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REVIEW

Advances in the Synthesis of Neonicotinoids

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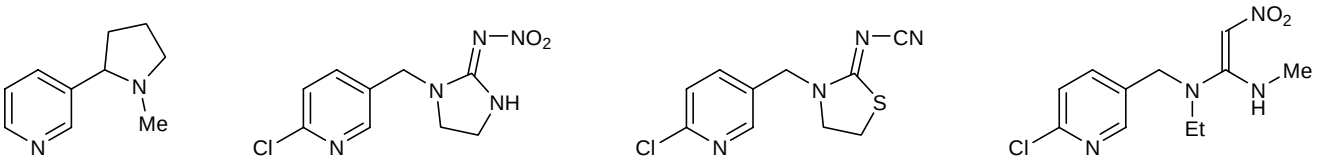
Abstract—The review discusses methods of synthesis of neonicotinoids which constitute a new group of insecticides structurally related to nicotine and acting as insect acetylcholine receptor agonists.

1. INTRODUCTION

Modern crop production cannot develop without chemical means for pest control, which are referred to as pesticides [1–3]. The use of pesticides allows the crop yield to be raised by about one third with simultaneous improvement of the quality. Insecticides are quite necessary pesticides, which ensure successful protection from plant pests. On the other hand, as a result of over-year application of the same insecticides, insects become insusceptible (i.e., resistant) to these chemicals; therefore, the assortment of accessible insecticides should be continuously renewed, and insecticides with novel mechanisms of action should be sought for to avoid addiction. For that reason, the application of organochlorine and organophosphorus insecticides has been canceled in due time, and they have been replaced by pyrethroids. However, in the recent years insects become more and more resistant to pyrethroids, and their use will be strongly restricted soon. It is quite obvious that an alternative to pyrethroids may be new insecticides which are called neonicotinoids. They have become commercially available in 1990s [4–9]. The mechanism of insecticidal activity of neonicotinoids is based on their ability to bind to nicotine acetylcholine receptors in insects [10]. In this respect, neonicotinoids act in a way similar to the known alkaloid nicotine (**1**); its sulfuric acid salt was used previously as insecticide. The use of nicotine sulfate was abandoned owing to its high toxicity for humans and warm-blooded animals.

2. GENERAL CHARACTERISTICS OF NEONICOTINOIDS

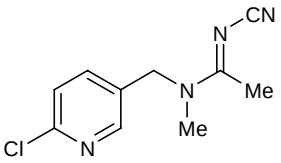
Up to now, the synthesis and properties of numerous compounds, which may be classed with neonicotinoids according to their structure and biological activity, have been reported in scientific and patent literature. Some of these substances have already found wide application in agriculture as insecticides, while the others are being developed. The present review discusses methods of synthesis of the most practically important neonicotinoids.

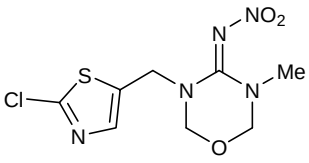

Nicotine (**1**)

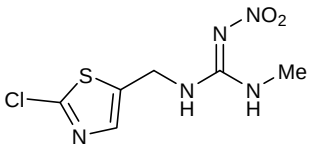
Imidacloprid (**2**)

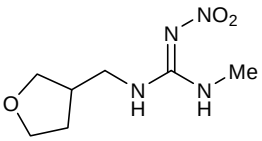
Thiacloprid (**3**)

Nitenpyram (**4**)


Acetamiprid (**5**)


Thiamethoxam (**6**)


Clothianidin (**7**)


Dinotefuran (**8**)

The most presently known neonicotinoid is imidacloprid (**2**); it is the active substance in such commercial insecticide preparations as Confidor, Gaucho, Prestige, Admire, and Premier [11–22] which are increasingly used in agriculture. The molecule of imidacloprid consists of two fragments, pyridine and 2-nitroiminoimidazolidine, which are linked through a methylene bridge. It is seen that imidacloprid (**2**) is structurally related to nicotine (**1**). Thiacloprid (**3**) [23], nitenpyram (**4**) [24, 25], and acetamiprid (**5**) [26–29] are the other neonicotinoids containing a chloropyridine fragment. In the recent years, one more neonicotinoid, thiamethoxam (**6**) [30–32] has found growing application; for example, it is the active component of Actara™. The molecule of thiamethoxam contains a chlorothiazole ring, which makes it essentially different from chloropyridine neonicotinoids **2**–**5**. An analogous chlorothiazole fragment is present in the molecule of clothianidin (**7**) [33]. Dinotefuran (**8**) [34] stands somewhat apart from neonicotinoids **2**–**7**; its molecule contains a tetrahydrofuran ring and a nitroguanidine fragment.

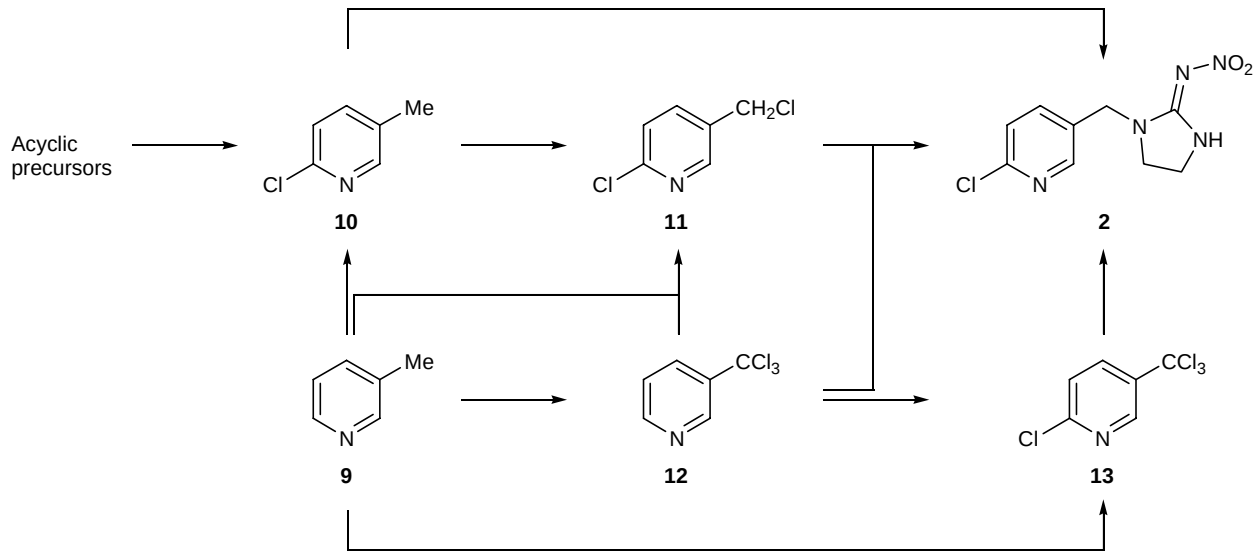
3. SYNTHESIS OF THE MOST IMPORTANT INTERMEDIATE PRODUCTS

With respect to their chemical structure, neonicotinoids may be divided into two groups: chloropyridine and chlorothiazole. Successful synthesis of neonicotinoids is largely determined by accessibility of the corresponding intermediate compounds of the chloropyridine and chlorothiazole series. It should be noted that prior to the discovery of neonicotinoids the synthesis of such compounds attracted no specific attention of researchers at both academic and industrial institutions. The synthesis of imidacloprid radically changed the situation. At present, numerous publications, especially in patent literature, deal with the development of new and improvement of existing methods for preparation of intermediate products necessary for the synthesis of neonicotinoids.

3.1. Synthesis of Chlorinated 3-Methylpyridine Derivatives

The key initial compound for the synthesis of chloropyridine neonicotinoids is 3-methylpyridine (**9**) which can be used as a basis for building up chloropyridine ring in imidacloprid, thiacloprid, acetamiprid, and nitenpyram. In order to convert 3-methylpyridine (**9**) into neonicotinoids **2**–**5**, it is necessary (1) to introduce a chlorine atom into the pyridine ring and (2) to activate the 3-methyl group. Therefore, the key intermediates in the synthesis of imidacloprid are various chlorinated derivatives of 3-methylpyridine: 2-chloro-5-methylpyridine (**10**), 2-chloro-5-chloromethylpyridine (**11**), 3-trichloromethylpyridine (**12**), and 2-chloro-5-trichloromethylpyridine (**13**). Compound **10** can be obtained starting from various acyclic precursors. The 2-nitroiminoimidazolidine ring can be attached to molecules **10**–**13** either directly or in parts in the final steps of the synthesis. Scheme 1 shows possible ways of transformation of 3-methylpyridine (**9**) into imidaclopride **2** through different chlorinated pyridines as intermediate products. It is seen that, among compounds **10**–**13**, 2-chloro-5-chloromethylpyridine (**11**) is the most convenient intermediate for the synthesis of neonicotinoids. Analysis of published data shows that methods for direct chlorination of 3-methylpyridine (**9**) to dichloro derivative (**11**) have not yet been developed. The reason is the very low reactivity of the pyridine ring in molecule **9** as compared to the methyl group. Introduction of a chlorine atom into the pyridine ring requires severe conditions under which all hydrogen atoms in the methyl group are also replaced by

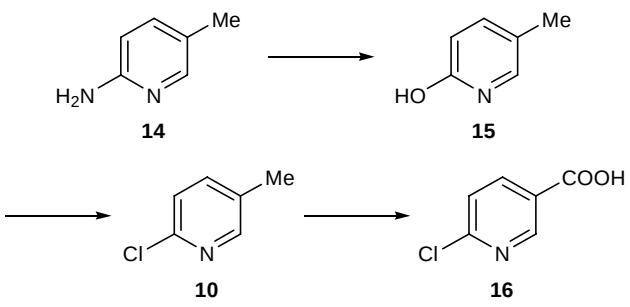
Scheme 1.



chlorine. Therefore, the major products in the chlorination of 3-methylpyridine are usually the corresponding trichloromethyl derivatives, 3-trichloromethylpyridine (**12**) and 2-chloro-5-trichloromethylpyridine (**13**). Like 2-chloro-5-methylpyridine (**10**), compounds **12** and **13** can be used in the synthesis of neonicotinoids either directly or via preliminary transformation into 2-chloro-5-chloromethylpyridine (**12**).

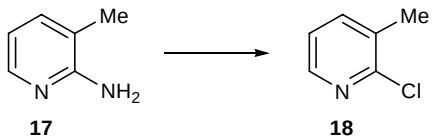
2-Chloro-5-methylpyridine 10. Up to now, development of convenient preparative procedures for the synthesis of 2-chloro-5-methylpyridine (**10**) has been the subject of a considerable number of studies. Compound **10** was obtained for the first time by Herz and Murty [35] from 2-amino-5-methylpyridine (**14**). Compound (**14**) was initially treated with sodium nitrite in the presence of sulfuric acid, and the subsequent decomposition of diazonium salt thus formed afforded 75% of 2-hydroxy-5-methylpyridine (**15**). Reaction of the latter with a mixture of phosphorus pentachloride and phosphoryl chloride on heating gave 2-chloro-5-methylpyridine (**10**) (Scheme 2). Oxidation of (**10**) with potassium permanganate resulted in formation of 6-chloronicotinic acid (**16**, yield 71%) which is also used in the synthesis of neonicotinoids.

Scheme 2.



A direct transformation of aminopyridine **14** into 2-chloro-5-methylpyridine (**10**) is also possible. Brown [36] obtained chloro derivative **10** by diazotization of **14** with sodium nitrite in hydrochloric acid, followed by thermal decomposition of the resulting diazonium salt. The reaction of 2-amino-5-methylpyridine **14** with methyl nitrite in methanol saturated with hydrogen chloride was described in patents [37, 38]; compound **10** was thus obtained in 86.1% yield. 2-Methoxy-5-methylpyridine (yield 9.3%) and 5-methylpyridin-2(1*H*)-one were also formed as by-products. According to [39], 2-chloro-3-methylpyridine (**18**), which is isomeric to **10**, can also be obtained following an analogous procedure. The reaction of 2-amino-3-methylpyridine (**17**) with butyl nitrite in a solution of HCl in methanol gave 84.2% of **18** (Scheme 3).

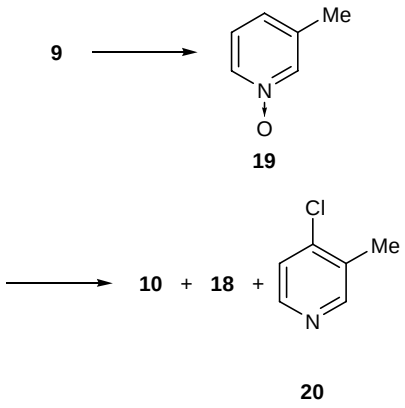
Scheme 3.



The reaction of 3-methylpyridine *N*-oxide (**19**) with phosphoryl chloride was also used to obtain 2-chloro-5-methylpyridine (**10**). It was presumed [40] that the process follows ionic addition–elimination pattern. Pyridine *N*-oxides are readily available from the corresponding pyridines via oxidation with hydrogen

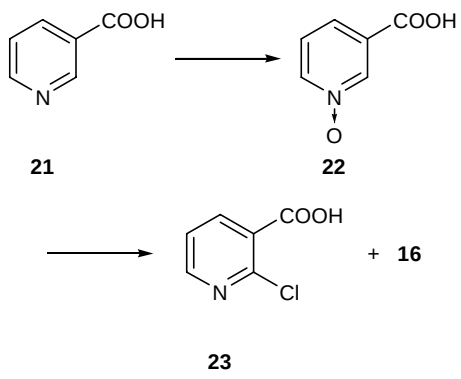
peroxide. Heating of *N*-oxide **19** with phosphoryl chloride was shown [40] to afford a mixture of chloro derivatives **10**, **18**, and **20** at a ratio of 27:30:43 in an overall yield of 77% (Scheme 4).

Scheme 4.



Various improved procedures have been proposed in order to increase the yield of 2-chloro-5-methylpyridine (**10**). As shown in [41–43], the reaction of *N*-oxide **19** with phosphoryl chloride in methylene chloride in the presence of diisopropylamine leads to formation of a mixture containing 81% of 2-chloro-5-methylpyridine (**10**), 15% of 2-chloro-3-methylpyridine (**18**), and 1% of initial 3-methylpyridine (**9**). Kaufmann and Gallenkamp [44, 45] proposed to use in addition to the above components various chlorophosphoric acid esters or amides. For example, in the presence of diisopropylamine and *N*,*N*-diethyldichlorophosphoramide, a mixture consisting of 82% of 2-chloro-5-methylpyridine (**10**) and 18% of 2-chloro-3-methylpyridine (**18**) was obtained in an overall yield of 83%. Various acid chlorides were also found [46] to increase the yield of **10**. A mixture containing 70% of 2-chloro-5-methylpyridine (**10**) and 30% of 2-chloro-3-methylpyridine (**18**) was formed in an overall yield of 52% when the reaction was carried out in the presence of *p*-toluenesulfonyl chloride and triethylamine. According to the data of [40], the above procedure for the synthesis of chlorinated pyridines cannot be applied directly (i.e., without some modifications) to the preparation of 6-chloronicotinic acid (**16**) from nicotinic acid (**21**). *N*-Oxide **22** obtained from acid **21** reacted with phosphoryl chloride to give 75% of a mixture of 6- and 2-chloro derivatives **16** and **23** at a ratio of 14:86 (Scheme 5). On the other hand, the procedure is quite applicable to the synthesis of 2-chloronicotinic acid [47].

Scheme 5.

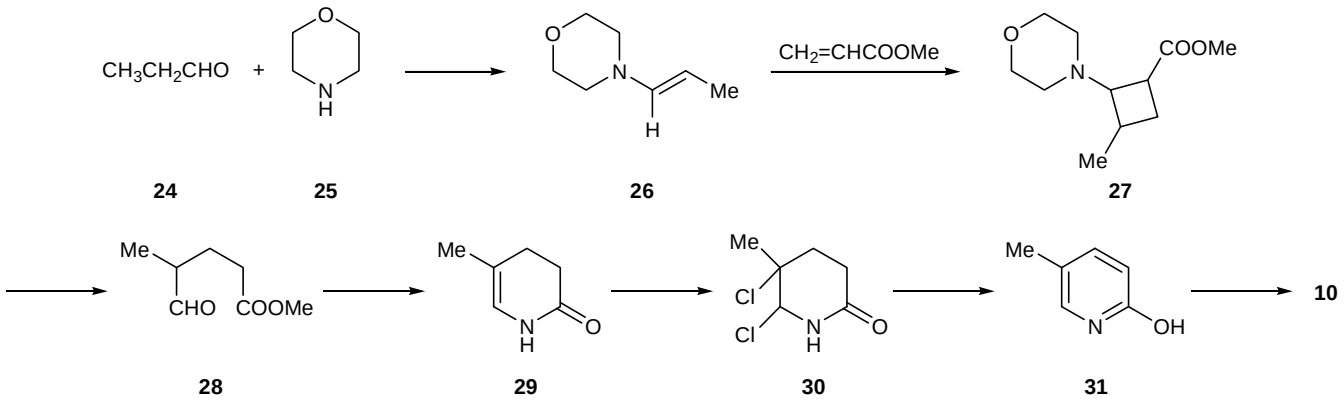


A number of publications describe the synthesis of 2-chloro-5-methylpyridine (**10**) from various acyclic precursors. In particular, compound **10** was obtained from propionaldehyde (**24**) and derivatives of acrylic acid [48, 49]. Initially, propionaldehyde was converted into enamine **26** by reaction with morpholine (**25**). The reaction of **26** with methyl acrylate gave substituted cyclobutane derivative **27** which was subjected to hydrolysis with aqueous acetic acid to obtain methyl 4-formylpentanoate (**28**). Cyclization of the latter by the action of ammonium acetate afforded 50–70% of dihydropyridinone **29** which was treated with chlorine or sulfuryl chloride. Dichloro derivative **30** thus formed underwent thermal dehydrochlorination with formation of 2-hydroxy-5-methylpyridine (**31**). Finally, compound **31** was converted into the target 2-chloro-5-methylpyridine (**10**) by the action of phosphorus pentachloride or phosphoryl chloride (Scheme 6). Osborne and Bailey [50, 51] synthesized 2-chloro-5-methylpyridine (**10**) in an overall yield of more than 80% by successive reactions of dihydropyridinone **29** with chlorine in 1,2,4-trichlorobenzene and with phosphoryl chloride on heating without isolation of intermediate products **30** and **31**.

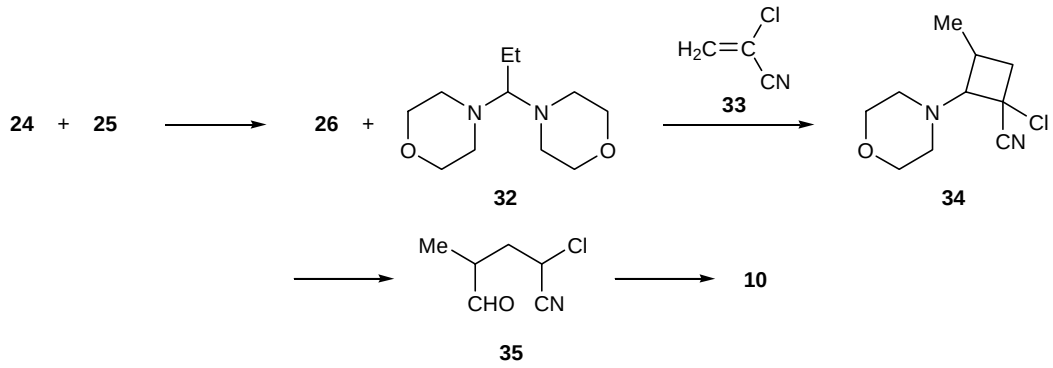
Another synthesis of 2-chloro-5-methylpyridine (**10**) from propionaldehyde was reported in [52]. In the first step, propionaldehyde (**24**) reacted with morpholine (**25**) to give a mixture of enamine **26** and aminal **32**. This mixture (without separation) was brought into reaction with α-chloroacrylonitrile **33** to obtain substituted cyclobutane **34**. Hydrolysis of **34** with sulfuric acid in acetonitrile afforded 2-chloro-4-formylpentanenitrile (**35**), and cyclization of the latter into 2-chloro-5-methylpyridine (**10**) was effected by the action of hydrogen chloride in dimethylformamide (Scheme 7).

Propionaldehyde (**24**) was also used as initial compound in the synthesis of 2-chloro-5-methylpyridine (**10**), covered by patent [53]. Its reaction with benzyl-

Scheme 6.



Scheme 7.

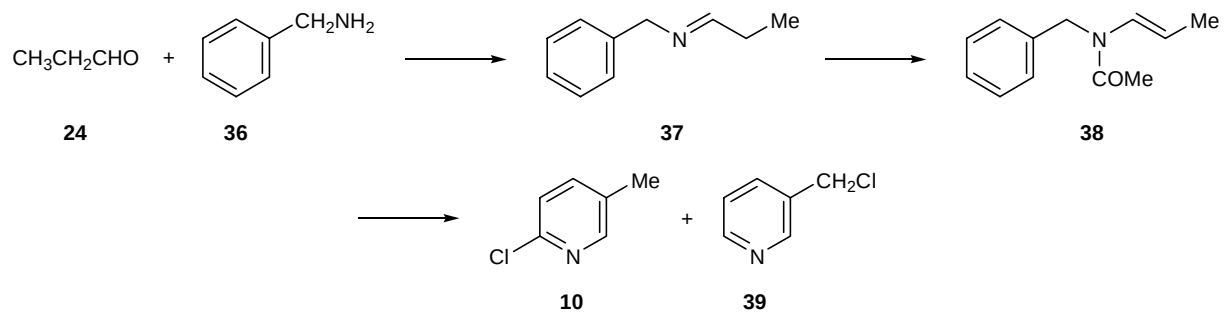


amine (**36**) in the presence of potassium hydroxide led to enamine **37** (yield 93%) which was treated with acetic anhydride in the presence of triethylamine to obtain substituted acetamide **38**, and cyclization of the latter by the action of phosphoryl chloride in dimethylformamide afforded 67.5% of 2-chloro-5-methylpyridine (**10**) and benzyl chloride (**39**) (Scheme 8).

A fairly simple procedure for the synthesis of 2-chloro-5-methylpyridine (**10**) via reaction of propionaldehyde (**24**) with acetonitrile (**40**) (or acetamide) and phosphoryl chloride in dimethylformamide was described in [54] (Scheme 9). The yield of **10** was 25–32%. According to [54], cyclization of *cis*-2-pentenenitrile under analogous conditions gives chloropyridine **10** in 40% yield.

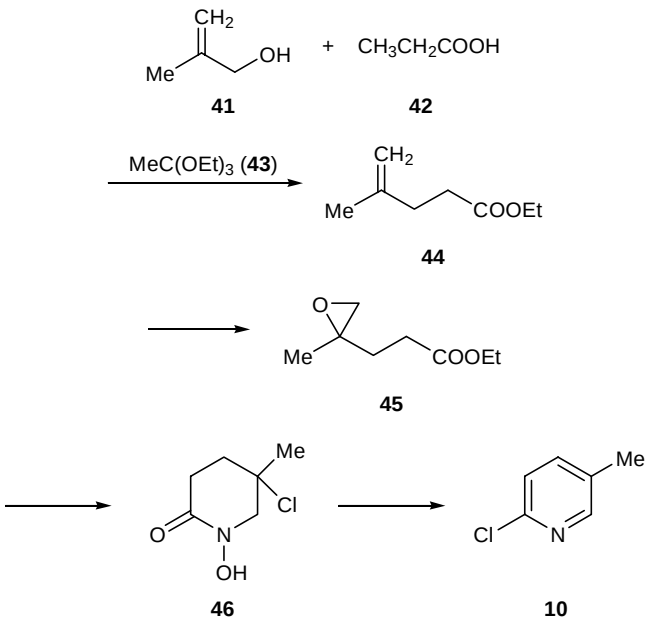
Nelson and Stephen [55–57] described the synthesis of 2-chloro-5-methylpyridine (**10**) from 2-methyl-2-propen-1-ol (**41**) and propionic acid (**42**) (Scheme 10). In the first stage, Claisen condensation of compounds **41** and **42** in the presence of triethyl orthoacetate (**43**) gave 85% of unsaturated ester **44**. Epoxidation of the double bond in **44** with *m*-chloroperoxybenzoic acid afforded epoxy derivative **45** in high yield, and the latter was subjected to heterocyclization by the action of hydroxylamine. As a result, 74% of dihydroxypiperidinone **46** was obtained. In the final stage,

Scheme 8.



Scheme 9.

Scheme 10.

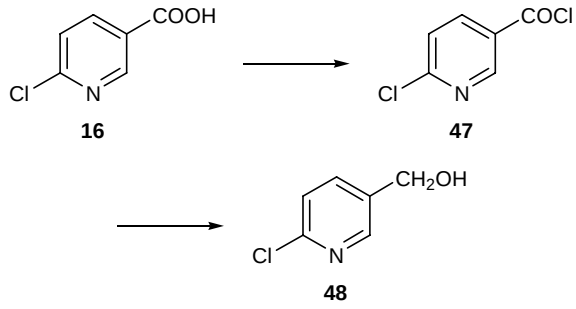


compound **46** was converted into 2-chloro-5-methylpyridine (**10**) by treatment with thionyl chloride.

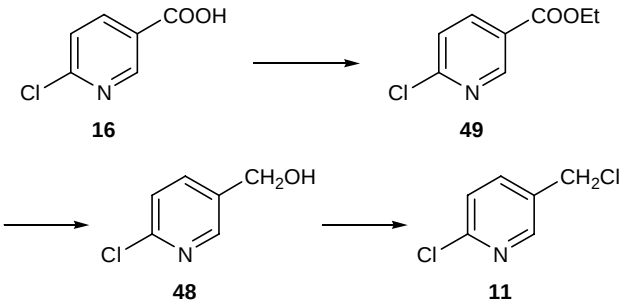
2-Chloro-5-chloromethylpyridine (11). As follows from the above schemes, 2-chloro-5-chloromethylpyridine (**11**) is the key intermediate product in the synthesis of imidacloprid. Compound **11** was isolated for the first time in quantitative yield by reaction of 2-chloro-5-hydroxymethylpyridine (**48**) with thionyl chloride [58]. An analogous transformation was described in [59]. Hydroxymethylpyridine (**48**) can be obtained in several ways from 6-chloronicotinic acid (**16**). According to [60], 6-chloronicotinic acid (**16**) was converted into the corresponding acid chloride **47** by treatment with phosphorus pentachloride and phosphoryl chloride. The subsequent reduction of **47** with sodium tetrahydridoborate gave compound **48** (Scheme 11). An alternative procedure is based on the direct reduction of carboxylic acid **16** with lithium tetrahydridoaluminate. In this case, the yield of alcohol **48** was 45% [61].

Morland *et al*. [62] also synthesized dichloro derivative **11** from 6-chloronicotinic acid (**16**). Acid **16** was initially converted into ethyl ester **49** (yield 89%) by reaction with ethanol in the presence of sulfuric acid. The ester group in **49** was reduced with sodium tetrahydridoborate to obtain 92% of alcohol **48**, and the latter was converted into 2-chloro-5-chloromethylpyridine (**11**) in 74.5% yield by treatment with thionyl chloride (Scheme 12). According to [63], ester **49** can be prepared in 92.3% yield by reaction of 6-chloronicotinic acid (**16**) with triethyl orthoformate in boiling toluene.

Scheme 11.

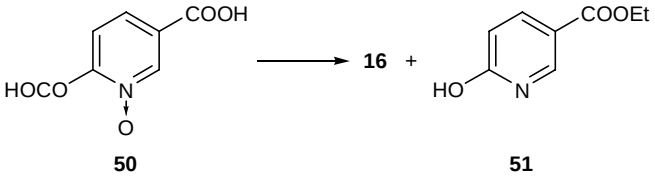


Scheme 12.



Several procedures have been developed for the synthesis of 6-chloronicotinic acid (**16**). A mixture of 6-chloro and 6-hydroxy derivatives **16** and **51** at a ratio of 55:45 was obtained in an overall yield of 97% by reaction of isocinchomeronic acid *N*-oxide (**50**) with acetic anhydride and triethylamine in methylene chloride, followed by treatment with an aqueous solution of sodium hydroxide [64] (Scheme 13). 6-Hydroxynicotinic acid (**51**) also attracts interest from the viewpoint of synthesis of neonicotinoids.

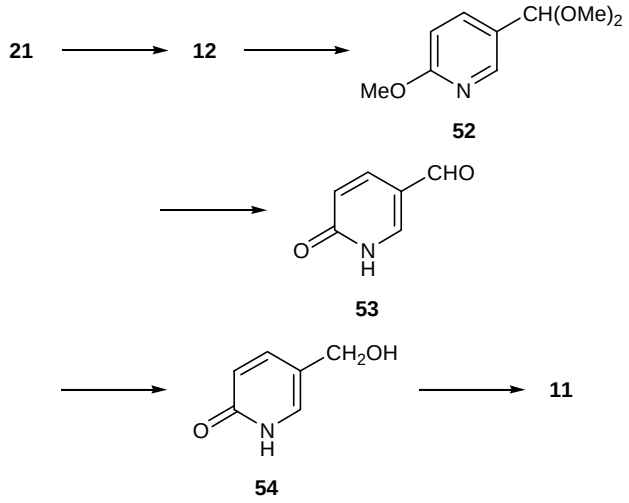
Scheme 13.



2-Chloro-5-chloromethylpyridine (**11**) can also be prepared from nicotinic acid (**21**). According to patent

[65], treatment of acid **21** first with thionyl chloride and then with a mixture of phosphorus trichloride and chlorine gave 89% of 3-trichloromethylpyridine (**12**). The subsequent reaction of **12** with sodium methoxide in methanol afforded methoxy derivative **52** in 83% yield, and hydrolysis of **52** with hydrochloric acid resulted in formation of 81% of 2-oxopyridine-5-carbaldehyde (**53**). The aldehyde group in **53** was hydrogenated over Raney nickel to obtain 78% of hydroxymethylpyridinone **54**, and the latter was converted into 2-chloro-5-chloromethylpyridine (**11**) in 96% yield by reaction with a mixture of phosphorus pentachloride and phosphoryl chloride (Scheme 14).

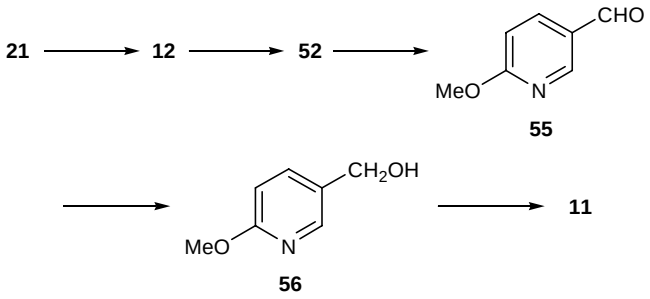
Scheme 14.



Somewhat different reaction sequence leading to chloromethylpyridine **11** from nicotinic acid (**21**) was covered by patent [66]. As in the preceding procedure, nicotinic acid (**21**) was initially converted into compound **12** and then into dimethoxymethylpyridine **52**. Compound **52** was subjected to partial hydrolysis with hydrochloric acid (1 h at room temperature). Aldehyde **55** thus formed (yield 82%) was hydrogenated over Raney nickel. As a result, hydroxymethylpyridine **56** was isolated in quantitative yield. Treatment of **56** with phosgene in the presence of dimethylformamide gave 88% of 2-chloro-5-chloromethylpyridine (**11**) (Scheme 15).

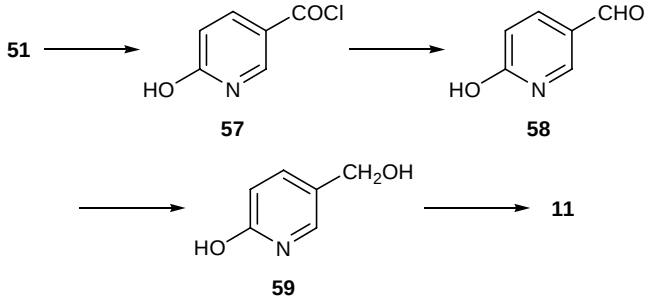
Werbitzky and Studer [67] described the synthesis of 2-chloro-5-chloromethylpyridine (**11**) from 6-hydroxynicotinic acid (**51**). Treatment of **51** with thionyl chloride gave 85% of the corresponding carbonyl chloride **57** which was converted into aldehyde **58** (yield 74%) by hydrogenation over 5% Pd/C on heating under pressure. Further hydrogenation of **58**

Scheme 15.



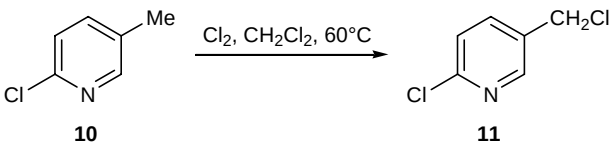
over palladium catalyst under pressure at room temperature afforded 94% of dihydroxy compound (**59**), and the reaction of **59** with a mixture of phosphorus pentachloride and phosphoryl chloride on heating led to 2-chloro-5-chloromethylpyridine (**11**) (Scheme 16). 6-Hydroxynicotinic acid **51** can also be obtained by enzymatic oxidation of nicotinic acid (**21**) [68, 69].

Scheme 16.



A fairly simple procedure for the synthesis of 2-chloro-5-chloromethylpyridine (**11**) was proposed in [70, 71]. Compound **11** was obtained in 65% yield by controlled chlorination of 2-chloro-5-methylpyridine (**10**) in methylene chloride on heating at 60°C for 10 h (Scheme 17). Here, sodium carbonate was used to bind liberated hydrogen chloride. According to patent [72], the chlorination of 2-chloro-5-methylpyridine (**10**) was carried out in the presence of azobis(isobutyronitrile) with simultaneous removal of liberated hydrogen chloride by intermittently adding a solution of potassium carbonate to the reaction mixture. The yield of 2-chloro-5-chloromethylpyridine (**11**) was 68.0%, and 2-chloro-5-dichloromethylpyridine and 2-chloro-5-trichloromethylpyridine (**13**) were formed as by-products (yield 19.2 and 0.4%, respectively).

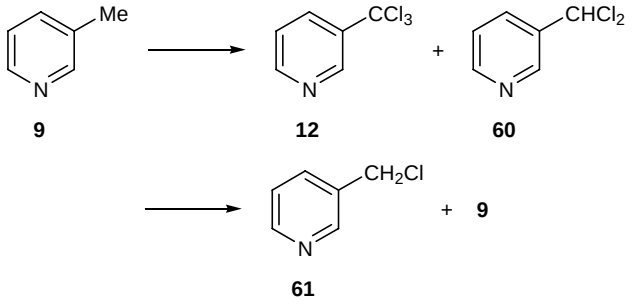
Scheme 17.



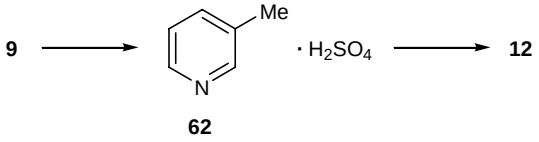
3-Trichloromethylpyridine (12). Methods of preparation of compound **12** can be divided into two groups. The first of these includes procedures based on direct chlorination of 3-methylpyridine (**9**). According to procedures of the second group, 3-methylpyridine (**9**) is initially oxidized to nicotinic acid (**21**) which is then converted into compound **12**.

Whittaker [73, 74] obtained 3-trichloromethylpyridine (**12**) in 36% yield by passing a mixture of 3-methylpyridine (**9**), chlorine, and nitrogen over chromium catalyst at 220°C (contact time 8.3 s). Apart from the target compound, 3-dichloromethylpyridine (**60**, 14%), 3-chloromethylpyridine (**61**, 12%), and unreacted 3-methylpyridine (**9**, 10%) were detected among the products (Scheme 18). Jelich and Lindel [75] proposed a procedure for the synthesis of 3-trichloromethylpyridine (**12**) via transformation of 3-methylpyridine (**9**) into hydrogen sulfate **62** and subsequent chlorination of **62** in the presence of benzamide on heating under irradiation (Scheme 19). Compound **12** was thus obtained in more than 80% yield.

Scheme 18.



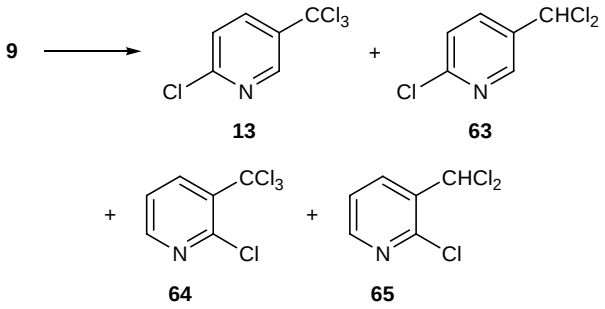
Scheme 19.



It is well known that oxidation of 3-methylpyridine (**9**) gives nicotinic acid in a high yield. Several methods have been developed for the transformation of nicotinic acid into 3-trichloromethylpyridine (**12**). One of these [76] is based on the reaction of acid **21** with phenylphosphonic dichloride and phosphorus pentachloride. Compound **12** was also obtained in 55% yield by treatment of **21** with dichlorophenylphosphine, phosphorus trichloride, and chlorine [77]. Another modification involves reaction of nicotinic acid (**21**) with dichlorophenylphosphine, phenylphosphonic dichloride, and chlorine (yield of **12** 96%) [78, 79]. Dainter *et al*. [80] reported on a fairly simple procedure for the transformation of nicotinic acid (**21**) into 3-trichloromethylpyridine (**12**) via reaction with phosphorus pentachloride. The yield of the target product was 64%. As noted above, 3-trichloromethylpyridine (**12**) can be synthesized in two steps with an overall yield of 89% by treatment of nicotinic acid (**21**) with thionyl chloride and subsequent transformation of nicotinoyl chloride by the action of phosphorus trichloride and chlorine [65, 66].

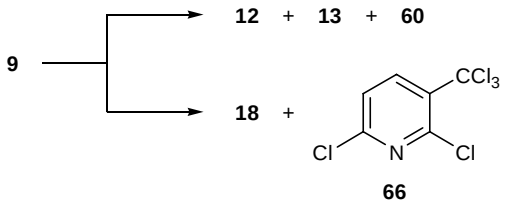
2-Chloro-5-trichloromethylpyridine (13). Compound **13** is the key intermediate product in the synthesis of various herbicides. Therefore, procedures for its preparation on a large scale were developed before the discovery of neonicotinoids. These procedures are based mainly on the chlorination of 3-methylpyridine (**9**) under severe conditions. According to the data of [81], the gas-phase chlorination of 3-methylpyridine (**9**) with chlorine in the presence of carbon tetrachloride at 350°C gives 2-chloro-5-trichloromethylpyridine (**13**) and 2-chloro-5-dichloromethylpyridine (**63**) as the major products, while 2-chloro-3-trichloromethylpyridine (**64**) and 2-chloro-3-dichloromethylpyridine (**65**) are the minor ones (Scheme 20).

Scheme 20.



The chlorination of **9** under extremely drastic conditions was described in [82, 83]. A mixture of 3-methylpyridine (**9**), carbon tetrachloride, nitrogen, and chlorine was passed through a glass tube heated to 400°C (contact time 9 s). The resulting mixture of products contained 3-trichloromethylpyridine (**12**, 1.8%), 3-dichloromethylpyridine (**60**, 0.2%), 2-chloro-5-trichloromethylpyridine (**13**, 74.4%), 2-chloro-3-trichloromethylpyridine (**18**, 12.7%), and 2,6-dichloro-3-trichloromethylpyridine (**66**, 6.2%) (Scheme 21). The chlorination of **9** in the gas phase in the presence of water and carbon tetrachloride as diluents and hexachloro-1,3-butadiene as radical initiator gave 2-chloro-5-trichloromethylpyridine (**13**) in 27% yield [84].

Scheme 21.

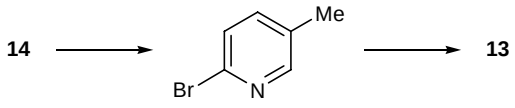


66

One more procedure for the chlorination of **9** was given in [85–87]. Gaseous chlorine was passed through a boiling solution of 3-methylpyridine (**9**) in carbon tetrachloride under UV irradiation. The product mixture was separated by thin-layer chromatography. A mixture of three compounds was thus isolated in an overall yield of 10–15%; the major component of this mixture was 2-chloro-5-trichloromethylpyridine (**13**). The other components were 2-chloro-3-trichloromethylpyridine (**64**) and bis(trichloromethyl)pyridine. Much better results were obtained by chlorination of 3-methylpyridine hydrochloride which was prepared by passing gaseous hydrogen chloride through a solution of **9** in carbon tetrachloride. The chlorination of 3-methylpyridine hydrochloride on heating under UV irradiation (4 h) afforded 2-chloro-5-trichloromethylpyridine (**13**) as the major product.

Nishiyama *et al*. [88] synthesized 2-chloro-5-trichloromethylpyridine (**13**) from 2-amino-5-methylpyridine (**14**). Initially, compound **14** was converted into 2-bromo-5-methylpyridine (**67**) via diazotization with sodium nitrite in the presence of hydrobromic acid and bromine, and the chlorination of **67** under UV irradiation afforded 2-chloro-5-trichloromethylpyridine (**13**) (Scheme 22).

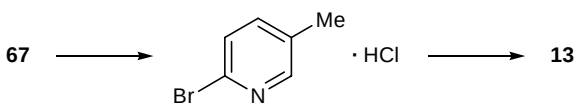
Scheme 22.



67

Cartwright [85–87, 89] patented a procedure for the synthesis of 2-chloro-5-trichloromethylpyridine (**13**), according to which 2-bromo-5-methylpyridine (**67**) was treated with dry hydrogen chloride in carbon tetrachloride to obtain hydrochloride **68**, and the latter was subjected to chlorination under ultraviolet urradiation (Scheme 23).

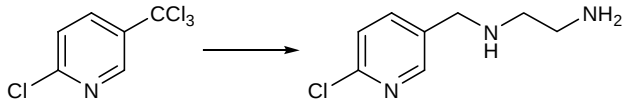
Scheme 23.



68

2-Chloro-5-trichloromethylpyridine (**13**) can be utilized in several ways in the synthesis of neonicotinoids. First of all, reduction of **13** gives less chlorinated 3-methylpyridine derivatives. The reduction of **13** with zinc or tin gave more than 80% of 2-chloro-5-chloromethylpyridine **11**. The minor products were 2-chloro-5-dichloromethylpyridine (**63**, 3.5%) and 2-chloro-5-methylpyridine (**10**, 11.4%). Nasu *et al*. **[**91] obtained 2-chloro-5-dichloromethylpyridine (**63**) in more than 70% yield by reduction of 2-chloro-5-trichloromethylpyridine (**13**) with triphenylphosphine. Ieno and Kawanami [92] found that hydrogenation of 2-chloro-5-trichloromethylpyridine (**13**) over Raney nickel in the presence of ethylenediamine leads to formation of 66% of diamine **69** (Scheme 24) which is used in the synthesis of imidacloprid (**2**) (see below).

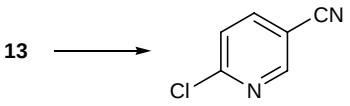
Scheme 24.



13 **69**

The reaction of 2-chloro-5-trichloromethylpyridine (**13**) with ammonium chloride in the presence of copper oxide at 200°C afforded 6-chloropyridine-3-carbonitrile (**70**) in more than 70% yield [93] (Scheme 25). Compound **70** can also be used in the synthesis of neonicotinoids, e.g., via hydrolysis to 6-chloronicotinic acid.

Scheme 25.



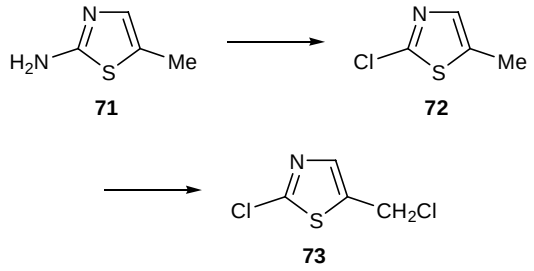
70

3.2. Synthesis of 2-Chloro-5-chloromethylthiazole

2-Chloro-5-chloromethylthiazole (**73**) is the key compound in the synthesis of chlorothiazole neonicotinoids. The first procedures for the preparation of compound **73** utilized 2-amino-5-methylthiazole (**71**) as starting material. Aminothiazole **71** was first treated with sodium nitrite in hydrochloric acid to obtain the corresponding diazonium salt whose subsequent decomposition afforded 2-chlorothiazole (**72**). Com-

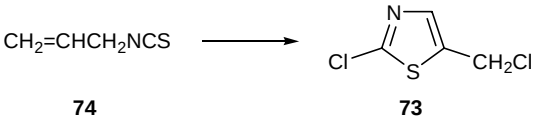
pound **72** was then chlorinated with *N*-chlorosuccinimide to give **73** [94–97] (Scheme 26).

Scheme 26.



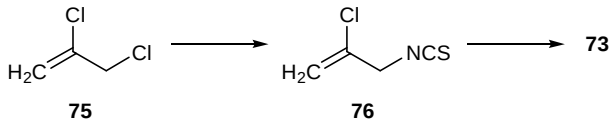
Beck and Heitzer [98–100] developed a procedure for the synthesis of 2-chloro-5-chloromethylthiazole (**73**) by chlorination of allyl isothiocyanate (**74**) with a large excess of chlorine (Scheme 27). The yield of **73** was more than 50%.

Scheme 27.



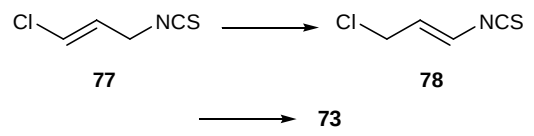
An alternative procedure, which also involves isothiocyanates, was described in [96, 101–105]. It implies initial reaction of 2,3-dichloro-1-propene (**75**) with potassium thiocyanate on heating, which leads to isothiocyanate **76**. The latter is then subjected to chlorination with chlorine or sulfuryl chloride to obtain target thiazole **73** (Scheme 28).

Scheme 28.



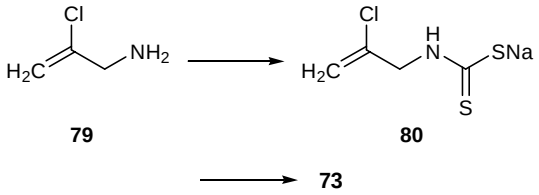
Matsuda *et al*. [106] obtained 2-chloro-5-chloromethylthiazole (**73**) in about 70% yield by chlorination of 3-chloro-1-isothiocyanato-1-propene (**78**) Compound **78** was synthesized in 90% yield by isomerization of 3-chloro-1-isothiocyanato-2-propene (**77**) on heating in boiling xylene in the presence of copper(II) chloride (Scheme 29).

Scheme 29.



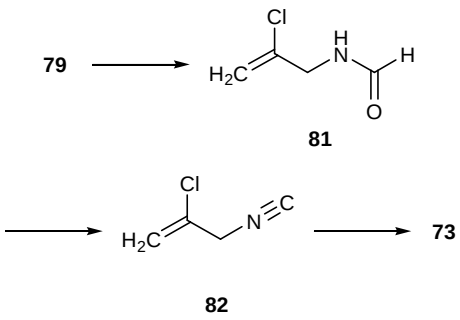
A procedure for the synthesis of 2-chloro-5-chloromethylthiazole (**73**) from 2-chloro-2-propenylamine (**79**) was developed in [107, 108]. The reaction of amine **79** with carbon disulfide in alkaline medium gave 85% of sodium dithiocarbamate **80** which was oxidized with iodine or hydrogen peroxide to the corresponding disulfide, and cyclization of the latter by the action of sulfuryl chloride led to formation of thiazole **73** in 30% yield (Scheme 30).

Scheme 30.



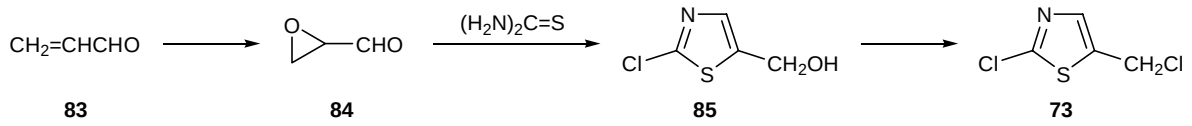
A different reaction sequence leading to 2-chloro-5-chloromethylthiazole (**73**) from 2-chloro-2-propenylamine (**79**) was proposed in [108–110]. Amine **79** reacted with ethyl formate to give *N*-(2-chloro-2-propenyl)formamide (**81**) in a high yield. Compound **81** was dehydrated by treatment with thionyl chloride in dimethylformamide in the presence of sodium carbonate to obtain 80% of isonitrile **82**, and cyclization of **82** with sulfur dichloride resulted in formation of thiazole **73** in 50% yield (Scheme 31). The reaction of formamide **81** with thionyl chloride and sulfur dichloride allowed 2-chloro-5-chloromethylthiazole (**73**) to be obtained in one step in 42% yield.

Scheme 31.

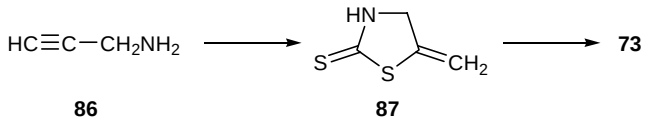


Acrolein (**83**) was used as initial compound in the synthesis of 2-chloro-5-chloromethylthiazole (**73**) according to patent [111]. Oxidation of the double C=C bond in **83** with hydrogen peroxide in alkaline medium gave oxirane **84**. The reaction of **84** with thiourea afforded 2-amino-5-hydroxymethylthiazole (**85**) which was converted into chloromethylthiazole **73** (Scheme 32). As shown in [108, 112, 113], compound

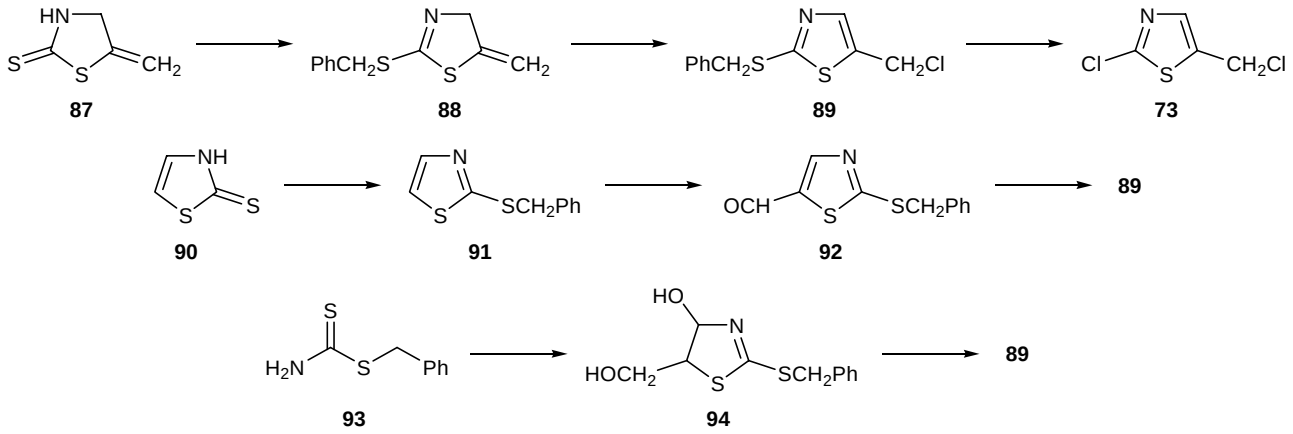
Scheme 32.



Scheme 33.



Scheme 34.

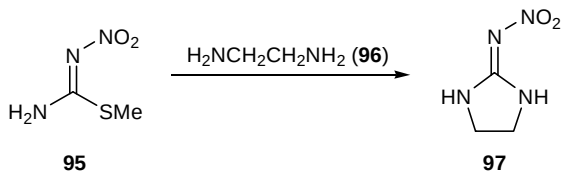


73 can be obtained in 80–90% yield by chlorination of 5-methylene-1,3-thiazolidine-2-thione (**87**). The latter is available via reaction of amine **86** with carbon disulfide (yield 90%, Scheme 33). Several procedures have been developed for the preparation of 2-chloro-5-chloromethylthiazole (**73**) through 2-benzysulfanyl derivative **89** [108]. The reaction of 5-methylene-1,3-thiazolidine-2-thione (**87**) with benzyl bromide gave 70% of sulfide **88** [114], and chlorination of **88** with sulfuryl chloride led to formation of chlorothiazole **89** in 60% yield. Replacement of the benzylsulfanyl group in **89** via chlorination resulted in target 2-chloro-5-chloromethylthiazole (**73**) (Scheme 34). Another version utilized thiazole-2-thione **90** [115] which was alkylated with benzyl bromide to obtain 80% of 2-benzylsulfanylthiazole (**91**). Compound **91** was treated with phosphoryl chloride in dimethylformamide, and aldehyde **92** thus formed (yield 35%) was hydrogenated over platinum catalyst to the corresponding alcohol. Replacement of the hydroxy group in the latter by chlorine by the action of thionyl chloride afforded 2-benzylsulfanyl-5-chloromethylthiazole (**89**) in an overall yield of 60% (Scheme 34). Compound **89** was also synthesized from dithiocarbamate **93** [115]. For this purpose, dithiocarbamate **93** was brought into cyclization with 2,3-epoxypropionaldehyde, which resulted in formation of dihydrothiazole **94** (yield 85%). Treatment of **94** with thionyl chloride gave 90% of chloromethylthiazole **89**.

3.3. Synthesis of 2-Nitroiminoimidazolidine

2-Nitroiminoimidazolidine (**97**) is one of the most convenient intermediate products for building up the imidazolidine fragment in the imidacloprid molecule. Several procedures for the synthesis of 2-nitroiminoimidazolidine were developed. Hafner and Evans [116] obtained this compound in 72.1% yield by reaction of *S*-methyl-*N*-nitroisothiourea (**95**) with ethylenediamine (**96**) in water on heating (Scheme 35).

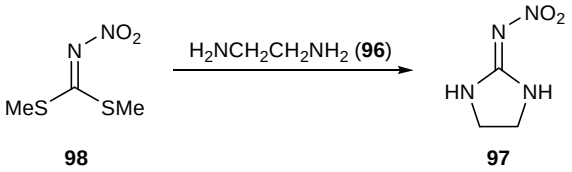
Scheme 35.



The reaction of dimethyl nitrocarbonimidodithioate (**98**) with diamine **96** gave 96.1% of imidazolidine **97**

[117] (Scheme 36). Initial compound **98** can be synthesized in 41% yield by reaction of dimethyl carbonimidodithioate nitrate with trifluoroacetic anhydride in chloroform.

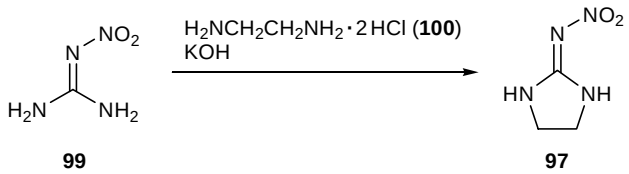
Scheme 36.



98 **97**

Presumably, the most convenient procedure for the synthesis of 2-nitroiminoimidazolidine (**97**) is that proposed by McKay and Wright [118, 119]. According to the authors, compound **97** is formed by reaction of nitroguanidine (**99**) with ethylenediamine dihydrochloride (**100**) and potassium hydroxide in water on heating (Scheme 37). Here, the yield of **97** was 65.4%. However, in keeping with the data of [117], the above procedure gives only 37% of 2-nitroiminoimidazolidine (**97**).

Scheme 37.



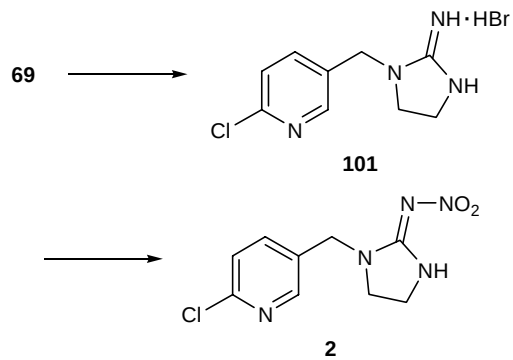
99 **97**

4. SYNTHESIS OF CHLOROPYRIDINE NEONICOTINOIDS

4.1. Imidacloprid

Synthetic approaches to imidacloprid (**2**) were developed for the first time by Shiokawa *et al*. [120–122] using nitromethylene derivatives as examples. By reaction of diamine **69** with cyanogen bromide in toluene the authors obtained iminoimidazolidine derivative **101** which was converted into compound **2** in a low yield by treatment with nitric acid in the presence of sulfuric acid [121, 122] (Scheme 38).

Scheme 38.

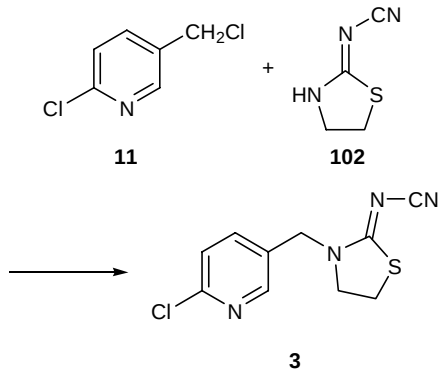


Kojima *et al*. [117] synthesized imidacloprid (**2**) in 80% yield by reaction of *N*-(2-chloro-5-pyridylmethyl)-ethylenediamine (**69**) with dimethyl nitrocarbonimidodithioate (**98**) in methylene chloride. Diehr [123] succeeded in preparing compound **2** in 90.2% yield by condensation of 2-chloro-5-chloromethylpyridine (**11**) with 2-nitroiminoimidazolidine (**97**) on heating in boiling acetonitrile in the presence of potassium carbonate (to bind liberated hydrogen chloride) and cesium chloride as catalyst. Likewise, reaction of stoichiometric amounts of compounds **11** and **97** in the presence of potassium carbonate afforded 80–90% of imidacloprid (**2**) [124, 125]; it was proposed to use acetonitrile as solvent.

4.2. Thiacloprid

The synthesis of thiacloprid (**3**) was described in patents [126, 127]. It was obtained by reaction of 2-chloro-5-chloromethylpyridine (**11**) with anion generated from 2-cyanoiminothiazolidine (**102**) by the action of, e.g., sodium hydride (Scheme 39).

Scheme 39.



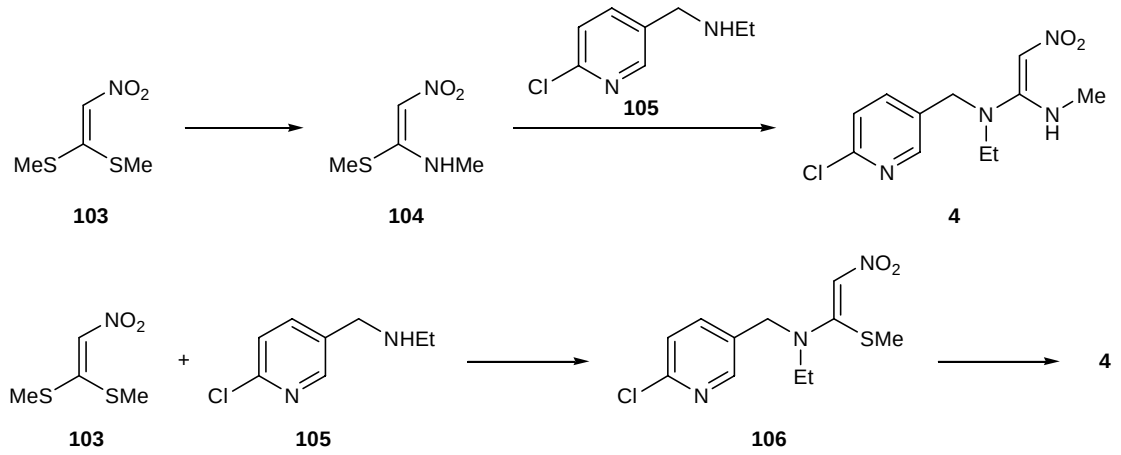
11 **102**

3

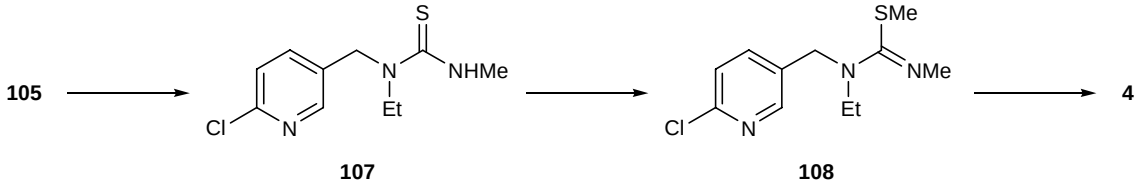
4.3. Nitenpyram

Several schemes may be applied to the synthesis of nitenpyram (**4**) [25, 128–130]. One of these includes initial reaction of 1,1-bis(methylsulfanyl)-2-nitroethylene (**103**) with methylamine to give substituted nitroethylene **104**. Aminolysis of nitro compound **104** with *N*-(6-chloro-3-pyridylmethyl)ethylamine (**105**) leads to nitenpyram **4** (Scheme 40). Another version implies that compound **103** is initially subjected to aminolysis with **105**. Tertiary amine **106** thus obtained

Scheme 40.



Scheme 41.



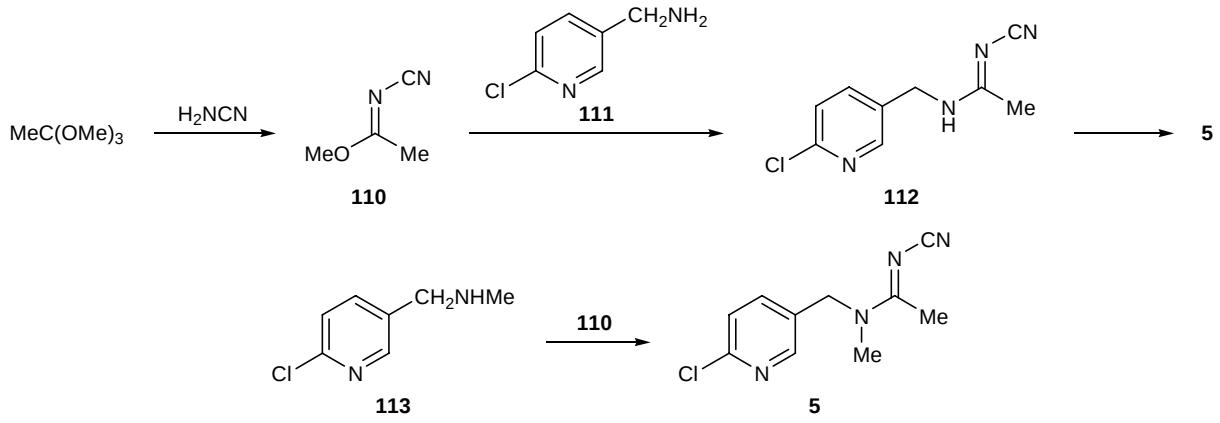
is treated with methylamine. One more procedure is based on the reaction of ethylaminopyridine **105** with methyl isothiocyanate, which leads to substituted thiourea **107**. Compound **107** is then alkylated at the sulfur atom via successive reactions with sodium hydride and methyl iodide, and the resulting *S*-methylisothiourea **108** reacts with nitromethane, yielding compound **4** (Scheme 41).

4.4. Acetamiprid

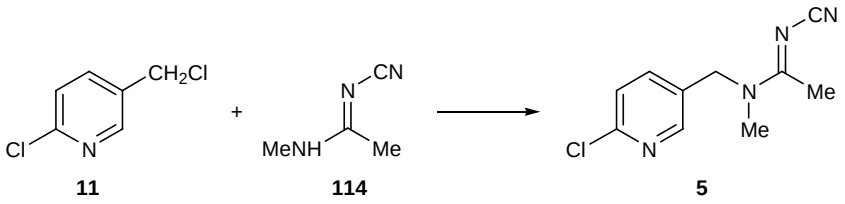
Scheme 42 illustrates the synthesis of acetamiprid (**5**) described in [29, 131]. In the first step, the reaction of trimethyl orthoacetate (**109**) with cyanamide gave methyl *N*-cyanoacetimidate (**110**) in high yield. The subsequent condensation of **110** with 6-chloro-3-pyridylmethylamine (**111**) quantitatively afforded compound **112**, and the secondary amino group in **112** was alkylated with dimethyl sulfate. Compound **5** can also be obtained in one step by condensation of methyl *N*-cyanoacetimidate (**110**) with *N*-(6-chloro-3-pyridylmethyl)methylamine (**113**).

Liu *et al*. [132] synthesized acetamiprid (**5**) in 40% yield from 2-chloro-5-chloromethylpyridine (**11**) and *N*-cyano-*N'*-methylacetamidine (**114**) (Scheme 43). The reaction was carried out by heating the reactants in acetonitrile in the presence of potassium carbonate.

Scheme 42.



Scheme 43.



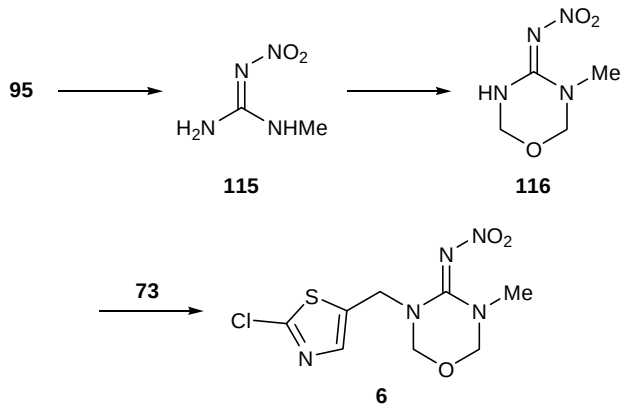
11 **114** **5**

5. SYNTHESIS OF CHLOROTHIAZOLE NEONICOTINOIDS

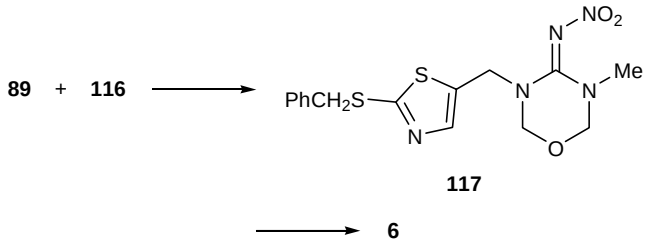
5.1. Thiamethoxam

Thiamethoxam (**6**) was synthesized for the first time in 1991; its molecule contains thiazole and tetrahydro-1,3,5-oxadiazine rings. A special scheme was developed for the synthesis of **6** [32, 108, 133–136] starting from *S*-methyl-*N*-nitroisothiourea (**95**). Compound **95** reacted with methylamine in ethanol to give 94% of *N*-methyl-*N′*-nitroguanidine **115**. The reaction of **115** with an aqueous solution of formaldehyde and formic acid led to formation of tetrahydro-1,3,5-oxadiazine **116** in 71% yield. The target neonicotinoid **6** was synthesized in 71% yield by alkylation of **116** with 2-chloro-5-chloromethylthiazole (**73**) in dimethylformamide in the presence of potassium carbonate (Scheme 44). Following an alternative scheme [108, 115], thiamethoxam (**6**) was obtained by reaction of benzyl sulfide **89** with 1,3,5-oxadiazine **116** to give compound **117** (yield 65%) and the subsequent chlorination of **117** (yield of **6** 80%) (Scheme 45).

Scheme 44.



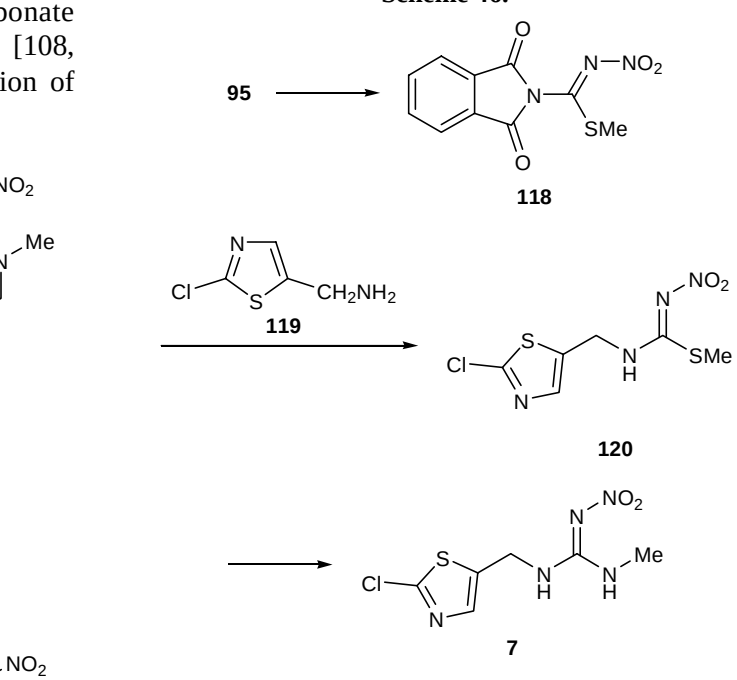
Scheme 45.



5.2. Clothianidin

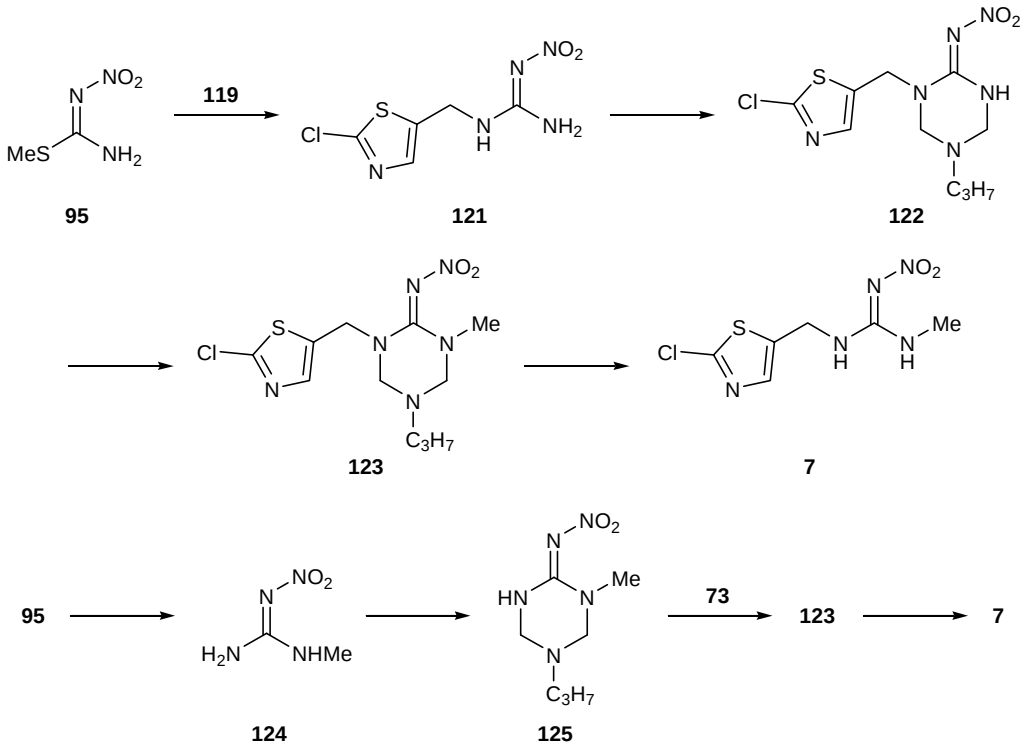
The scheme of synthesis of neonicotinoid clothianidin (**7**) was given in [96, 137, 138]. According to that scheme, initial *S*-methyl-*N*-nitroisothiourea (**95**) reacted with phthaloyl dichloride to give *N*-[methylsulfanyl(nitroimino)methyl]phthalimide (**118**). The reaction of (**118**) with 5-aminomethyl-2-chlorothiazole (**119**) led to thiazole **120**, and the latter was converted into clothianidin (**7**) by treatment with methylamine (Scheme 46).

Scheme 46.



Two alternative methods for the preparation of clothianidin (**7**) were described in [139, 140]. The first of these begins with the reaction of isothiourea (**95**) with 5-aminomethyl-2-chlorothiazole (**119**) to obtain nitroguanidine derivative **121** in 83% yield. Compound **121** reacts with formaldehyde and propylamine,

Scheme 47.



yielding 88% of triazine **122**. Alkylation of **122** with methyl iodide results in formation of substituted hexahydro-1,3,5-triazine **123** in 60% yield, and hydrolysis of the latter with a solution of hydrochloric acid in ethanol affords 86% of target product **7** (Scheme 47). In the second procedure, isothiourea **95** reacts first with methylamine to afford 84% of *N*-methyl-*N'*-nitroguanidine (**124**) which is then brought into reaction with formaldehyde and propylamine. Substituted hexahydrotriazine **125** is thus obtained in 92% yield. Alkylation of **125** with 2-chloro-5-chloromethylthiazole (**73**) gives 90% of compound **123** which is converted into clothianidin (**7**) following the same procedure as in the first version.

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