New Carboxylic Acid Amides of the Pyrrole Series: Synthetic Routes and Biological Aspects

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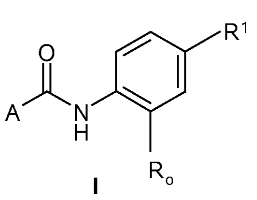
Complex II inhibitors play an important role in agrochemical fungicide research and have been known for more than 40 years. With the introduction of *ortho*-substituted heterocyclic amides, a breakthrough in activity level and spectrum within this class was achieved. In the meantime all major agrochemical companies have entered this field. In this paper, a special complex II subclass, the pyrrole carboxamides, will be introduced in more detail and the synthesis of selected compounds as well as a short biological SAR analysis of the pyrrole subclass will be discussed.

Key words: Complex II, Fungicidal Activity, Carboxin, *ortho*-Substituted Anilines, Pyrrole Carboxylic Acids, Pyrrole Carboxamides

Introduction

Carboxylic acid amides which inhibit Complex II in the mitochondrial respiration chain have been known as fungicides for more than 40 years and play a significant role in agrochemical fungicide research [1]. The first important representative of this chemical class, carboxin (**1**), an old seed-treatment compound was introduced to the market in 1966. A breakthrough in this area was achieved with the discovery of the *ortho*-substituted phenyl amide class (Fig. 1), Monsanto and BASF being the pioneers [2, 3]. With this type of compound the biological spectrum could be broadened and the efficacy significantly increased. Boscalid, the first commercial compound of this type, was introduced into the market in 2003. Further compounds of this class are close to market introduction and will enter the market by 2011 (Table 1). The new *ortho*-substituted amides, which have been announced, will play an important role in future resistance management and mixtures with triazoles, strobilurines or other fungicides will deliver valuable solutions for controlling major diseases in cereals and other market segments.

Some of our own research in the Complex II area is described in this paper. We only describe here a selected topic, the pyrrole carboxylic acid amides. For an overview of other heterocyclic acid amides of the Complex II area, a selection of Syngenta patent publications is given [4 – 11].



A = phenyl or heterocycle
R_o = substituted phenyl, heterocycle or cycloalkyl
R^1 = H, halogen;
A = heterocycle
R_o = phenyl (BASF, see [2]);
A = pyrazole
R_o = cycloalkyl (Monsanto, see [3])

Fig. 1. A first general structure of *ortho*-substituted amides.

Two Promising Leads from the Pyrrole Area and Strategies for their Optimization

With the discovery of our two first pyrrole leads **8a** and **8b** [12] (see Fig. 2) in 1998, we had our first breakthrough, but both compounds lack sufficient control of the cereal key disease Septoria leaf blotch. The insufficient biological spectrum and efficacy in the field stopped further progression of these compounds at an early stage.

Fig. 2 illustrates the possibilities for structure variations of the lead compounds **8a**, **b**. In the next chapters, variations of the heterocycle (incl. fine-tuning), amide linker, ring A and ring B will be described in more detail.

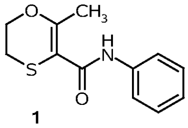
Modifications of the pyrrole part

We focused our synthesis work on three major topics: 1) pyrrole-2-carboxylic acid derivatives, 2) variations of the substitution pattern of the pyrrole-3-carb-

Table 1. Selected carboxylic acid amides sales products inhibiting Complex II.

Common name	Company	Year of market introduction	Sales 2005 in Mio $[a]
Carboxin (**1**)	Uniroyal	1966	85
Mepronil (**2**)	Kumiai	1980	< 10
Flutolanil (**3**)	Nihon Noyaku	1984	45
Furametpyr (**4**)	Sumitomo	1997	< 10
Boscalid (**5**)	BASF	2003	105
Penthiopyrad (**6**)	Mitsui Toatsu, Du Pont (EU)	2009/10 (introduction planned in EU)	≥ 80 (estimated peak sales)
Bixafen (**7**)	Bayer	2010/11 (introduction planned)	> 150 (estimated peak sales)

[a] Data from Phillips McDougall.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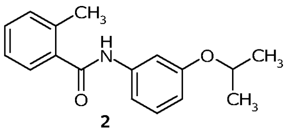
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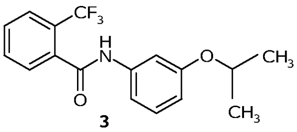
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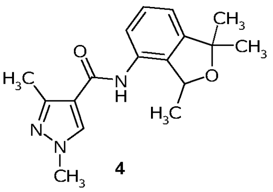
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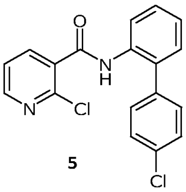
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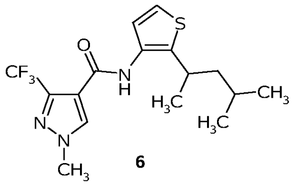
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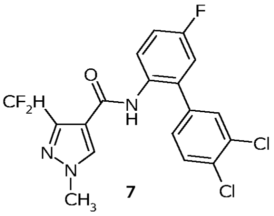
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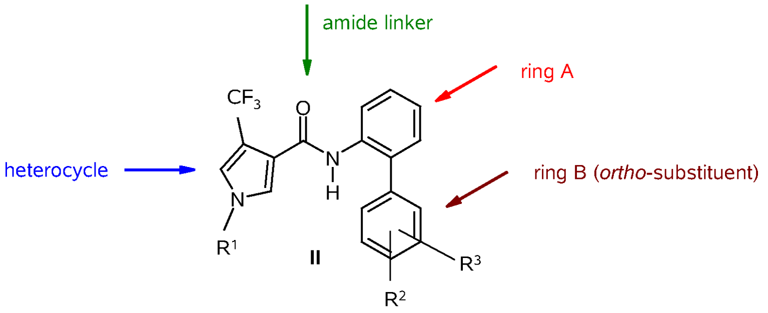


$R^1 = CH_3$, R^2 = 4-F, R^3 = H: **8a**

$R^1 = CH_3$, R^2 = 4-Cl, R^3 = H: **8b**

Fig. 2. General formula of pyrrole amides of the biphenyl type **II**.

oxylic acid and 3) bicyclic (bridged) pyrrole carboxylic acids (see Fig. 3).

All the compounds shown in Fig. 3 were prepared in our laboratories. In the next chapter we describe the synthesis of some selected pyrrole carboxylic acid derivatives.

For the synthesis of the pyrrole-3-carboxylic acid moiety we used either the van Leusen Tosmic approach [4, 13] (Scheme 1) or the ketoester/glycine route [14] (Scheme 2). Both routes can be used for the synthesis of kilogram quantities. We preferred the Tosmic route owing to the fact that this was the shorter

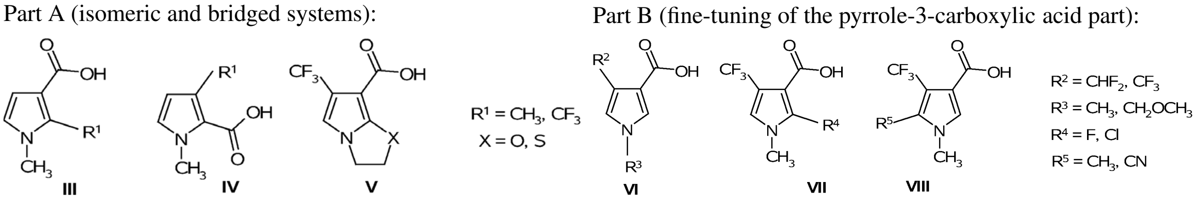
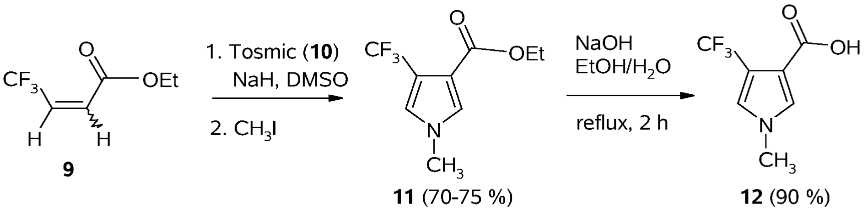
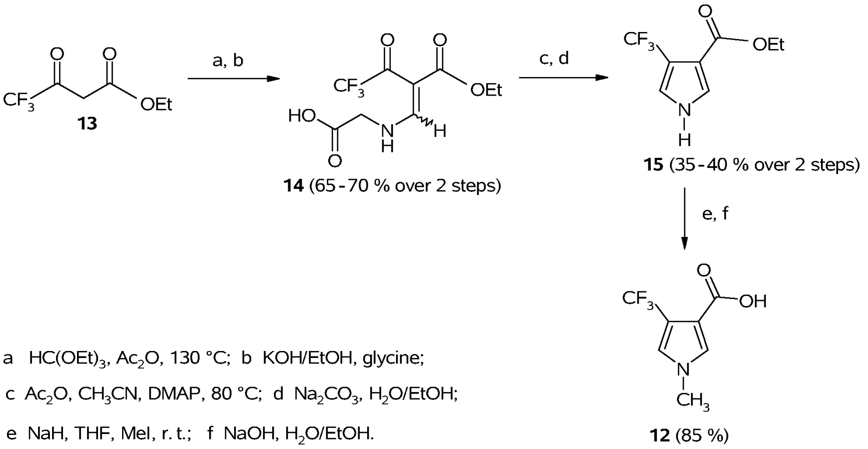


Fig. 3. Variations of the pyrrole acid part.



Scheme 1. Synthesis of 1-methyl-4-(trifluoromethyl)pyrrole-3-carboxylic acid **12** (Tosmic route) [4, 13].

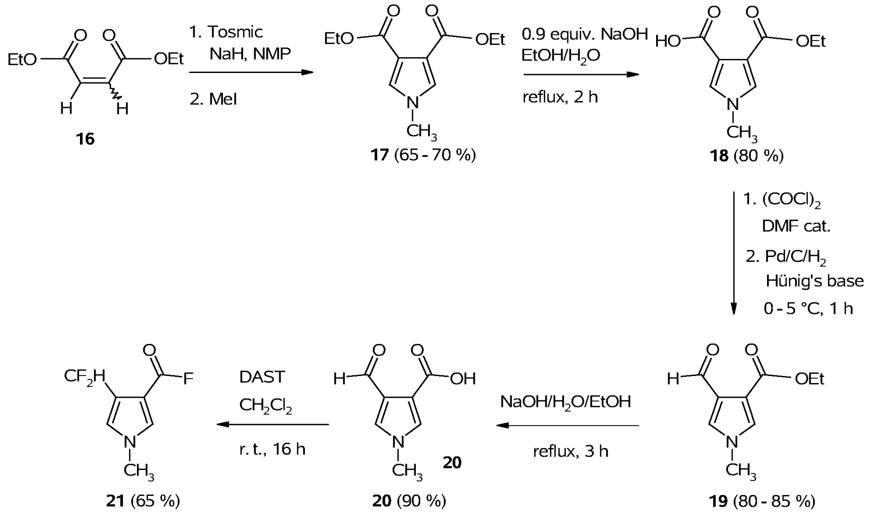


Scheme 2. Synthesis of pyrrole-3-carboxylic acid **12** (glycine route) [14].

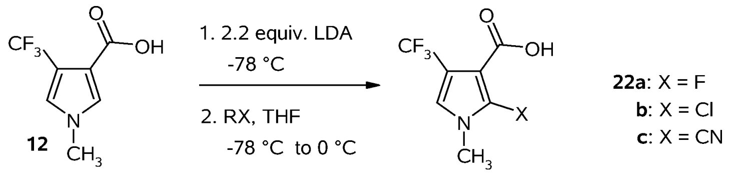
route. The starting material for the Tosmic route is the substituted acrylic ester **9**, which is commercially available, even on larger scale. In Scheme 1 the synthesis of the trifluoromethyl-substituted pyrrole acid **12** is shown. The reaction of the fluorinated unsaturated ester **9** with Tosmic (tosylmethylisocyanide, **10**) in the presence of sodium hydride, followed by methylation with methyl iodide delivered the pyrrole acid ethylester **11** in an overall yield of 65 – 70 %. Basic hydrolysis of **11** could be performed using standard conditions leading to the target pyrrole acid **12** in very good yield.

The starting materials for the glycine route are β-ketoesters, which are in most cases also commercially available. In Scheme 2 the synthesis of 1-methyl-3-trifluoromethyl-pyrrole-3-carboxylic acid (**12**) using the glycine route is described. The reaction sequence starts with the well known reaction of the trifluorinated β-ketoester **13** with formic acid orthoethylester leading to a trifluoromethyl-containing enolether intermediate, which after treatment with glycine in the presence of sodium hydroxide, gave the glycine derivative **14** in 65 – 70 % yield over 3 steps. The cyclization of the glycine derivative **14** works best using Ac_2O in acetonitrile in the presence of DMAP at 70 – 80 °C. Removal of the acetyl group could easily be achieved by treatment of **15** with sodium carbonate in a water/ethanol mixture. Methylation using MeI/NaH conditions and basic hydrolysis gave the final pyrrole-3-carboxylic acid **12**.

A more demanding task was the introduction of a CF_2H group in 4-position of the pyrrole 3-carboxylic acid. Here we could not use a fluorine building block approach, but were forced to use a special approach. Our synthesis starts with the van Leusen sequence using maleic acid diethylester (**16**) and Tosmic (**10**) as starting materials [4, 13]. The reaction was best carried out in NMP using NaH as a base. The



Scheme 3. Synthesis of 4-difluoromethyl-1-methylpyrrole-3-carbonyl acid fluoride (**21**) [15].



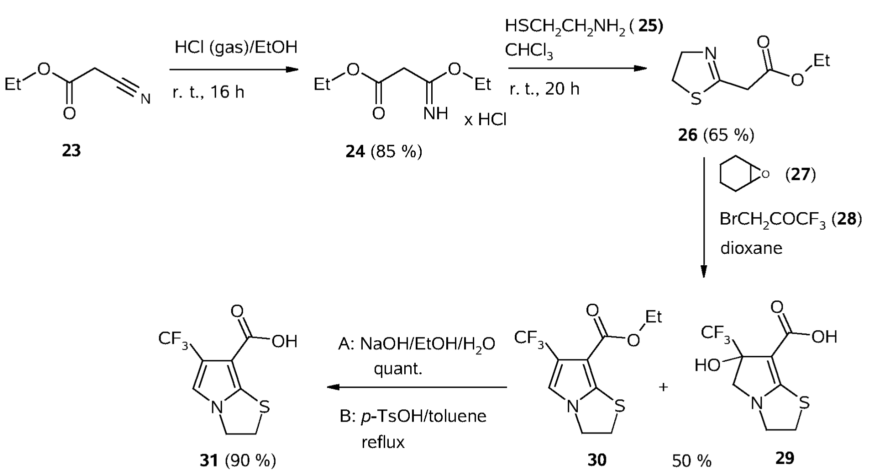
electrophile/yield: X = F, *N*-fluorobis(phenylsulfonyl)amine (55 %)
X = Cl, hexachloroethane (65 %)
X = CN, 1-cyanobenzotriazole (45 %)

Scheme 4. Synthesis of 2-substituted 1-methyl-4-trifluoromethylpyrrole-3-carboxylic acids **22a** – **c** [15].

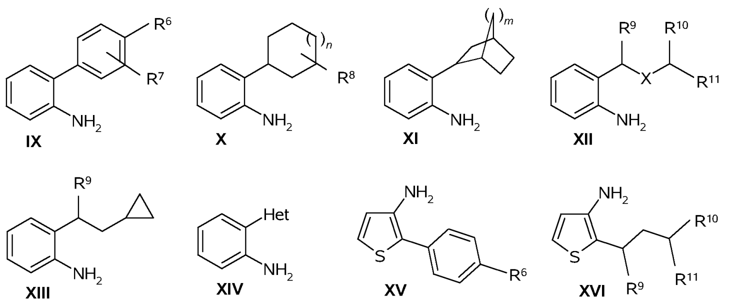
methylation again works well as described earlier in this paper. The yields of the resulting 1-methyl-pyrrole-3,4-dicarboxylic acid ester (**17**) are good (highest yield: 70 %). The trick now is to break the symmetry in this molecule. Selective monohydrolysis under basic conditions, preparation of the acid chloride and reduction under modified Rosenmund conditions using Hünig's base, delivered 4-formyl-1-methylpyrrole-3-carboxylic acid ester (**19**) in good yield. Basic hydrolysis and treatment of the resulting 4-formylpyrrole-3-carboxylic acid (**20**) with an excess of DAST (diethylaminosulfurtrifluoride) gave 4-difluoromethyl-1-methylpyrrole-3-carbonyl fluoride (**21**) in reasonable yield (Scheme 3). The acid fluoride **21** could be used directly for further amide synthesis [15].

As final fine-tuning examples, the introduction of fluorine, chlorine and cyano substituents in 2-position of the pyrrole moiety are described (Scheme 4). Starting from carboxylic acid **12**, the introduction of electrophiles could easily be achieved by use of a DOM (directed *ortho* metallation) approach. Treatment of the pyrrolecarboxylic acid **12** with 2.2 equivalents of LDA (lithium diisopropylamide) at −78 °C and quenching of the resulting dianion with an appropriate electrophile (*e. g. N*-fluorobis(phenylsulfonyl) amine for the introduction of fluorine) gave the 2-substituted pyrrolecarboxylic acids **22a** – **c** in moderate to good yields.

As an example of a more exploratory approach, the synthesis of the bicyclic pyrrolecarboxylic acid **31** will be given (see Scheme 5). The synthesis starts with the reaction of cyanoacetic ethylester (**23**) with hydrogen chloride gas in ethanol, which delivered the iminoether **24** in very good yield. Treatment of the iminoether **24** with cysteamine **25** gave the dihydrothiazole acetic acid ester **26**, which after reaction with bromotrifluoroacetone (**28**) in the presence of cyclohexene oxide (**27**) as a neutral acid scavenger delivered a mixture of the desired trifluoromethyl-substituted pyrrolecarboxylic acid ester **30** and the corresponding hydroxyl group containing acid **29** (*ca.* 50 % overall yield). The target molecule 6-trifluoromethyl-2,3-dihydropyrrolo[2,1-*b*]thiazole-7-carboxylic acid (**31**) could then easily be obtained by first treatment of the obtained mixture of acid **29** and the corresponding pyrrole ester **30** with sodium hydroxide (hydrolysis of



Scheme 5. Synthesis of 6-trifluoromethyl-2,3-dihydropyrrolo[2,1-*b*]thiazole-7-carboxylic acid (**31**) [16].



R^6,R^7 = H, halo, CH_3, CF_3, OCF_3, CN
R^8 = H, CH_3, Et, CF_3
R^9 = H, F, CH_3, Et, CF_3
R^{10}, R^{11} = CH_3, Et
X = CH_2, O, S
Het = thienyl, pyidyl, pyrimidinyl
n = 0–2
m = 1, 2

Fig. 4. Modifications of the aniline part.

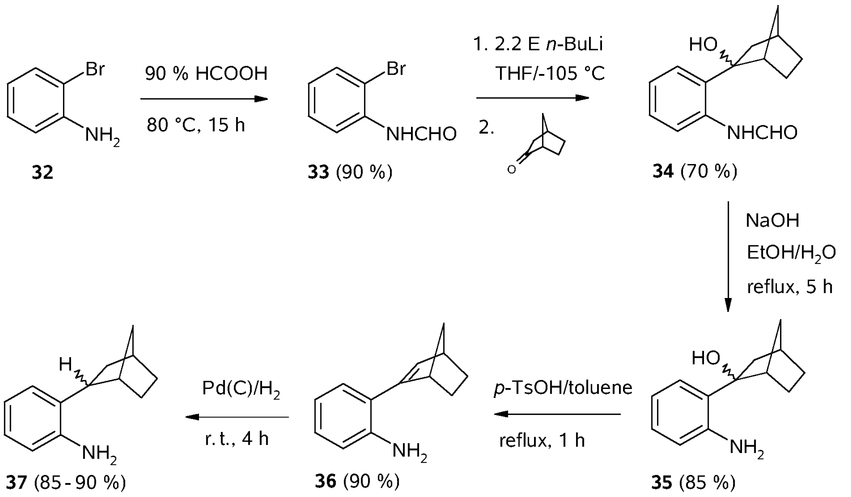
the ester) and then boiling the resulting pyrrolecarboxylic acid mixture with *p*-TsOH in toluene.

Modifications of the aniline part

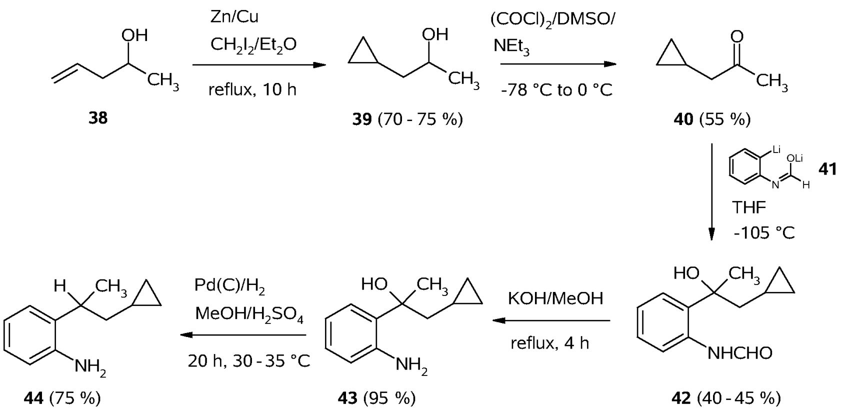
Although the Complex II area was (and still is) very competitive, and many heterocyclic acid amide structures were already disclosed in patent applications of other companies when we entered the field, we thought that the aniline part in particular offers plenty of opportunities for finding patentable pyrrole carboxamides showing good biological profile and activity level. In Fig. 4 an overview of prepared *ortho*-substituted aniline subclasses, is given.

For the synthesis of *ortho*-substituted anilines, organometallic chemistry was in many cases the key to success. As a first example the synthesis of 2-(2-norbornyl)phenylamine (**37**) will be described in more detail (Scheme 6). The starting material was 2-bromoaniline (**32**), which was easily transformed into the formic acid amide **33** using formic acid as the formylation agent. The anilide **33** was treated with 2.2 equivalents of *n*-butyllithium in THF at −105 °C, and the resulting dianion (*o*-lithiophenyllithioformamide) [17] was quenched with norbornan-2-one to give the *ortho*-substituted tertiary alcohol **34** in good yields. Basic hydrolysis of the amide using sodium hydroxide and an acid-catalyzed elimination reaction delivered the corresponding aniline **36**, which was transformed in excellent yield into 2-(2-norbornyl)phenylamine (**37**) by use of a palladium-catalyzed hydrogenation.

2-(2-cyclopropyl-1-methylethyl)phenylamine (**44**) is an example for a compound bearing a cyclopropyl unit in the *ortho*-substituted sidechain (Scheme 7). The synthesis starts with a Simmons-Smith reaction, using 2-hydroxy-4-pentene (**38**) as the olefin precursor to give 2-hydroxy-3-cylopropylpropane (**39**) in good yield. Swern oxidation and reaction of the resulting ketone **40** with *ortho*-lithiophenyllithioformamide (**41**), generated as already described in Scheme 6, delivered



Scheme 6. Synthesis of 2-(2-norbornyl)phenylamine (**37**) [18].

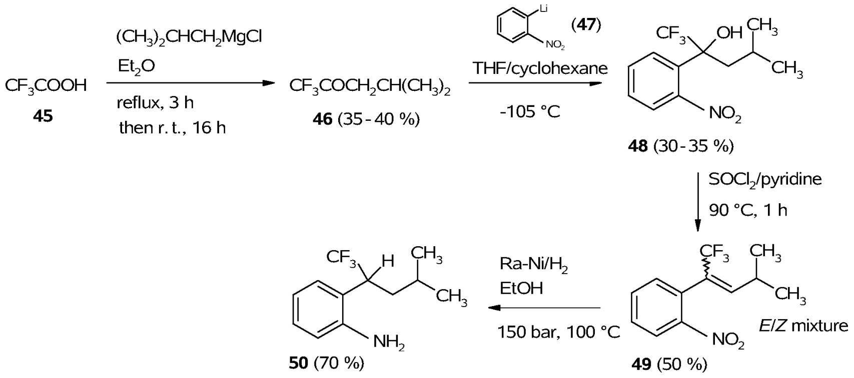


Scheme 7. Synthesis of 2-(2-cyclopropyl-1-methylethyl)-phenylamine (**44**) [18].

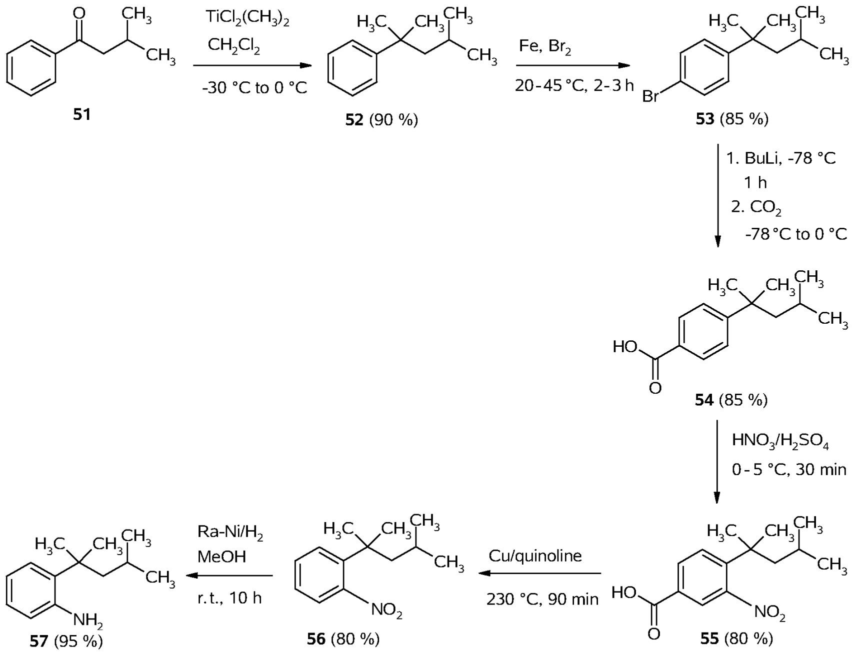
the *ortho*-substituted anilide **42** in moderate to good yields. Basic hydrolysis of the amide **42** and palladium catalyzed hydrogenolysis of the resulting tertiary alcohol **43** in the presence of sulfuric acid gave the target amine **44** in reasonable yield.

Other *ortho*-substituents of interest are alkyl sidechains containing a trifluoromethyl group at the benzylic CH_2 position. As representative of this type of compounds, we discuss here the synthesis of 2-[3-methyl-1-(trifluoromethyl)butyl]phenylamine (**50**) (Scheme 8). The synthesis of this aniline derivative starts with the reaction of trifluoroacetic acid (**45**) with isobutylmagnesium chloride leading to trifluoromethylisobutyl ketone (**46**) in moderate yield (35–40 %) [19]. As this reaction sequence could be done on larger scale (> 100 g) without any difficulties, the moderate yield in this early step is no problem. Reaction of the ketone **46** with *ortho*-lithiated nitrobenzene (**47**) [20], generated from 2-bromonitrobenzene by reaction with *sec*-BuLi at −105 °C, gave the *ortho*-substituted nitrobenzene derivative **48** in unoptimized yields of 30–35 %. In our hands *tert*-BuLi turned out to be inferior in the metallation step to *sec*-BuLi and gave yields of only 20–25 %. The elimination of the hydroxy group could be achieved by applying thionyl chloride/pyridine reaction conditions at 90 °C. This reaction delivered a mixture of E/Z isomers of the nitrobenzene derivative **49** in fair yields. For the final hydrogenation steps (reduction of the double bond and the nitro group) we had to use more drastic conditions (100 °C/150 bar). Raney Nickel turned out to be the most favorable catalyst for this reduction, and the final phenylamine derivative **50** was obtained in yields of 70–75 %.

The synthesis of anilines bearing sterically more demanding alkane sidechains was another topic of interest. Scheme 9 shows a route, which allows the synthesis of 2-(1,1,3-trimethylbutyl)phenylamine (**57**)



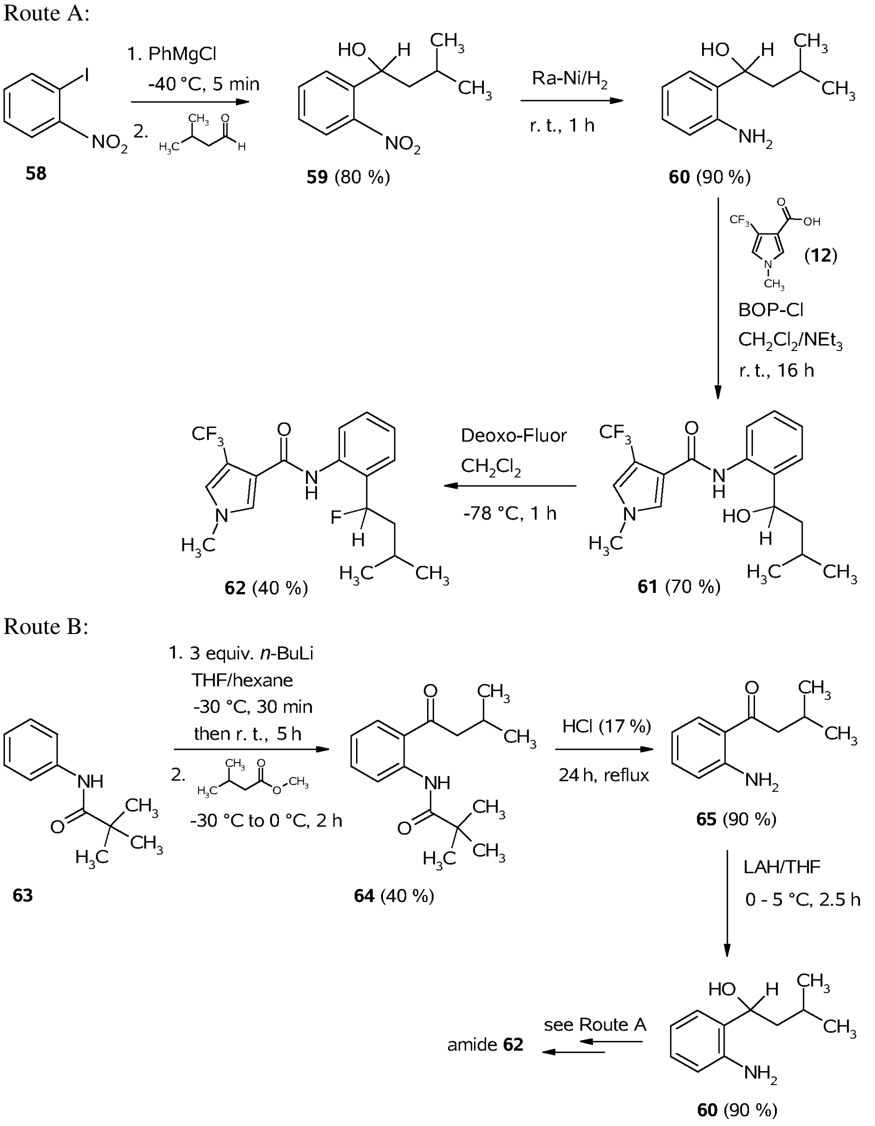
Scheme 8. Synthesis of 2-[3-methyl-1-(trifluoromethyl)butyl]phenylamine (**50**) [18].



Scheme 9. Synthesis of 2-(1,1,3-trimethylbutyl)phenylamine (**57**) [22].

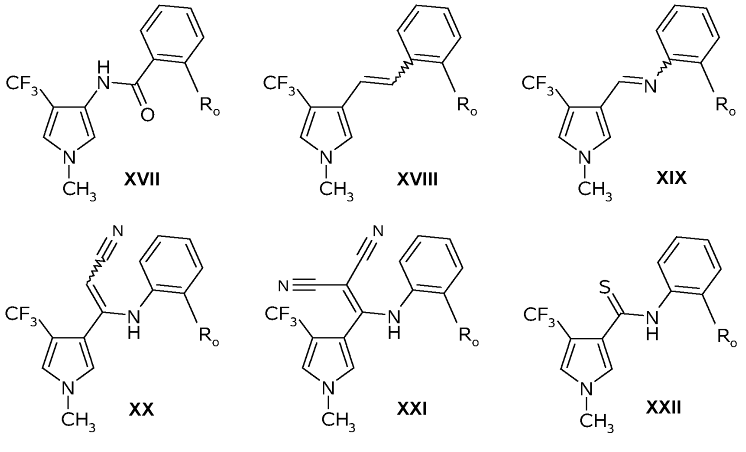
and close analogs (C_4–C_8 sidechain containing derivatives). The synthesis of amine **57** starts with the reaction of isobutylphenylketone with dichlorodimethyltitanium [21] which delivers (1,1,3-trimethylbutyl) benzene (**52**) in excellent yields. Iron-catalyzed bromination and reaction of the bromobenzene derivative **53** with butyllithium led to the lithio intermediate, which after quenching with CO_2 gave the benzoic acid derivative **54** in very good yield. Nitration in the presence of sulfuric acid and subsequent decarboxylation using the classical Cu/quinoline approach delivered the *ortho*-substituted nitrobenzene derivative **56**, which after reduction with Raney Nickel under standard conditions gave the target molecule 2-(1,1,3-trimethylbutyl)phenylamine (**57**).

As a last contribution to the topic of *ortho*-substituted sidechains, we describe the synthesis of compounds, which bear a fluorine atom in the alkyl sidechain. As the synthesis of the corresponding anilines turned out to be very diffult, we introduced the fluorine atom in an amide intermediate. As a representative pyrrolecarboxylic acid amide we discuss here 1-methyl-4-(trifluoromethyl)pyrrole-3-carboxylic acid [2-(1-fluoro-3-methylbutyl)phenyl]amide (**62**) (Scheme 10). The two synthesis routes invented in our laboratories had a broader scope and could also be used for the synthesis of analogous heterocyclic carboxamides. The first step of route A used Knochel technology [23] for the formation of 2-nitrophenylmagnesium chloride, which was generated from



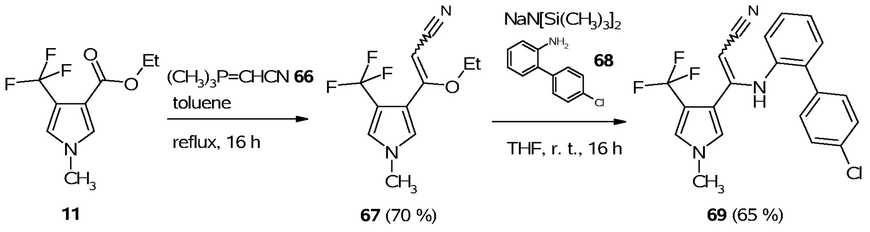
Scheme 10. Synthesis of 1-methyl-4-(trifluoromethyl)pyrrole-3-carboxylic acid [2-(1-fluoro-3-methylbutyl)phenyl]amide (**62**) (routes A and B) [26].

2-iodonitrobenzene (**58**) *via* reaction with phenylmagnesium chloride. The resulting Grignard intermediate was quenched with 3-methylbutyraldehyde giving the *ortho*-substituted nitrobenzene **59**, which after reduction with Raney Nickel delivered 1-(2-aminophenyl)-3-methylbutan-1-ol (**60**) in a very good overall yield. For the synthesis of the aniline derivative **60**, an alternative synthesis route was worked out in our laboratories (route B, Scheme 10), which used pivaloyl anilide (**63**) as starting material. Reaction of **63** with 3 equivalents of *n*-BuLi and quenching the resulting dianion [24] with isovaleric methylester led to the *ortho*-substituted pivaloyl anilide **64**, which after hydrolysis with 17 % aqueous hydrogen chloride solution gave the aniline **65**. Reduction with LAH (lithium aluminium hydride) gave 1-(2-aminophenyl)-3-methylbutan-1-ol (**60**) in excellent yields. Treatment of the alcohol-group containing aniline derivative **60** with 1-methyl-3-(trifluoromethyl)pyrrole-3-carboxylic acid (**12**) in the presence of BOP-Cl (bis-(2-oxo-3-oxazolidinyl)phosphinic chloride) and triethylamine led to the pyrrolecarboxylic acid amide **61** [25] in good yield, which after treatment with Deoxofluor (bis(2-methoxyethyl)amino-



R_o = *p*-halophenyl, 1,3-dimethylbutyl

Fig. 5. Modifications of the amide linker (exploratory approaches) [27].



Scheme 11. Synthesis of 3-(4'-chlorobiphenyl-2-ylamino)-3-(1-methyl-4-trifluoromethyl)-1*H*-pyrrol-3-yl)acrylonitrile (**69**) [27–29].

sulfur trifluoride) at low temperatures (−78 °C) delivered 1-methyl-4-(trifluoromethyl)pyrrole-3-carboxylic acid [2-(1-fluoromethylbutyl)phenyl]amide (**62**) in moderate yield.

Modifications of the pharmacophore (exploratory approaches)

To substitute the amide linker (Fig. 5) is a risky approach and the chances of losing biological activity is very high. In Scheme 11 a few exploratory approaches covering this topic are summarized.

As an example we describe the synthesis of 3-(4′-chloro-biphenyl-2-ylamino)-3-(1-methyl-4-trifluoromethyl-1*H*-pyrrol-3-yl)acrylonitrile (**69**). The straightforward synthesis of this amide starts with a Wittig-type reaction [28] of 4-trifluoro-methyl-1-methylpyrrole-3-carboxylic acid ethyl ester (**11**) with (trimethyl-λ^5-phosphanyliden)acetonitrile (**66**) in boiling toluene, which led to the acrylonitrile derivative **67**. Nucleophilic displacement of the ethoxygroup by the *ortho*-substituted aniline **68** in the presence of sodium(bistrimethyl-silyl)amide [29] gave the final pyrrolylacrylonitrile derivative **69** in fair yields.

Complex II Mode of Action and Biological Properties of Selected Amides

Biochemical mode of action (Complex II inhibition)

Complex II is the succinate dehydrogenase of the tricarboxylic acid or Krebs cycle and catalyzes the oxidation of succinate to fumarate, coupled to the reduction of ubiquinone to ubiquinol. Complex II contains four subunits (A–D), the inhibitor binding site being located in a steric binding pocket composed of parts of subunits B, C and D [30]. The killing effect of all Complex II inhibitors relies on the disruption of the tricarboxylic acid (TCA) cycle.

Inhibitors of the mitochondrial respiration chain play an important role in agrochemical fungicidal research. The most important targets for fungicides in the respiration chain are Complexes II and III. Compounds inhibiting Complex III such as azoxystrobin (best selling fungicide in 2005) [31] and pyraclostrobin [32] in the meantime are key players in the fungicide market. The importance of Complex II inhibitors (old example: carboxin) has increased in the last years with the discovery of broad spectrum compounds such as boscalid, bixafen and penthiopyrad. Some of our new pyrrole carboxamides (PCAs, see Fig. 6) as well as for ex-

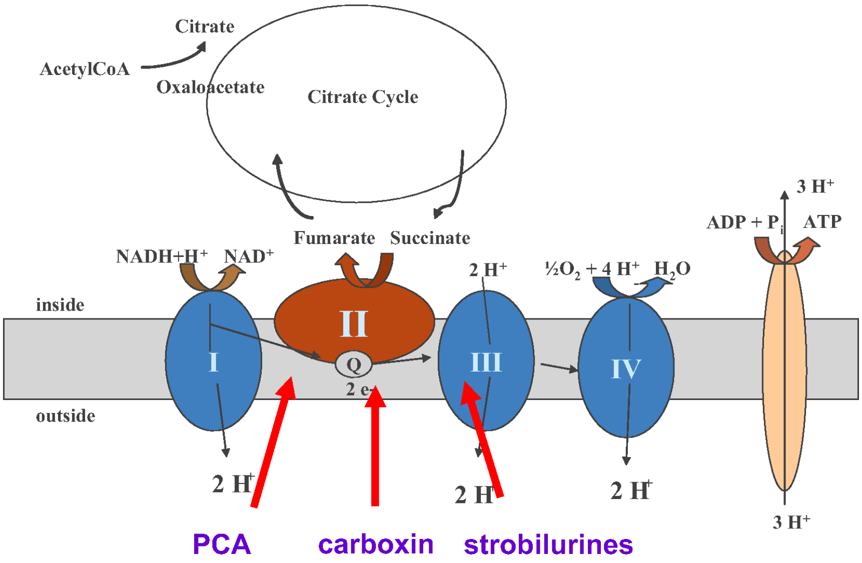


Fig. 6. Schematic representation of the respiration chain (containing Complexes I – IV).

ample boscalid show high level of intrinsic activities against grey mould and early blight on tomatoes [33]. Fungal resistance within the strobilurin class (powdery mildews and Septoria leaf blotch in wheat) make this class of Complex III inhibitors less important for future research activities and increases the importance of development compounds which have different modes of action, such as heterocyclic carboxamides of the Complex II class.

Biological properties of selected amides [34]

The biological spectrum covered by the pyrrole carboxamide class is impressive and covers a major part of relevant agrochemical diseases such as leaf spots, mildews, moulds, rusts and smuts. It is not a goal to discuss here all the aspects of SAR of the pyrrole carboxamide class. We present here a simplified SAR analysis (Fig. 7) covering brown rust on wheat, grey mould on grapes and early blight on tomatoes. Of course the results of the analysis are not exactly the same for all pathogens, and have to be regarded as rough guidelines. The pyrrole part, in our opinion, was very well optimized. The CF_3 group in 4-position, CH_3 at the nitrogen atom and no further substituents in 2-position turned out to be very favorable for the biological activity. Substitution of the amide linker (CONH) by other groups whilst maintaining the activity on a reasonable level, as expected, turned out to be almost impossible. The only group, which delivered good activity was the thioamide group: all the other approaches choosen by us (see Fig. 5, exploratory approaches) led to less active or completely inactive compounds. For the aryl part, phenyl and thienyl turned out to be useful ring systems delivering appropriate activity. As a last, but very important feature of the amide class, the influence of the *ortho*-substituent R_O on activity will be discussed. As we learned early in this field, halophenyl substituents in the *ortho* position, particularly 4-fluorophenyl, turned out to be interesting, when we look at the activity level of grey mould on grapes and early blight on tomatoes. Some alkyl sidechains also turned out to be useful *ortho*-substituents, especially for delivering good activity against brown rust. A favorable sidechain was 1,3-dimethylbutyl but the 3-methylbutyl substituent also delivered acceptable activity. Compounds either bearing a trifluoromethyl group or two methyl groups at the benzylic position tend to be less active than the unsubstituted or monomethyl-substituted sidechains. Although some pyrrole carboxamides showed very good activity and an interesting biological spectrum in the glasshouse, the field performance, especially the control of Septoria leaf blotch on wheat, was not at the same level of the best market standards. This means that, to deliver a market compound of the pyrrolecarboxamide class, further optimization work has to be done.

BASF, Bayer and Mitsui in the meantime have clearly proven with the pyridine carboxamide boscalid (BASF), and the two pyrazole carboxamides bixafen (Bayer) and penthiopyrad (Mitsui) that efficient control of major agrorelevant diseases is achievable in the

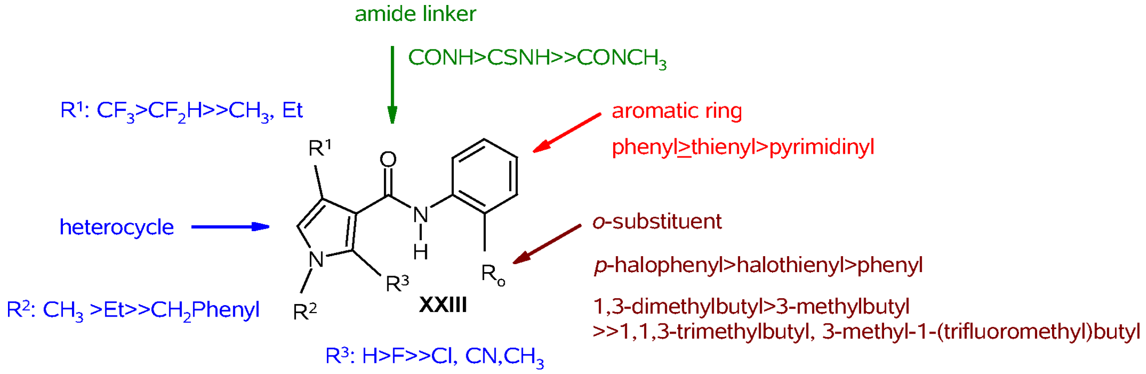


Fig. 7. Simplified SAR picture for the pyrrole carboxamide class covering brown rust on wheat, grey mould on grapes and early blight on tomato (related to glasshouse data).

field of heterocyclic carboxamides. The broadness of activity of the heterocyclic carboxamides made (and still makes) them very attractive for fungal agrochemical companies, and all the major players were (and some still are) highly active in this field. It may be that the pyrazole carboxamide class will be able to deliver further development compounds of the Complex II area.

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