 1.14 eq. Oxone, pH maintained between 8 and 9 with 4N NaOH, 20 °C, 80 min, 92.2% yield, purity 97.6%].[163]



Scheme 35. Synthesis of fluensulfone (**XXIX**).

5.2. Tioxazafen (XXX)

Tioxazafen (**XXX**), currently under development by Monsanto, is a compound which is claimed to be useable in seed treatment for the control of nematodes in corn and soy.[164] Tioxazafen (**XXX**) belongs to a new class of nematicides, namely the 3,5-disubstituted-1,2,4-oxadiazoles. The mode of action of the molecule remains unknown. The benzamide oxime is prepared in high yields from the benzo nitrile (**237**). The product **238** is subsequently treated with the 2-thiophenecarbonyl chloride (**239**) to produce tioxazafen (**XXX**) in high yields and purity (Scheme 36).[165]



Scheme 36. Synthesis of tioxazafen (**XXX**).

6. Conclusion

This review has showcased the broad range of chemistries used to discover or produce the active ingredients reaching commercialization in the agrochemical industry. It can be seen throughout this review that the strong need for cost effective agrochemicals is not seen as a limiting factor for molecular complexity. On the contrary, the cost of goods challenges facing the industry were taken as an opportunity for researchers to develop unprecedented reactions and explore new catalysts and resulting in new tools for the future. It is worth pointing out that the reactions used for manufacturing agrochemicals need to work reliably on very large scale to produce, in some cases, thousands of tons of active ingredients. Optimizing reactions for industrial scale, such as the world largest production volume of a palladium-catalyzed Suzuki-Miyaura coupling, is not a trivial task, and certainly gives an opportunity for scientists in the industry to extend the boundaries of chemistry.

We would also hope that some bioactive molecules described in this review could spark new ideas in other areas of life science. If not the active ingredient themselves, the new building blocks described in this review could undoubtedly be used in other research projects.[166]

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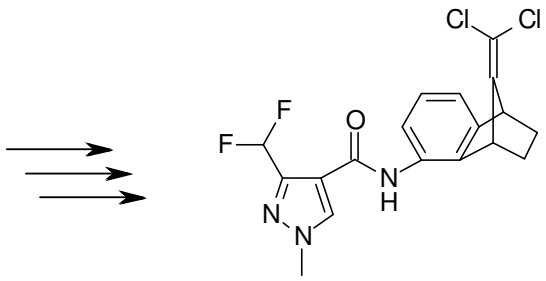
Graphical abstract



II

Synthesis of benzovindiflupyr (**II**) and 29 other agrochemicals reaching the crop protection market.