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Halogenated formyl- and diformylpyrroles: Methods of preparation and synthetic potential

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Pyrrole and its derivatives are representatives of azaheterocyclic systems with a powerful synthetic range, pronounced biomedical potential, and wide application. In addition, the pyrrole cycle is a basic structural element of vital porphyrin macrocycles, which are key fragments of chlorophyll, heme, vitamin B12, and bile pigments. In recent decades, significant attention of researchers focused on developing methods for obtaining various types of functionalized pyrroles as potential sources of bioactive compounds. Among them, pyrrole derivatives with a synthetically significant aldehyde group and halogen atoms are of particular interest. At the same time, the mass of accumulated original works devoted to the synthesis and chemical transformations of most of their types requires generalization. This, in turn, became a strong basis for a detailed analysis and systematization of methods for the synthesis and directed structural modification of halogenated (di)formylpyrroles in reports published during 2000-2025.

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1. Introduction

Functionalized pyrroles occupy a prominent place in the chemistry of heterocyclic compounds due to their pronounced synthetic and biomedical properties.[1–4] The importance of the pyrrole nucleus as a molecular scaffold for the construction of bioactive molecules is confirmed by the creation of such drugs as atorvastatin,[5] tolmetin,[6] ketorolac,[7] licofelone[8] and sunitinib[9] (**Fig. 1**). In addition, pyrrole derivatives have found practical applications as dyes,[10,11] photosensitizers,[12] organocatalysts,[13] enzyme-activated[14] and fluorescent[15] probes.

Analysis of literature sources showed that the available review works systematized achievements in the field of synthesis and structural modification of various pyrrole systems[16–19] and pyrrolo-imidazole alkaloids[20]. A number of works have highlighted the biomedical potential of functionalized and condensed pyrroles.[21–23] In this context, it is worth noting the reviews,[24,25] which highlight the issues of isolation from natural raw materials, biological activity, chemical synthesis and derivatization of pyrrole-2-carboxaldehydes. The presence of such a structural fragment in natural products has significantly stimulated research into the synthesis and chemical transformations of various types of pyrrole-containing aldehydes, additionally modified with other functional groups, primarily halogen atoms. We have recently summarized the methods of preparation[26], synthetic transformations and some aspects of practical application[27] of halogenated pyrrole-2-carbaldehydes. To form a complete picture of modern achievements in the chemistry of halogenated formylpyrroles, it seemed reasonable to analyze and systematize the array of data relating to methods of synthesis and directed structural modification of halogen-containing pyrrolo-3-carbaldehydes, pyrrolo-4-carbaldehydes, pyrrolo-5-carbaldehydes, and pyrrolo-dicarbaldehydes.

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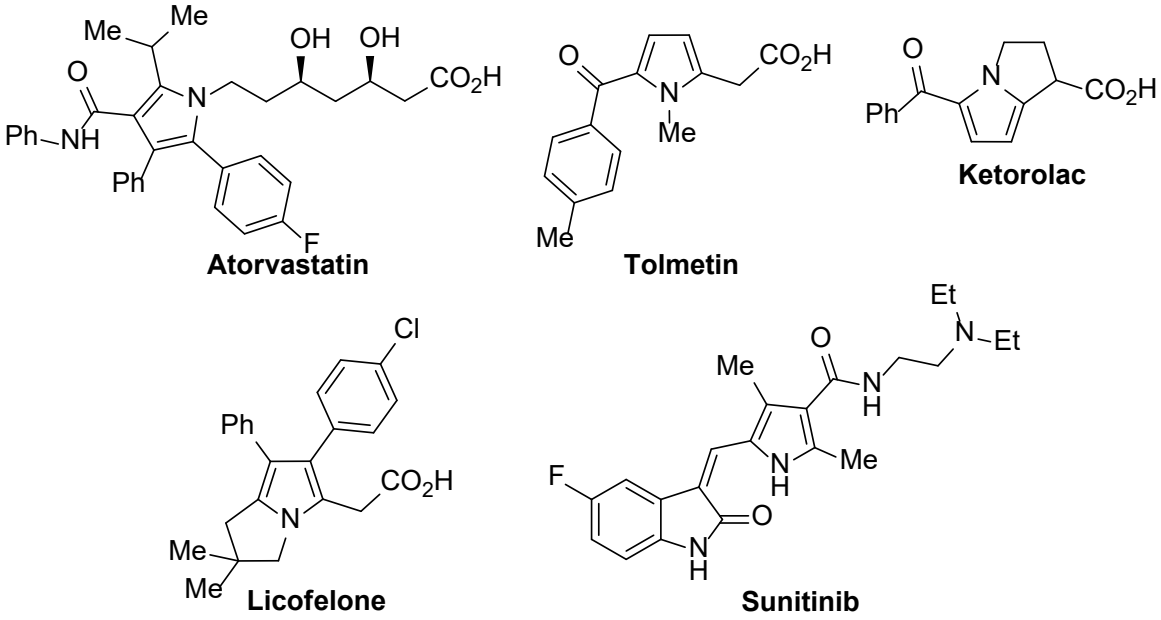
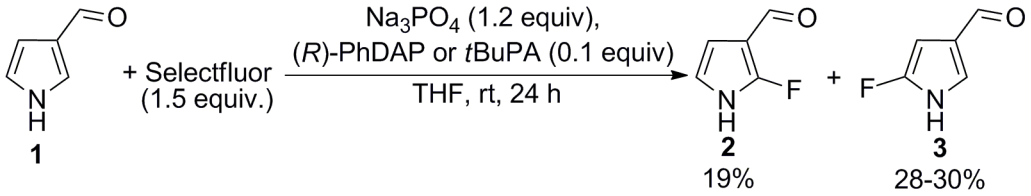


Fig. 1. Medicinal drugs containing the pyrrole nucleus.

2. Methods of synthesis of halogen-containing formyl and diformylpyrroles

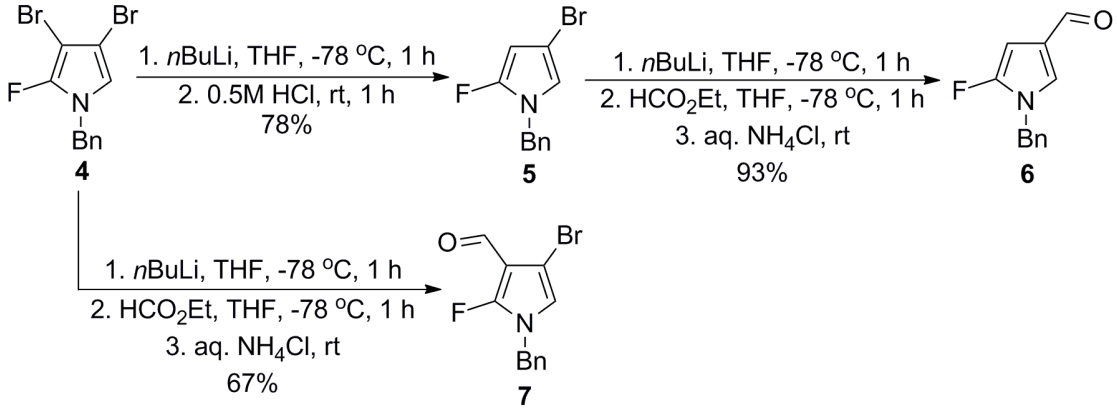
2.1. Synthesis of halogen-containing 3-formylpyrroles

For the synthesis of fluorine-containing 3-formylpyrroles, a method of mild fluorination based on anionic phase catalysis using Selectfluor, phosphoric acid and a base in a non-polar solvent was developed. Thus, the fluorination of 1*H*-pyrrole-3-carbaldehyde **1** in the presence of Na_3PO_4 and dual axially chiral anionic phase transfer catalysts (*t*BuPA or (*R*)-PhDAP) in THF gave a mixture of 2-fluoro-1*H*-pyrrole-3-carbaldehyde **2** and 5-fluoro-1*H*-pyrrole-3-carbaldehyde **3** with yields of 19 and 28-30%, respectively (**Scheme 1**).[28]



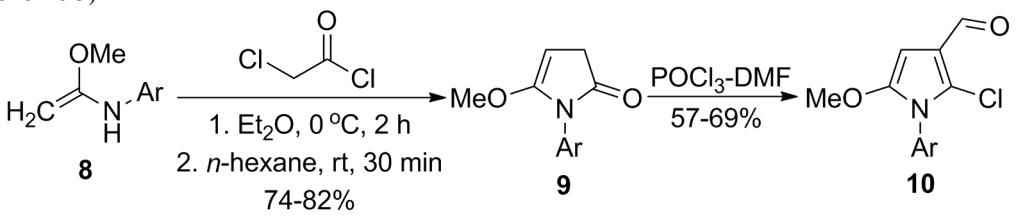
Scheme 1. Synthesis of fluorine-containing 3-formylpyrroles **2** and **3** by direct fluorination of 3-formylpyrroles by Selectfluor under anionic phase catalysis conditions.

The authors of work[29] developed an efficient method for the synthesis of 2- and 5-fluoropyrrole-3-carbaldehydes from bromopyrrole precursors by regioselective debromolithiation with subsequent interaction of the formed carbanions with the appropriate electrophile. For example, dibromofluoropyrrole **4** was hydrodebrominated using *n*-BuLi followed by treatment with aqueous HCl, leading to 4-bromo-2-fluoropyrrole **5**. Debromolithiation of the latter and treatment of the formed carbanion with ethyl formate produced 1-benzyl-5-fluoro-1*H*-pyrrole-3-carbaldehyde **6** in 93% yield, whereas 3,4-dibromo-2-fluoropyrrole **4** under similar reaction conditions gave 1-benzyl-4-bromo-2-fluoro-1*H*-pyrrole-3-carbaldehyde **7** (**Scheme 2**).



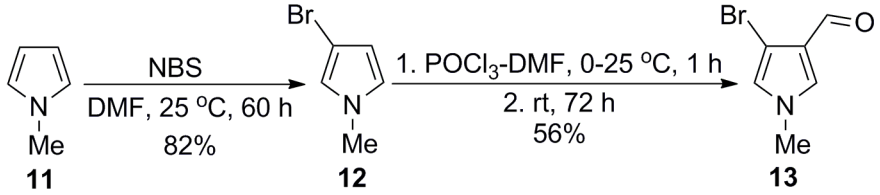
Scheme 2. Synthesis of fluorine-containing 3-formylpyrroles **6** and **7** by regioselective debromolithiation/formylation of dibromofluoropyrrole **4**.

1-Aryl-5-methoxypyrrol-2-ones **9** synthesized from *N*-(1-methoxyvinyl)anilines **8** and chloroacetyl chloride were transformed into the corresponding 1-aryl-2-chloro-5-methoxypyrrole-3-carbaldehydes **10** under Vilsmeier-Haack reaction conditions (**Scheme 3**).[30]



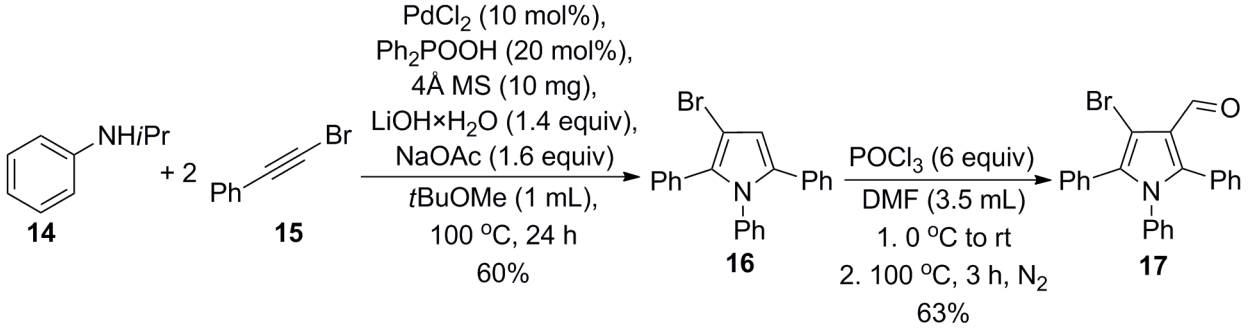
Scheme 3. Synthesis of 1-aryl-2-chloro-5-methoxypyrrole-3-carbaldehydes **10** by chloroformylation of 1-aryl-5-methoxypyrrol-2-ones **9**.

4-Bromo-1-methyl-1*H*-pyrrole-3-carbaldehyde **13** was prepared by bromination of 1-methyl-1*H*-pyrrole **11** with NBS and subsequent formylation of the resulting 3-bromo-1-methyl-1*H*-pyrrole **12** (**Scheme 4**).[31]



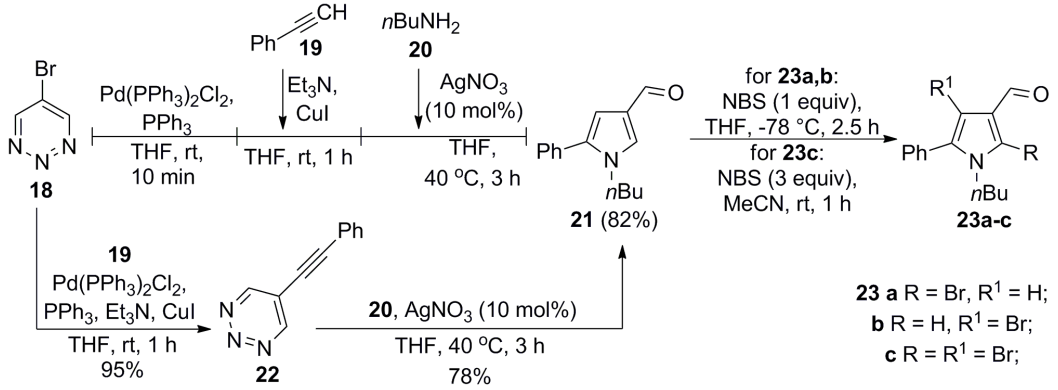
Scheme 4. Synthesis of 4-bromo-1-methyl-1*H*-pyrrole-3-carbaldehyde **13** by sequential bromination/formylation of 1-methyl-1*H*-pyrrole **11**.

The formylation of pyrrole **16**, obtained by Pd-catalyzed tandem cyclization of *N*-isopropylaniline **14** from bromomethynylbenzene **15**, was successfully used for the synthesis of 4-bromo-1,2,5-triphenyl-1*H*-pyrrole-3-carbaldehyde **17** (**Scheme 5**).[32]



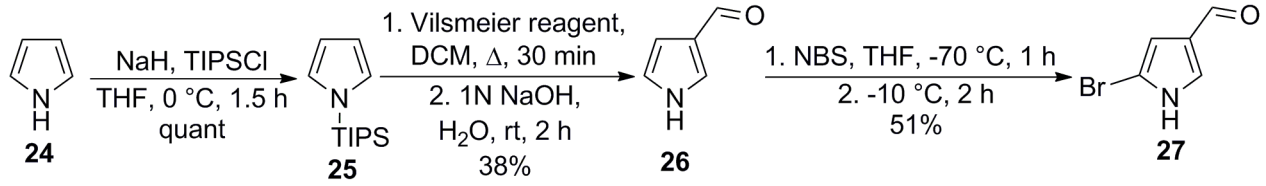
Scheme 5. Synthesis of 4-bromo-1,2,5-triphenyl-1*H*-pyrrole-3-carbaldehyde **17** by formylation of 4-bromo-1,2,5-triphenyl-1*H*-pyrrole **16**.

Bromination of pyrrole-3-carbaldehyde **21**, synthesized by the interaction of 5-bromo-1,2,3-triazine **18**, phenylacetylene **19**, butylamine **20**, with 1 equiv of NBS at –78 °C in THF led to the formation of an isomeric mixture of 2-bromo- **23a** and 4-bromopyrrole-3-carbaldehydes **23b** with yields of 69 and 13%, respectively. Instead, treatment of pyrrole **21** with 3 equiv of NBS in acetonitrile at room temperature gave 2,4-dibromopyrrole-3-carbaldehyde **23c** in 84% yield (**Scheme 6**).[33]



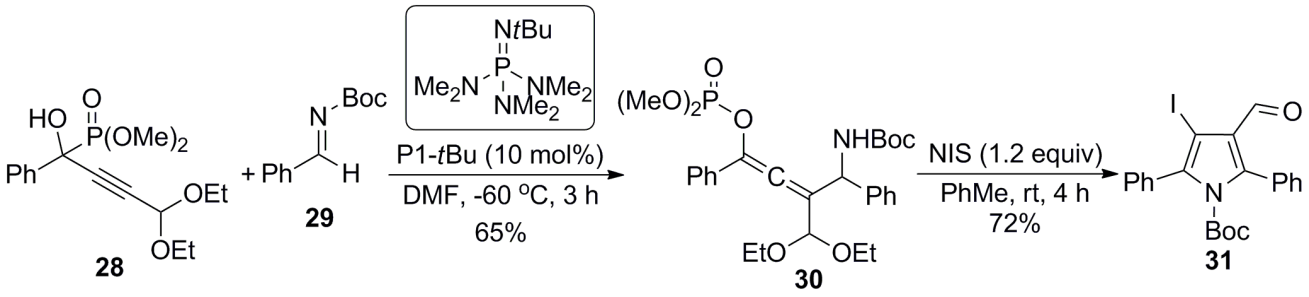
Scheme 6. Synthesis of bromine-containing pyrrole-3-carbaldehydes **23a-c** by bromination of 5-phenylpyrrole-3-carbaldehyde **21**.

The protocol for the synthesis of the structural fragment of the potassium-competitive acid secretion blocker (P-CAB) vonoprosan fumarate (TAK-438) 5-bromo-1H-pyrrole-3-carbaldehyde **27** involves protection of the 1-position of pyrrole **24** with a triisopropylsilyl group, Vilsmeier formylation, and subsequent deprotection to yield 1*H*-pyrrole-3-carbaldehyde **26**. Bromination of the latter with NBS led to the target product **27** (**Scheme 7**).[34,35]



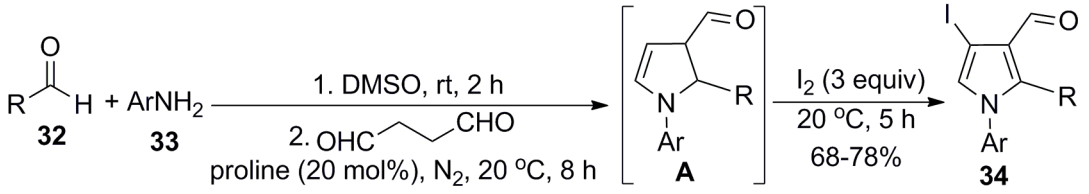
Scheme 7. Synthesis of 5-bromo-1*H*-pyrrole-3-carbaldehyde **27** by formylation of protected pyrrole **25**, deprotection, and subsequent bromination of 3-formylpyrrole **26**.

An efficient method for the synthesis of 4-iodo-2,5-diphenyl-1*H*-pyrrole-3-carbaldehyde **31** involves *N*-iodosuccinimide-mediated intramolecular cyclization with simultaneous deacetalization of polysubstituted homoalenylamine **30**, obtained by the interaction of phosphorylated acetylene **28** with imine **29** in the presence of a Bronsted base (P1-*t*Bu) (**Scheme 8**).[36]



Scheme 8. Synthesis of 4-iodo-2,5-diphenyl-1*H*-pyrrole-3-carbaldehyde **31** by intramolecular iodocyclization of polysubstituted homoalenylamine **30**.

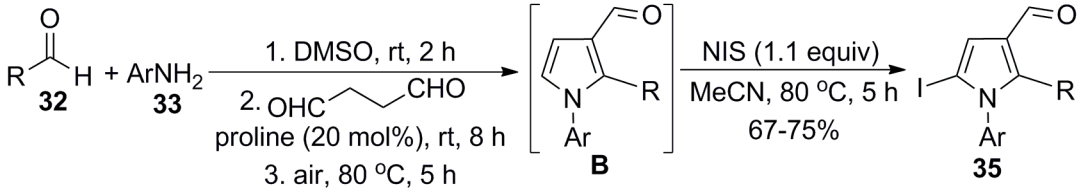
A library of 1,2-disubstituted 4-iodopyrrole-3-carbaldehydes **34** was synthesized by I_2-mediated regioselective C^4-iodination/aromatization of 3-formyldihydropyrrole **A**, obtained by proline-catalyzed Mannich reaction of succinaldehyde with imines generated *in situ* from aldehydes **32** and anilines **33** (**Scheme 9**).[37]



R = 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 3-Br-4-FC_6H_3, 3,4-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 3-NCC_6H_4, 4-NCC_6H_4, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 5-NO_2-furan-2-yl
Ar = 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4

Scheme 9. Synthesis of 1,2-disubstituted 4-iodopyrrole-3-carbaldehydes **34** by iodination/aromatization of 3-formyldihydropyrrole **A**.

When such a reaction is performed under aerobic oxidative aromatization conditions, 3-formylpyrroles **B** are formed, the subsequent NIS-mediated halogenation of which gives isomeric 5-iodopyrrole-3-carbaldehydes **35** (**Scheme 10**).[37]

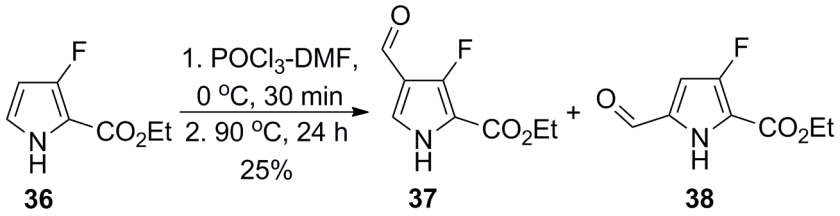


R = 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 4-NCC_6H_4, pyridin-3-yl, pyridin-4-yl
Ar = 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

Scheme 10. Synthesis of 5-iodopyrrole-3-carbaldehydes **35** by NIS-mediated halogenation of 3-formylpyrroles **B**.

2.2. Synthesis of halogen-containing 4-formylpyrroles

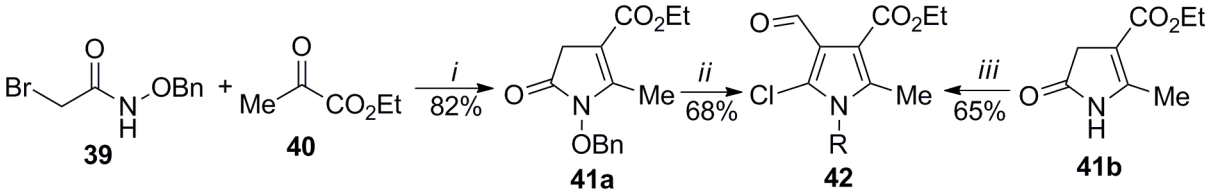
An attempt to obtain fluorine-containing pyrrole-4-carbaldehyde by Vilsmeier-Haack formylation of ethyl 3-fluoro-1*H*-pyrrole-2-carboxylate **36** resulted in a mixture of 4- and 5-formyl-containing regioisomers **37** and **38** in a ratio of 43:57, which were separated by flash chromatography (**Scheme 11**).[38]



36 **37** **38**

Scheme 11. Synthesis of 3-fluoro-4-formyl-pyrrole-2-carboxylate **37** by formylation of ethyl 3-fluoro-1*H*-pyrrole-2-carboxylate **36**.

In turn, formylation of carboxylate **41a**, obtained by cyclocondensation of α-bromoacethydroxamate **39** with ethyl pyruvate **40** or its *N*-unsubstituted analogue **41b**, proved successful for the synthesis of 5-chloro-4-formylpyrroles **42** (**Scheme 12**).[39,40]



R = H, OBn

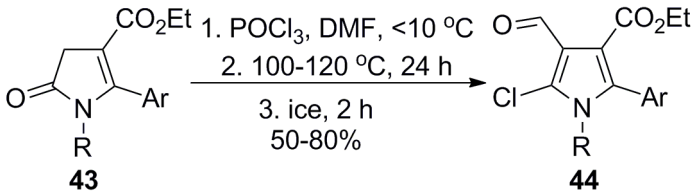
i: 1. K_2CO_3, NaI, THF, rt, 24 h. 2. *p*-TsOH, $CHCl_3$, 40 °C, 1 h

ii: 1. $POCl_3$, DMF, 100 °C, 24 h. 2. ice, 2 h

iii: $POCl_3$, DMF, 90 °C, 8 h

Scheme 12. Synthesis of ethyl 2-methyl-5-chloro-4-formylpyrrole-3-carboxylates **42** by formylation of ethyl 2-methyl-5-oxo-4,5-dihydropyrrole-3-carboxylates **41a,b**.

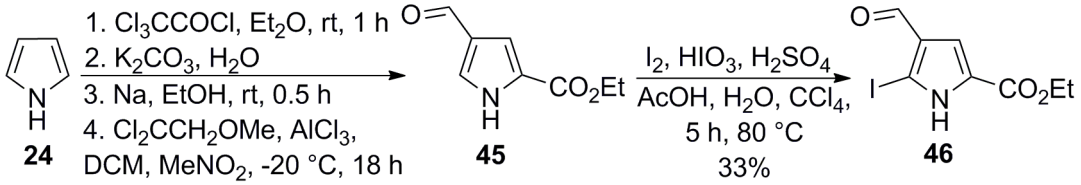
Similar formylation reaction conditions were used to obtain 2-aryl-4-formyl-5-chloro-1*H*-pyrrole-3-carboxylates **44** (**Scheme 13**).[41]



R = H, Ar = Ph; R = Bn, Ar = Ph; R = 4-ClC_6H_4, Ar = 4-ClC_6H_4

Scheme 13. Synthesis of 2-aryl-4-formyl-5-chloro-1*H*-pyrrole-3-carboxylates **44** by formylation of 2-aryl-5-oxo-4,5-dihydropyrrole-3-carboxylates **43**.

The synthesis of ethyl 5-iodo-4-formyl-1*H*-pyrrole-3-carboxylate **46**, a precursor for the construction of paullone derivatives, potential cyclin-dependent kinase (CDK) inhibitors, was realised by iodination of 4-formyl-1*H*-pyrrole-3-carboxylate **45** using the I_2/HIO_3 system (**Scheme 14**).[42]

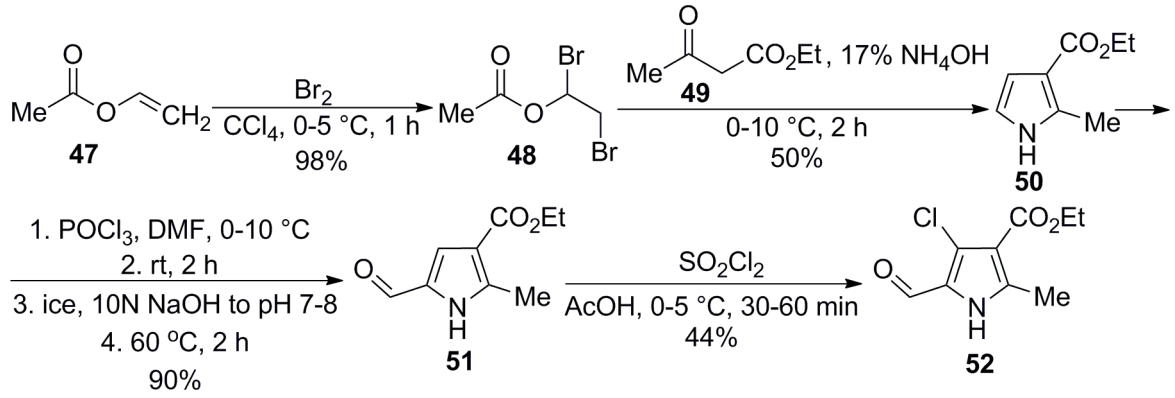


Scheme 14. Synthesis of ethyl 5-iodo-4-formyl-1*H*-pyrrole-3-carboxylate **46** by iodination of 4-formyl-1*H*-pyrrole-3-carboxylate **45**, obtained from pyrrole **24**.

2.3. Synthesis of halogen-containing 5-formylpyrroles

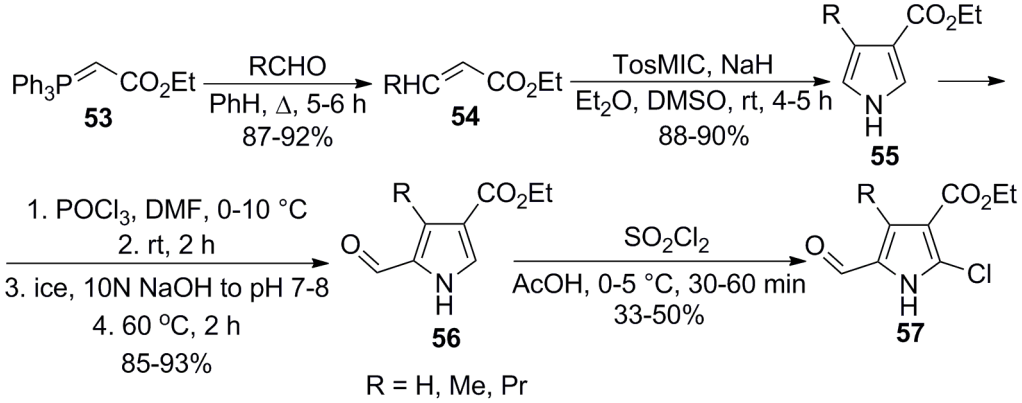
The authors of article[43] developed the synthesis of highly functionalized ethyl 2-methyl-5-formyl-4-chloro-1*H*-pyrrole-3-carboxylate **52**, a valuable building block for the design of analogs of the anticancer drug sunitinib, by formylating

pyrrole-3-carboxylate **50** with freshly prepared Vilsmeier reagent and subsequent chlorination of the resulting aldehyde **51** with SO_2Cl_2 (**Scheme 15**).



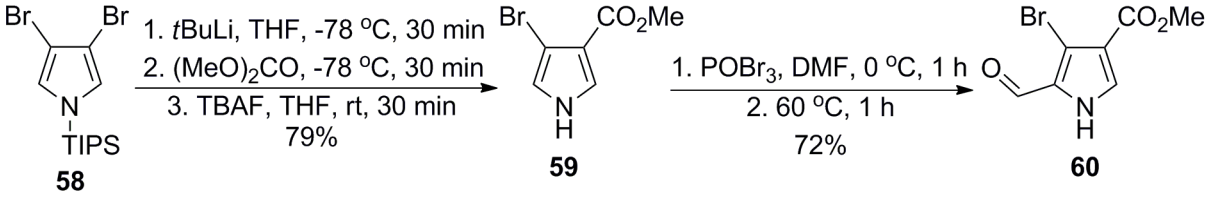
Scheme 15. Synthesis of ethyl 2-methyl-5-formyl-4-chloro-1*H*-pyrrole-3-carboxylate **52** by sequential formylation and chlorination of ethyl pyrrole-3-carboxylate **50**.

Additionally, the preparation of isomeric ethyl 5-formyl-2-chloro-1*H*-pyrrole-3-carboxylates **57** by sequential formulation and chlorination of pyrrole-3-carboxylates **55**, obtained in two stages from ylide **53,** is reported in work (**Scheme 16**).[43]



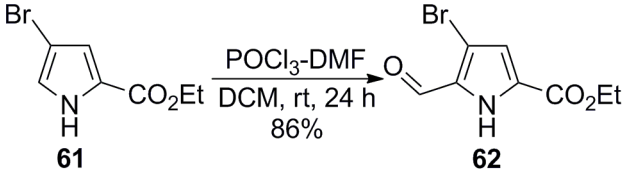
Scheme 16. Synthesis of ethyl 5-formyl-2-chloro-1*H*-pyrrole-3-carboxylates **57** from pyrrole-3-carboxylates **55**.

A convenient method for the synthesis of methyl 4-bromo-5-formyl-1*H*-pyrrole-3-carboxylate **60** consists in carboxylation of 3,4-dibromo-1-(triisopropylsilyl)-1*H*-pyrrole **58** and formylation of the resulting methyl 4-bromo-1*H*-pyrrole-3-carboxylate **59** using the $POBr_3$-DMF system (**Scheme 17**).[44]



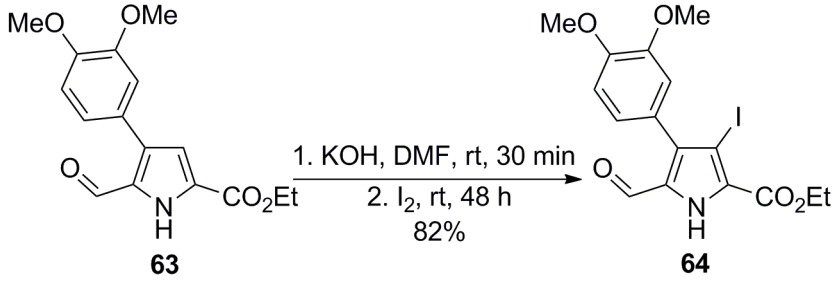
Scheme 17. Synthesis of methyl 4-bromo-5-formyl-1*H*-pyrrole-3-carboxylate **60** by stepwise carboxylation and formylation of 3,4-dibromo-1*H*-pyrrole **58**.

Ethyl 4-bromo-5-formylpyrrole-2-carboxylate **62** was obtained in high yield by formylation of ethyl 4-bromopyrrole-2-carboxylate **61** with Vilsmeier-Haack reagent in DCM solution at room temperature (**Scheme 18**).[45]



Scheme 18. Synthesis of ethyl 4-bromo-5-formylpyrrole-2-carboxylate **62** by formylation of ethyl 4-bromopyrrole-2-carboxylate **61**.

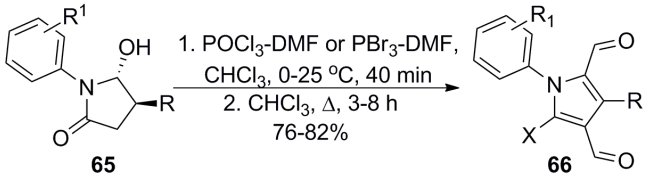
Ethyl 3-iodo-5-formylpyrrole-2-carboxylate **64** was synthesized by selective iodination with molecular iodine of the corresponding 3-unsubstituted analogue **63** (**Scheme 19**). [46]



Scheme 19. Synthesis of ethyl 3-iodo-5-formylpyrrole-2-carboxylate **64** by iodination of ethyl 5-formylpyrrole-2-carboxylate **63**.

2.4. Synthesis of halogen-containing diformylpyrroles

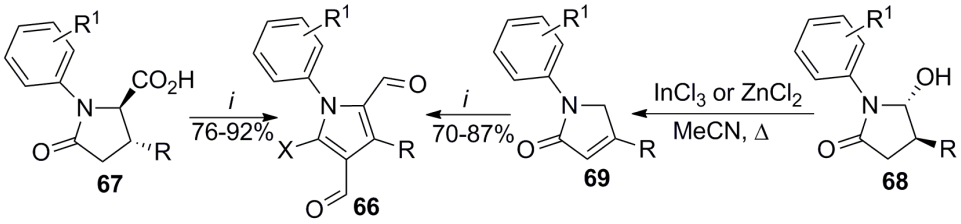
A combinatorial library of 5-halopyrrole-2,4-dicarbaldehydes **66** was obtained by treatment of substituted *trans*-1,4-diaryl-5-hydroxypyrrolidin-2-ones **65** with the Vilsmeier-Haack reagent (**Scheme 20**).[47]



R = Ph, R^1 = 4-Cl; R = Ph, R^1 = 4-Cl; R = Ph, R^1 = H; R = thiophen-2-yl, R^1 = 3-Cl-4-F;
R = thiophen-2-yl, R^1 = 3-Cl-4-F; R = Ph, R^1 = 3,4-Cl_2; R = Ph, R^1 = 4-Br; R = Ph, R^1 = 3,4-F_2;
X = Cl, Br

Scheme 20. Synthesis of 5-halopyrrole-2,4-dicarbaldehydes **66** by haloformylation of trans-1,4-diaryl-5-hydroxypyrrolidin-2-ones **65**.

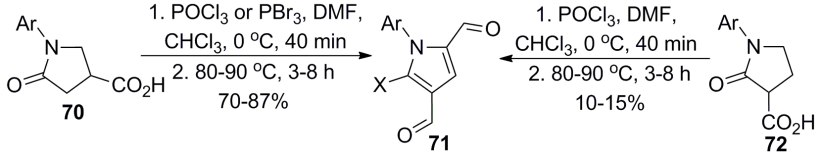
5-Halopyrrole-2,4-dicarbaldehydes **66** can also be synthesized in high yields by selective haloformylation with the Vilsmeier-Haack reagent of pyrrolidine-2-carboxylic acids **67** or 1,5-dihydropyrrol-2-ones **69** (**Scheme 21**).[48]



R = Ph, R^1 = H; R = Ph, R^1 = 4-F; R = Ph, R^1 = 4-Cl; R = Ph, R^1 = 4-Br;
R = thiophen-2-yl, R^1 = 3-Cl-4-F; R = thiophen-2-yl, R^1 = 3,4-Cl_2;
X = Cl, Br
i: 1. $POCl_3$ or PBr_3, DMF, $CHCl_3$, 0 °C, 40 min. 2. 80-90 °C, 3-8 h

Scheme 21. Synthesis of 5-halopyrrole-2,4-dicarbaldehydes **66** by formylation of pyrrolidine-2-carboxylic acids **67** or 1,5-dihydropyrrol-2-ones **69**.

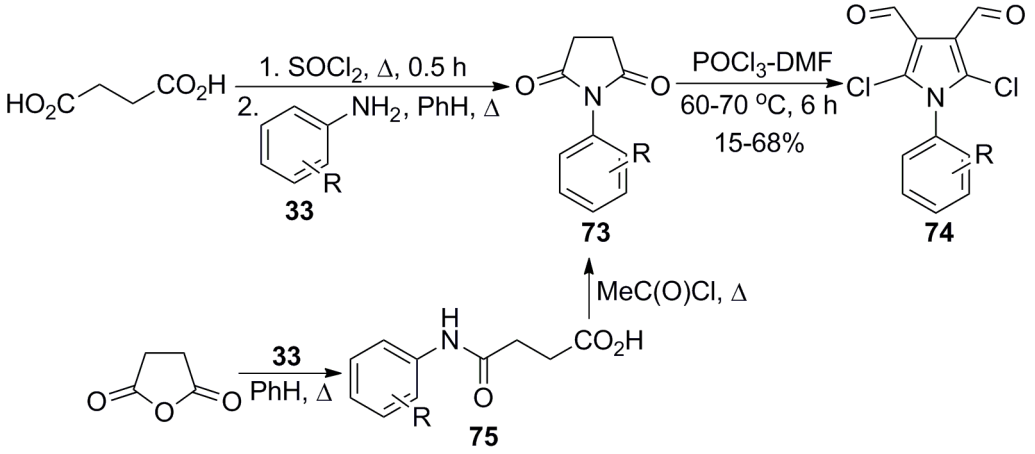
In a similar transformation, *N*-aryl-5-oxopyrrolidine-3-carboxylic acids **70** were tested as starting substrates, which gave *N*-aryl-5-halopyrrole-2,4-dicarbaldehydes **71** upon interaction with the Vilsmeier-Haack reagent in good yields. When starting from *N*-aryl-2-oxopyrrolidine-3-carboxylic acids **72**, the corresponding pyrrole-2,4-dicarbaldehydes **71** were obtained in yields of 10-15% (**Scheme 22**).[48]



Ar = 4-ClC_6H_4; 4-$MeOC_6H_4$; 4-BrC_6H_4; 3,4-$Cl_2C_6H_3$
X = Cl, Br

Scheme 22. Synthesis of *N*-arylpyrrole-2,4-dicarbaldehydes **71** by formylation of *N*-aryl-5-oxopyrrolidine-3-carboxylic acids **70** or *N*-aryl-2-oxopyrrolidine-3-carboxylic acids **72**.

N-Aryl-2,5-dichloropyrrole-3,4-dicarbaldehydes **74** were synthesized by chloroformylation of succinimides **73**, which were obtained by the interaction of succinic acid with $SOCl_2$ and aromatic amines **33**[49–52] or succinic anhydride with aromatic amines **33** and subsequent cyclization of 4-oxo-4-(arylamino)butanoic acids **75** with acetyl chloride[53] (**Scheme 23**).



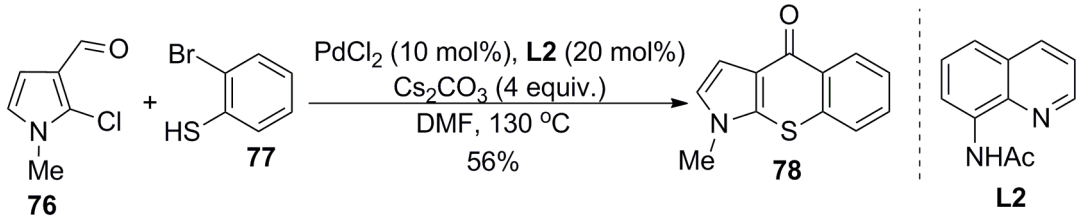
R = H, 2-Cl, 3-Cl, 3-OMe, 3-NO_2, 4-Me, 4-Cl, 4-OMe, 3,4-Cl_2, 3,4-Me_2, 3,5-Cl_2

Scheme 23. Synthesis of *N*-aryl-2,5-dichloropyrrole-3,4-dicarbaldehydes **74** by chloroformylation of succinimides **73**.

3. Synthetic potential of halogen-containing formyl- and diformylpyrroles

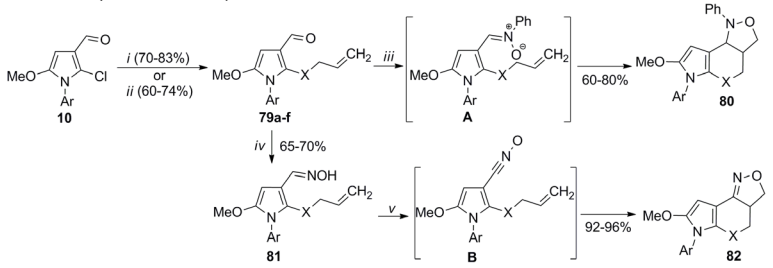
3.1. Chemical transformations of halogen-containing 3-formylpyrroles

The Pd-catalyzed reaction of 1-methyl-2-chloro-1*H*-pyrrole-3-carbaldehyde **76** with 2-bromothiophenol **77** was used to synthesize 1-methylthiochromeno[2,3-*b*]pyrrol-4(1*H*)-one **78** (**Scheme 24**).[54]



Scheme 24. Synthesis of 1-methylthiochromeno[2,3-*b*]pyrrol-4(1*H*)-one **78** by Pd-catalyzed reaction of 1-methyl-2-chloro-1*H*-pyrrole-3-carbaldehyde **76** with 2-bromothiophenol **77**.

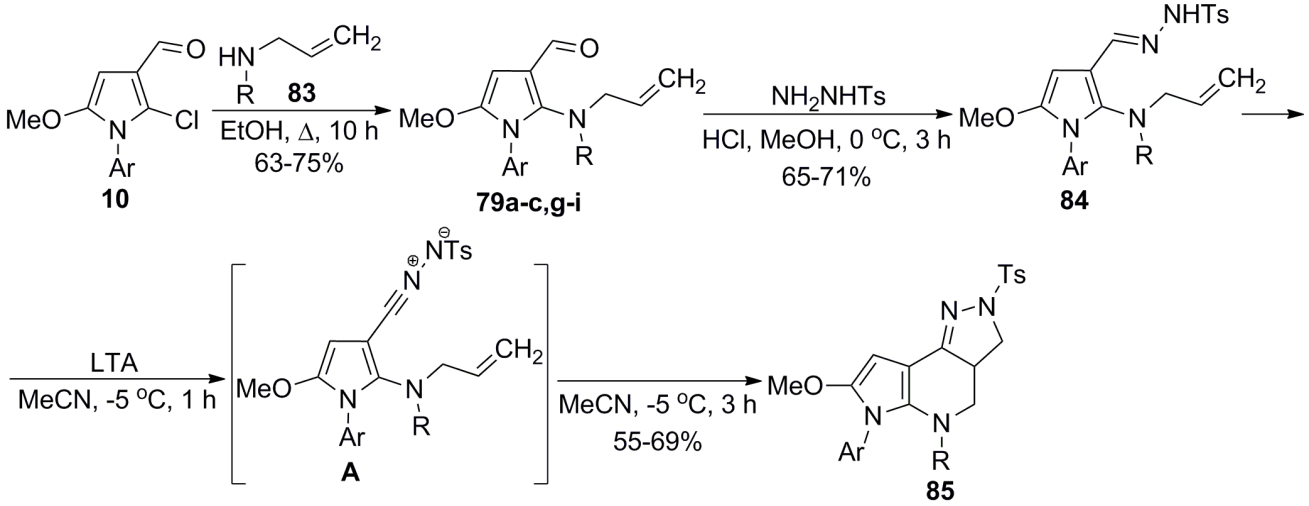
1-Aryl-5-methoxy-2-chloropyrrole-3-carbaldehydes **10** turned out to be convenient substrates for the synthesis of condensed polycyclic systems. For instance, their interaction with *N*-substituted allylamines or with *in situ* generated allylthiol produced the corresponding 2-allylamino- **79a-c** and 2-(allylsulfanyl)pyrrole-3-carbaldehydes **79d-f**, the treatment of which with freshly prepared phenylhydroxylamine gave intermediate nitrones **A**, which as a result of the intramolecular (3+2) cycloaddition reaction gave compounds of angular structure **80**. In addition, aldehydes **79** were converted under mild conditions to the corresponding oximes **81**, which upon oxidation with NaOCl formed *in situ* reactive nitrile oxides **B**, which spontaneously underwent intramolecular cycloaddition at room temperature to form tricyclic systems with a dihydroisooxazole core **82** (**Scheme 25**).[30]



79 a Ar = Ph, X = NMe; **b** Ar = 4-MeC_6H_4, X = NMe; **c** Ar = 4-$MeOC_6H_4$, X = NMe;
d Ar = Ph, X = S; **e** Ar = 4-MeC_6H_4, X = S; **f** Ar = 4-$MeOC_6H_4$, X = S
i (for **79a-c**): $NH(CH_2CH{=}CH_2)_2$, EtOH, Δ, 12 h
ii (for **79d-f**): 1. $BrCH_2CH{=}CH_2$, $NH_2C(S)NH_2$, EtOH, Δ, 1 h. 2. NaOH in EtOH, Δ, 1 h. 3. Δ, 30 min.
iii: PhNHOH, EtOH, Δ, 3 h
iv: $NH_2OH{\times}HCl$, $NaHCO_3$, EtOH, rt, 24 h
v: 1. aq. NaOCl, $CHCl_3$, 0 °C. 2. rt, 24 h

Scheme 25. Synthesis of isoxazolo[3,4-*d*]pyrrolo[2,3-*b*]pyridines **80** and pyrrolo[3',2':5,6]thiopyrano[4,3-*c*]isoxazoles **82** by intramolecular cyclization of 2-allylamino(thio)functionalized pyrrole-3-nitrones **A** and pyrrole-3-nitrile oxides **B**.

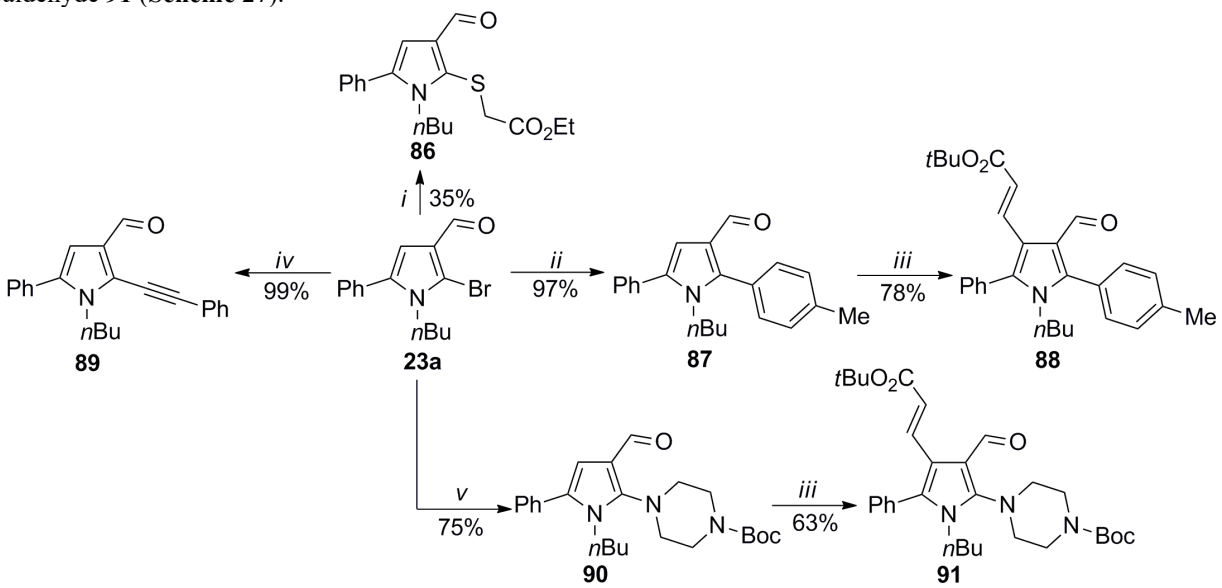
The use of 1-aryl-5-methoxy-2-chloro-1*H*-pyrrole-3-carbaldehydes **10** as synthesis blocks for the preparation of pyrazolo[3,4-*d*]pyrrolo[2,3-*b*]pyridines **85** involved their conversion into 2-alkenylamino-3-formylpyrroles **79** and subsequent modification to hydrazones **84**. Oxidation of the latter with lipoteichoic acid (LTA) led to intermediate nitrilimines **A**, which intramolecularly gave the target products via a [3+2]-dipolar cycloaddition scheme (**Scheme 26**).[55]



79 a Ar = Ph, R = Me; **b** Ar = 4-MeC_6H_4, R = Me; **c** Ar = 4-$MeOC_6H_4$, R = Me;
g Ar = Ph, R = allyl; **h** Ar = 4-MeC_6H_4, R = allyl; **i** Ar = 4-$MeOC_6H_4$, R = allyl

Scheme 26. 1-Aryl-5-methoxy-2-chloropyrrole-3-carbaldehydes **10** in the synthesis of pyrazolo[3,4-*d*]pyrrolo[2,3-*b*]pyridines **85**.

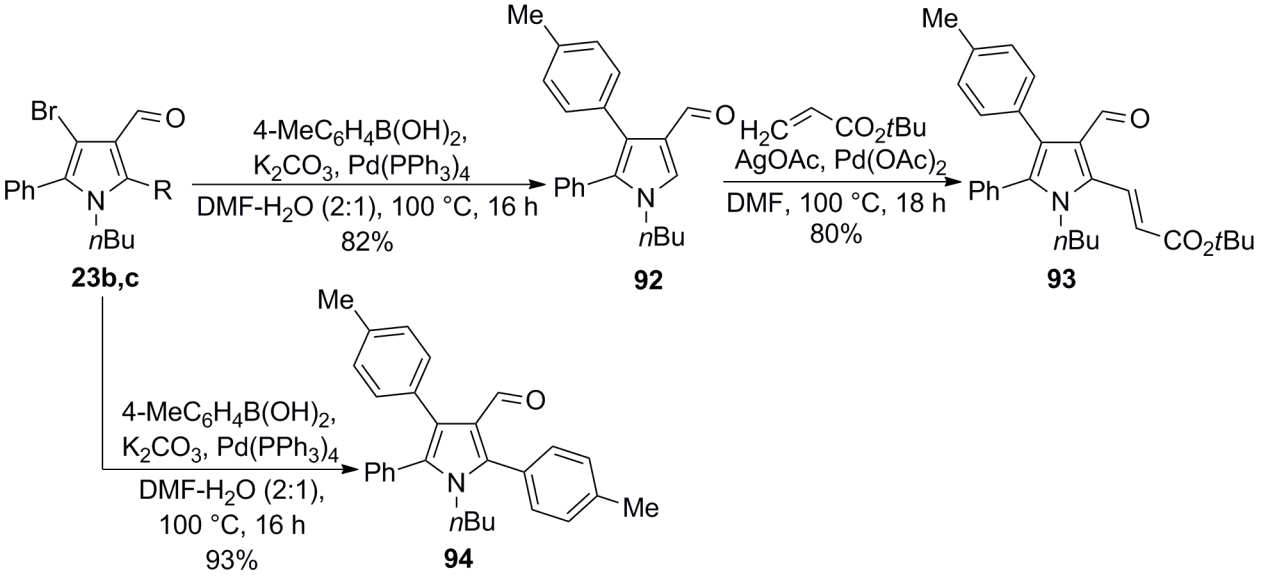
The synthetic possibilities of 2-bromopyrrole-3-carbaldehyde **23a** were tested to obtain various formyl-containing derivatives. Thus, the formation of a C–S bond in the synthesis of ethyl 2-[(1-butyl-3-formyl-5-phenyl-1*H*-pyrrol-2-yl)thio]acetate **86** was achieved by the interaction of pyrrole **23a** with ethyl 2-mercaptoacetate in alcohol in the presence of piperidine. Aldehyde **23a** was transformed in the Suzuki-Miyaura reaction with *p*-tolylboronic acid into the corresponding 2-arylpyrrole-3-carbaldehyde **87**, the Pd-catalyzed alkenylation of which produced polysubstituted pyrrole **88**. 1-Butyl-5-phenyl-2-(phenylethynyl)-1*H*-pyrrole-3-carbaldehyde **89** was isolated as the product of the Sonogashira reaction with phenylacetylene in quantitative yield. Pd-catalyzed Buchwald-Hartwig reaction with Boc-piperazine was used for the formation of C–N bond in the synthesis of derivative **90**, alkenylation of which yielded tetrasubstituted pyrrole-3-carbaldehyde **91** (**Scheme 27**).[33]



i: $HSCH_2CO_2Et$, piperidine, EtOH, 100 °C, 3 h
ii: 4-$MeC_6H_4B(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, DMF-H_2O (2:1), 100 °C, 16 h
iii: $H_2C{=}CHCO_2tBu$, AgOAc, $Pd(OAc)_2$, DMF, 100 °C, 18 h
iv: **19**, $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, Et_3N, THF, rt, 18 h
v: *tert*-butyl piperazine-1-carboxylate, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, PhMe, 100 °C, 18 h

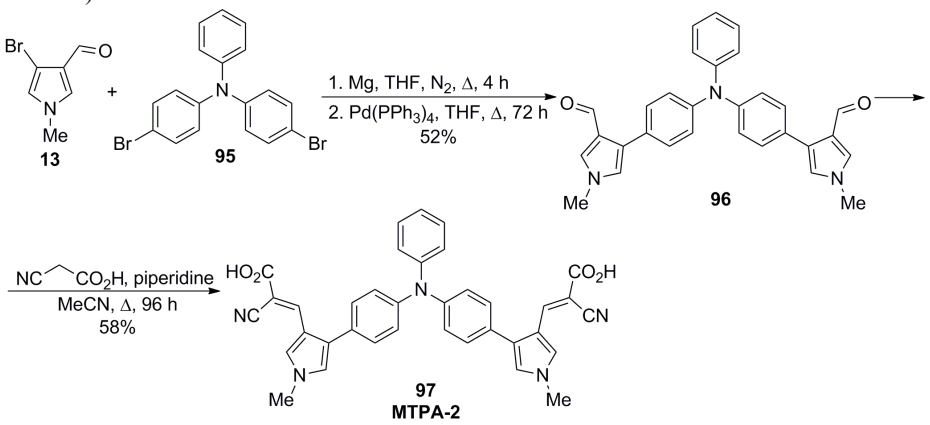
Scheme 27. Synthesis of polysubstituted pyrrole-3-carbaldehydes **86-91** from 2-bromopyrrole-3-carbaldehyde **23a**.

The Suzuki-Miyaura coupling reaction with *p*-tolylboronic acid converted 4-bromo- and 2,4-dibromopyrrole-3-carbaldehydes **23b,c** into tetra- and pentasubstituted pyrroles **92, 94**, respectively. Pyrrole-3-carbaldehyde **92** was used as a precursor in the synthesis of *tert*-butyl 3-(1-butyl-4-(*p*-tolyl)-5-phenyl-3-formyl-1H-pyrrol-2-yl)acrylate **93** (**Scheme 28**).[33]



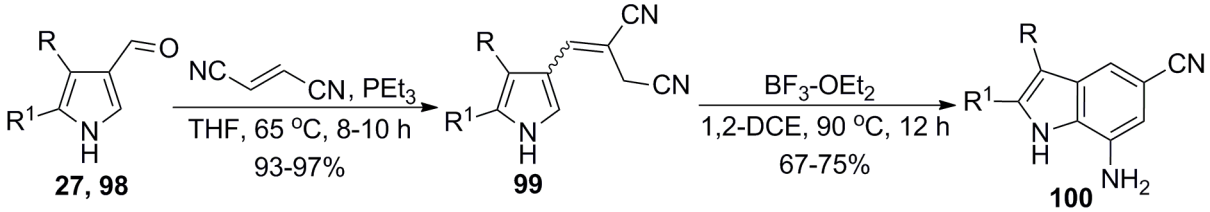
Scheme 28. Synthesis of polysubstituted pyrroles **92-94** from 4-bromo- and 2,4-dibromopyrrole-3-carbaldehydes **23b,c**.

4-Bromo-1-methyl-1*H*-pyrrole-3-carbaldehyde **13** has found application for the synthesis of the dual donor-π-acceptor type dye **MTPA-2 97** for solar cells. For instance, the interaction of pyrrole-3-carbaldehyde **13** with 4-bromo-*N*-(4-bromophenyl)-*N*-phenylaniline **95**, which involves the stage of the formation of Grignard reagent, led in the presence of a Pd-catalyst to derivative **96**, which in Knoevenagel condensation with cyanoacetic acid gave the target product **97** with a yield of 58% (**Scheme 29**).[31]



Scheme 29. Synthesis of **MTPA-2** dye **97** by the interaction of 4-bromo-1-methyl-1*H*-pyrrole-3-carbaldehyde **13** with 4-bromo-*N*-(4-bromophenyl)-*N*-phenylaniline **95** and subsequent Knoevenagel condensation with cyanoacetic acid.

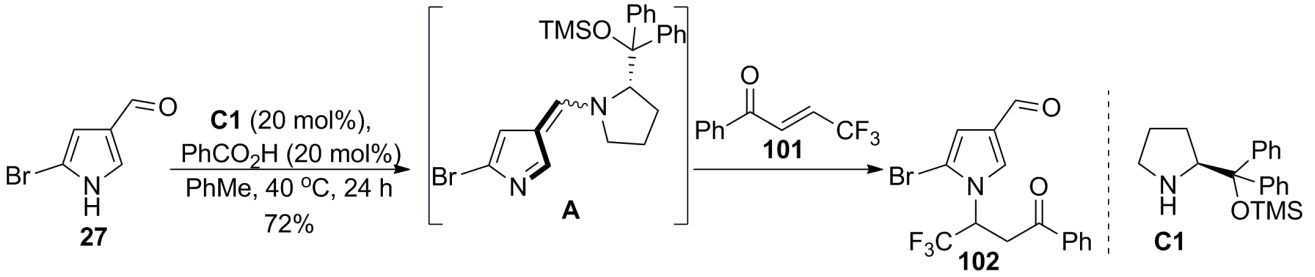
The authors of work[56] proposed an efficient method for the conversion of pyrrole-3-carbaldehydes into substituted 7-amino-5-cyanoindoles **100**. The three-component Wittig reaction of pyrrole-3-carbaldehydes **27, 98** with fumaronitrile and PEt_3 upon heating in THF led to the formation of 3-(2,3-dicyanoallyl)pyrroles **99** with moderate diastereoselectivity (4-bromo derivative *E/Z* = 5:3; 5-bromo derivative *E/Z* = 3:1). The synthesized allylic nitriles **99** in the presence of $BF_3 \cdot OEt_2$ underwent cyclization via the intramolecular Houben-Hoesch reaction to form indoles **100** (**Scheme 30**).



27 R = H, R^1 = Br; **98** R = Br, R^1 = H

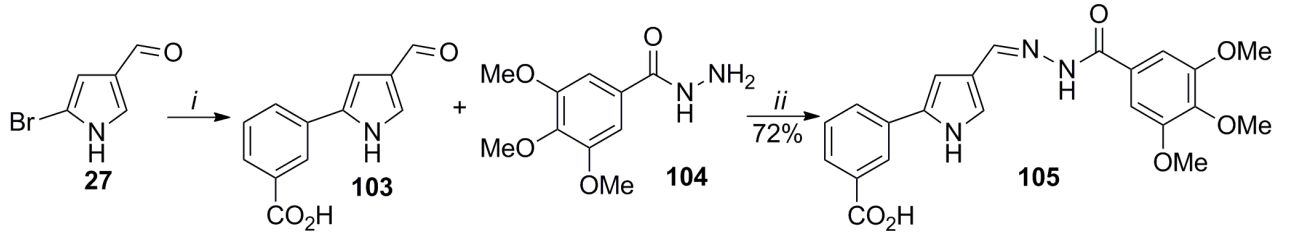
Scheme 30. Synthesis of 7-amino-5-cyanoindoles **100** by intramolecular Houben-Hoesch reaction of 3-(2,3-dicyanoallyl)pyrroles **99**.

The *aza*-Michael reaction of 5-bromo-1*H*-pyrrole-3-carbaldehyde **27** with trifluoromethyl crotonophenone **101** catalyzed by a chiral pyrrolidine derivative, which proceeds through the intermediate *aza*-dienamine intermediate **A**, leads to the *N*-functionalized pyrrole **102** (**Scheme 31**).[57]



Scheme 31. Synthesis of *N*-functionalized pyrrole **102** from 5-bromo-1*H*-pyrrole-3-carbaldehyde **27** and trifluoromethyl crotonophenone **101**.

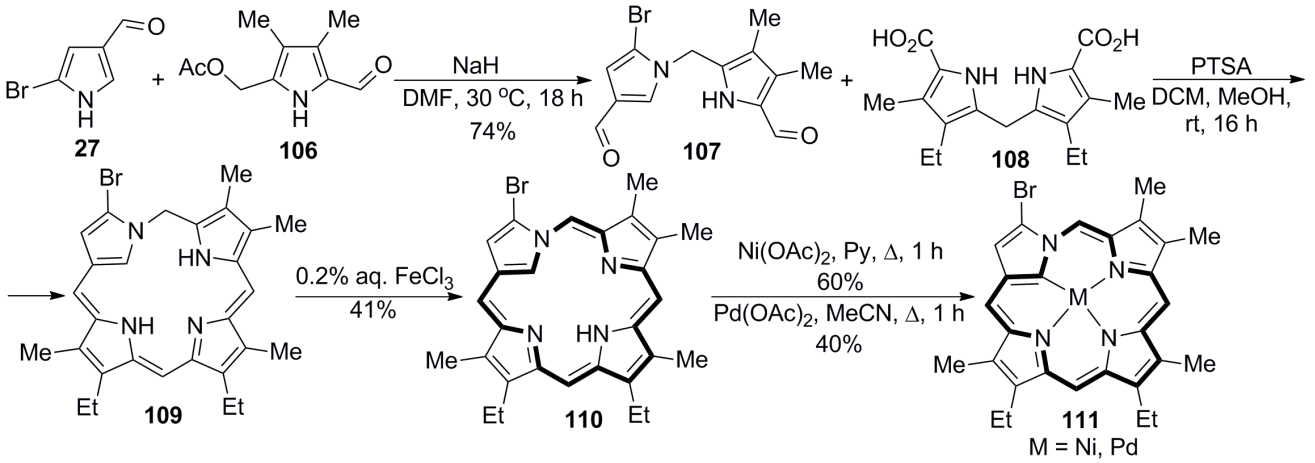
Obtained by the Suzuki-Miyaura reaction from 5-bromopyrrole-3-carbaldehyde **27**, 5-(3-carboxyphenyl)pyrrole-3-carbaldehyde **103** under microwave irradiation reacts with hydrazide **104** to form *N*-aroylhydrazone **105** which is a potential inhibitor of lactate dehydrogenase A (LDH-A) (**Scheme 32**).[58]



i: 3-$HO_2CC_6H_4B(OH)_2$, Pd(*N,N*-Dimethyl-alaninate)$_2$, Na_2CO_3, EtOH, H_2O, MW, 100 W, 120 °C, 5 min
ii: $NH_2NH_2 \times 2H_2O$, EtOH, MW, 130 W, 120 °C, 45 min

Scheme 32. Synthesis of *N*-aroylhydrazone **105** by condensation of 5-(3-carboxyphenyl)pyrrole-3-carbaldehyde **103** with hydrazide **104**.

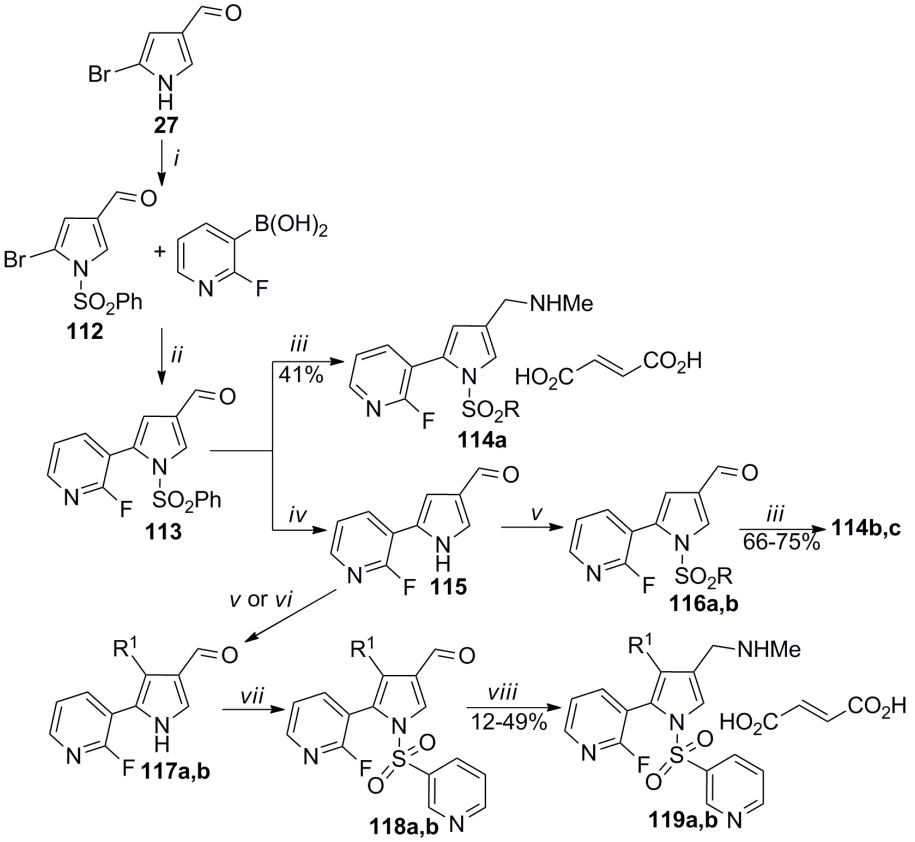
5-Bromo-1*H*-pyrrole-3-carbaldehyde **27** proved to be an effective precursor for the directed synthesis of 2-bromometalloporphyrinoids **111**. The technique suggested by the authors of article[59] involved interaction with 5-acetoxymethylpyrrole-2-carbaldehyde **106**, which led to diformyldipyrylomethane **107**, whose acid-catalyzed condensation with dicarboxydipyrylomethane **108** gave the intermediate florine **109**. Oxidation of the latter with an aqueous solution of $FeCl_3$ produces porphyrin **110**, which, when treated with $Ni(OAc)_2$ or $Pd(OAc)_2$, yields the corresponding metalloporphyrinoids **111** (**Scheme 33**).



Scheme 33. 5-Bromo-1*H*-pyrrole-3-carbaldehyde **27** in the synthesis of 2-bromometalloporphyrinoids **111**.

The synthesis of vonoprazan fumarate analogues, novel long-acting potassium-competitive acid secretion blockers (P-CABs) that would completely overcome the limitations of proton pump inhibitors (PPIs), started with the sulfonylation of 5-bromo-1*H*-pyrrole-3-carbaldehyde **27** under basic conditions. The resulting phenylsulfonylpyrrole **112** was converted by Suzuki-Miyaura cross-coupling to the 5-pyridyl derivative **113**, from which 1-(1*H*-pyrrol-3-yl)-*N*-methylmethanamine **114a** was obtained by reductive amination. In turn, desulfonylation of compound **113** was used to generate intermediate **115**, which was re-sulfonylated to obtain derivatives **116a,b**. Their further modification with an *N*-methylmethanamine

fragment led to the target compounds **114b,c**. Fluorination of intermediate **115** with 1-fluoro-2,6-dichloropyridinium triflate or chlorination with *N*-chlorosuccinimide (NCS) gave the corresponding 4-halopyrrole-3-carbaldehydes **117a,b**, which were sulfonylated to give derivatives **118a,b**. Their reductive amination synthesized the analogs of vonoprazane fumarate **119** (**Scheme 34**).[60] It is worth noting that the authors of article[35] used 5-bromopyrrole-3-carbaldehyde **27** for the synthesis of four observed metabolites of vonoprazane fumarate and their deuterium-labeled analogs.



114 a R = Ph, **b** R = thiophen-2-yl, **c** R = furan-2-yl

116 a R = thiophen-2-yl, **b** R = furan-2-yl

117-119 a R^1 = F, **b** R^1 = Cl

i: NaH, $PhSO_2Cl$, THF, rt

ii: $Pd(PPh_3)_4$, $NaHCO_3$, DME, H_2O, 80 °C

iii: 1. $NaBH_4$, 40% $MeNH_2$ in MeOH, MeOH, rt, 30 min. 2. fumaric acid, EtOH

iv: 8 mol/L NaOH, THF, MeOH, rt

v (for **117a**): 1-fluoro-2,6-dichloropyridinium triflate, THF, MeCN, rt

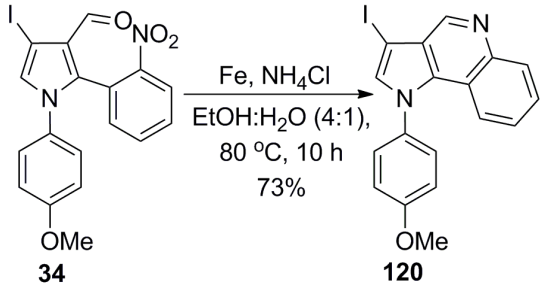
vi (for **117b**): NCS, DMF, 80 °C

vii: NaH, THF, 15-crown-5, 3-$PySO_2Cl$, rt

vii: 1. 40% $MeNH_2$ in MeOH, MeOH, rt, 30 min. 2. $NaBH(OAc)_3$, rt, 3 h. 3. fumaric acid, EtOH

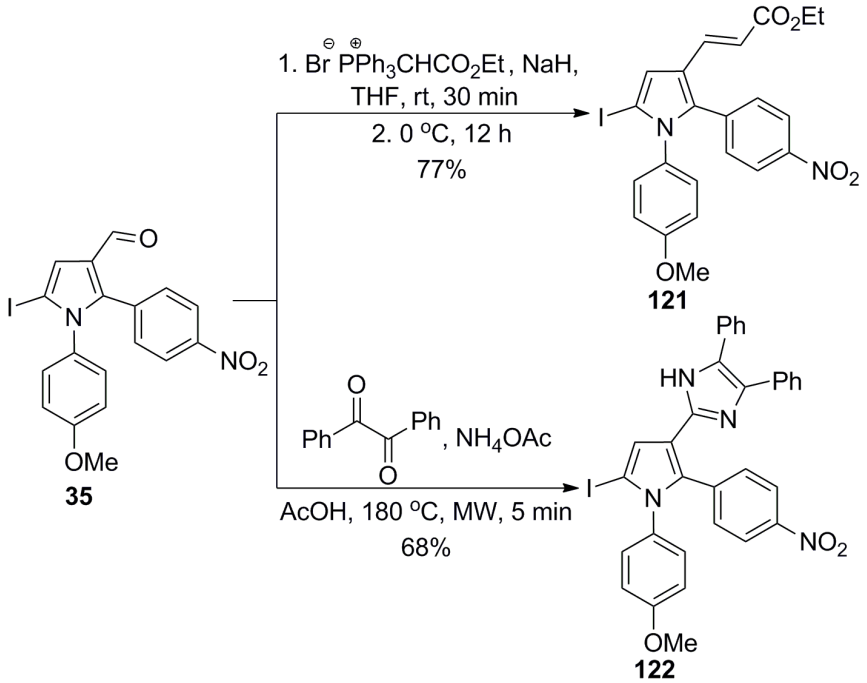
Scheme 34. Synthesis of vonoprazan fumarate analogues **114**, **119** from 5-bromo-1*H*-pyrrole-3-carbaldehyde **27**.

A convenient protocol for the synthesis of iodine-containing pyrrolo[3,2-*c*]quinolone **120** involves the reduction of the NO_2 group of 4-iodopyrrole-3-carbaldehyde **34** followed by intramolecular cyclization with the participation of the amino group formed *in situ* (**Scheme 35**).[37]



Scheme 35. Synthesis of pyrrolo[3,2-*c*]quinolone **120** by reductive intramolecular cyclization of 4-iodopyrrole-3-carbaldehyde **34**.

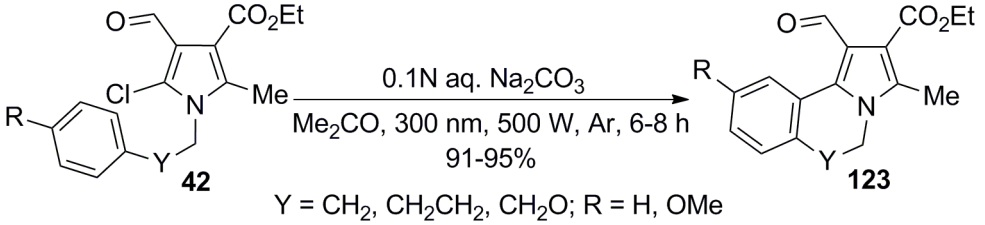
The isomeric 5-iodopyrrole-3-carbaldehyde **35** proved to be a convenient substrate for obtaining the corresponding 3-alkenyl-5-iodopyrrole **121** via the Wittig reaction, as well as for a microwave-assisted synthesis of (pyrrol-3-yl)imidazole **122** (**Scheme 36**).[37]



Scheme 36. Synthesis of 3-alkenyl-5-iodopyrrole **121** and (pyrrol-3-yl)imidazole **122** from 5-iodopyrrole-3-carbaldehyde **35**.

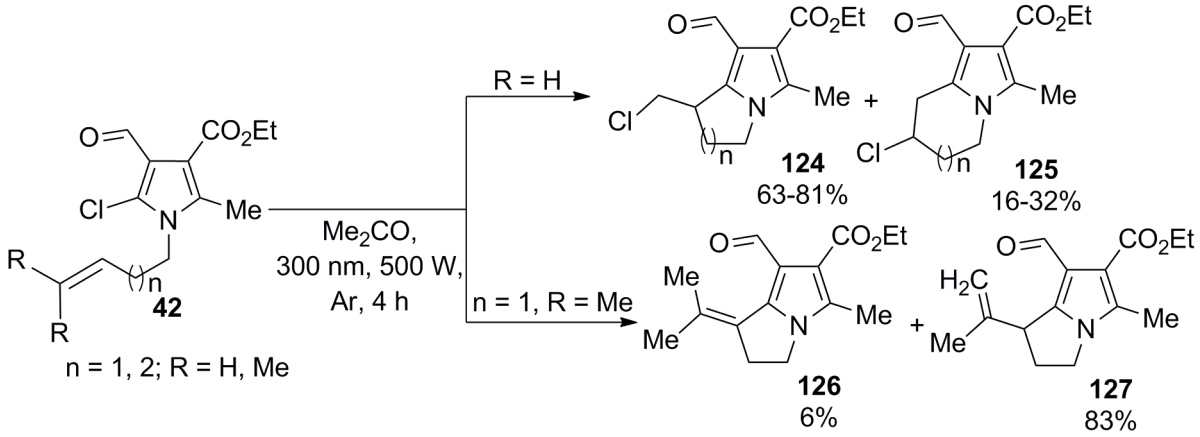
3.2. Chemical transformations of halogen-containing 4-formylpyrroles

Intramolecular photocyclization involving chlorine atoms and the ortho position of the aromatic nucleus of 5-chloro-*N*-(ω-arylalkyl)pyrrole-4-carbaldehydes **42** was successfully used to obtain functional derivatives of pyrrolo[2,1-*a*]isoquinoline, pyrrolo[1,2-*a*]benzazepine, and pyrrolo[1,2-*d*][1,4]benzoxazepines **123** (**Scheme 37**).[61]



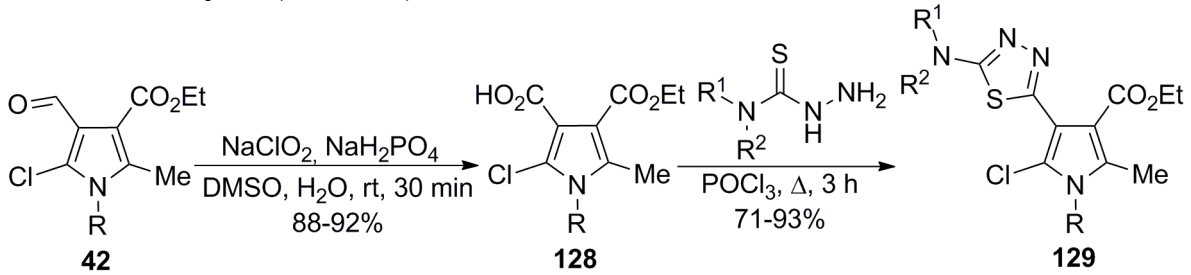
Scheme 37. Synthesis of pyrrolo[2,1-*a*]isoquinoline, pyrrolo[1,2-*a*]benzazepine and pyrrolo[1,2-*d*][1,4]benzoxazepines **123** by intramolecular photocyclization of 5-chloro-*N*-(ω-arylalkyl)pyrrole-4-carbaldehydes **42**.

Studying the photoinduced cyclization of *N*-(ω-alkenyl)-5-chloropyrrole-4-carbaldehydes **42**, the authors of work[62] obtained a mixture of chlorine-containing products of exo- **124** and endo- **125** cyclization in the case of but-3-en-1-yl and pent-4-en-1-yl derivatives. Instead, photoreaction of ethyl 2-methyl-4-formyl-5-chloro-1-(4-methylpent-3-en-1-yl)-1*H*-pyrrole-3-carboxylate **42** led to the formation of cyclization products with alkenyl fragments **126** and **127** (**Scheme 38**).



Scheme 38. Synthesis of pyrrolysines **124-127** and indolysines **124-125** by photoinduced cyclization of *N*-(ω-alkenyl)-5-chloropyrrole-4-carbaldehydes **42**.

A series of 4-(1,3,4-thiadiazol-2-yl)-containing pyrroles **129** were synthesized by a convenient method from ethyl 4-formyl-5-chloro-1*H*-pyrrole-3-carboxylates **42**, which were selectively converted to the corresponding pyrrole-4-carboxylic acids **128**. Their cyclocondensation with mono- or disubstituted thiosemicarbazides in boiling $POCl_3$ led to the target products **129** in 71-93% yields (**Scheme 39**).[63]

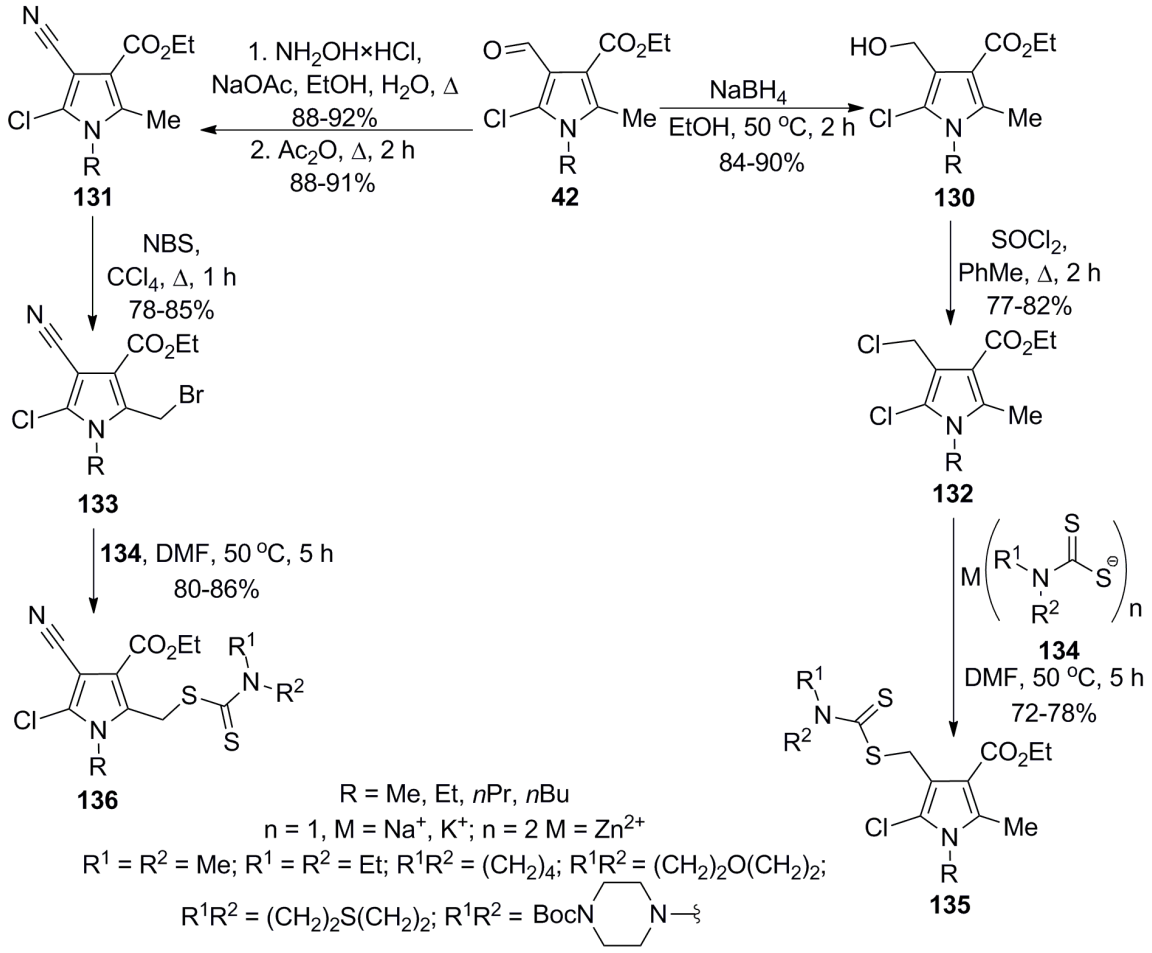


R = Me, Et, *n*Pr, *n*Bu, Bn

R^1 = H, R^2 = *c*Hex; R^1 = R^2 = Me; R^1 = H, R^2 = Ph; R^1 = H, R^2 = 4-MeC_6H_4; R^1 = H, R^2 = 4-$MeOC_6H_4$; R^1 = H, R^2 = 4-FC_6H_4; R^1R^2 = $(CH_2)_2O(CH_2)_2$

Scheme 39. Synthesis of 4-(1,3,4-thiadiazol-2-yl)-containing pyrroles **129** from ethyl 4-formyl-5-chloro-1*H*-pyrrole-3-carboxylates **42**.

Ethyl 4-formyl-5-chloro-1*H*-pyrrole-3-carboxylates **42** were used as templates for the construction of 4- and 2-dithiocarbamatemethyl-substituted pyrroles **135** and **136**. For instance, reducing the formyl group of pyrroles **42**, produced the corresponding 4-hydroxymethyl-substituted pyrroles **130**, and the action of hydroxylamine on derivatives **42** yielded oximes, which, when boiled in acetic anhydride, form cyanocarboxylates **131**. Further treatment of compounds **130** with $SOCl_2$ in boiling toluene led to 5-chloro-4-chloromethyl-1*H*-pyrrole-3-carboxylates **132**. Bromination of 5-chloro-4-cyano-1*H*-pyrrole-3-carboxylates **131** with *N*-bromosuccinimide (NBS) produced the corresponding 2-bromomethyl-5-chloro-4-cyano-1*H*-pyrrole-3-carboxylates **133**. The interaction of halomethyl derivatives **132** and **133** with alkali metal or zinc dithiocarbamates **134** in DMF solution at 50°C yielded 4- and 2-dithiocarbamatemethylpyrroles **135** and **136** (**Scheme 40**).[64]



R = Me, Et, *n*Pr, *n*Bu

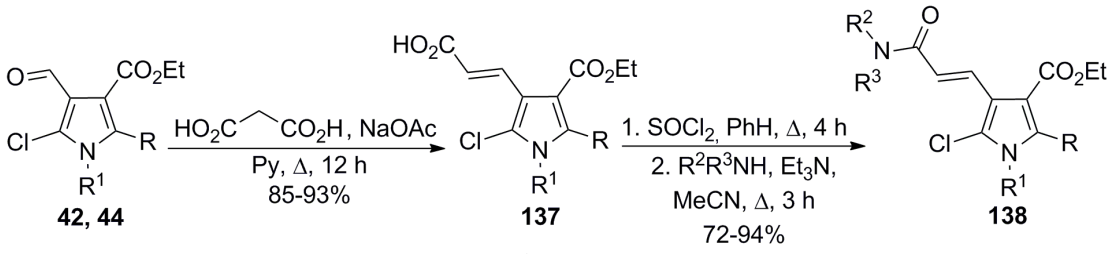
n = 1, M = Na^+, K^+; n = 2 M = Zn^{2+}

R^1 = R^2 = Me; R^1 = R^2 = Et; R^1R^2 = $(CH_2)_4$; R^1R^2 = $(CH_2)_2O(CH_2)_2$;

R^1R^2 = $(CH_2)_2S(CH_2)_2$; R^1R^2 = BocN N—

Scheme 40. Synthesis of 4- and 2-dithiocarbamatomethylpyrroles **135** and **136** from ethyl 4-formyl-5-chloro-1*H*-pyrrole-3-carboxylates **42**.

The aldehyde group of ethyl 4-formyl-5-chloropyrrole-3-carboxylates **42, 44** turned out to be convenient for obtaining 3-(pyrrol-4-yl)acrylamides **138**, potential antimicrobial agents. The corresponding 3-(pyrrol-4-yl)acrylic acids **137** were synthesized by Knoevenagel condensation with malonic acid, the stepwise treatment of which with $SOCl_2$ and amines led to the target amides **138** (**Scheme 41**).[65]



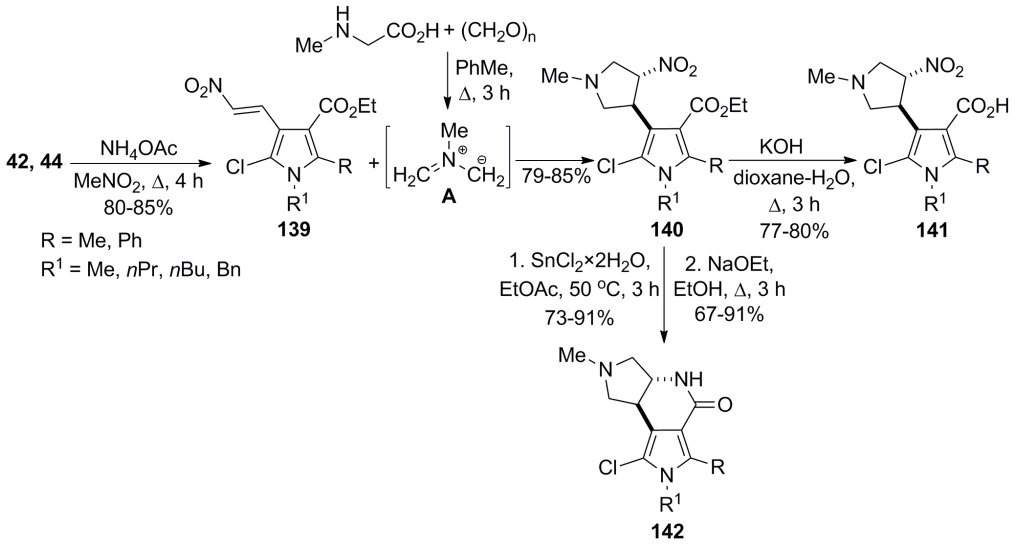
R = Me, Ph; R^1 = Me, *n*Pr, *n*Bu, Bn

R^2 = H, R^3 = Me; R^2 = R^3 = Me; R^2 = H, R^3 = 4-MeC_6H_4; R^2 = H, R^3 = 4-$MeOC_6H_4$;

R^2 = H, R^3 = 4-ClC_6H_4; R^2 = H, R^3 = 4-BrC_6H_4; R^2R^3 = $(CH_2)_4$; R^2R^3 = $(CH_2)_2O(CH_2)_2$

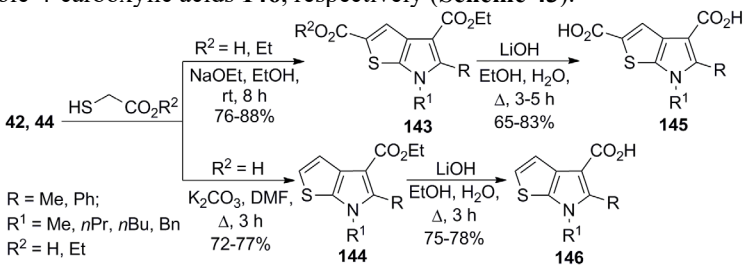
Scheme 41. Synthesis of 3-(pyrrol-4-yl)acrylamides **138** from ethyl 4-formyl-5-chloropyrrole-3-carboxylates **42, 44**.

Condensation of ethyl 4-formyl-5-chloropyrrole-3-carboxylates **42, 44** with nitromethane gave the corresponding nitrovinyl derivatives **139**, which underwent [2+3]-cycloaddition with *N*-methylazomethynylide **A**[66,67] to synthesize ethyl 4-(4-nitropyrrolidin-3-yl)-5-chloropyrrole-3-carboxylates **140**. Hydrolysis of the latter led to the corresponding acids **141**, and reductive cyclization led to hexahydrodipyrrolo[3,4-*b*:3',4'-*d*]pyridin-5(1*H*)-one derivatives **142** (**Scheme 42**).[68]



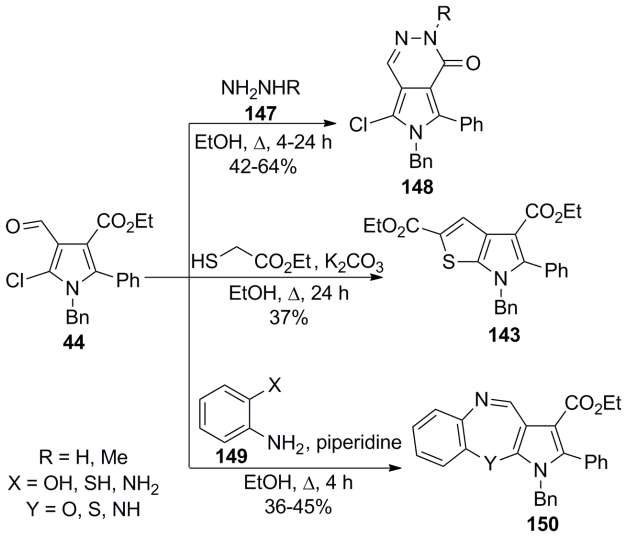
Scheme 42. Synthesis of 4-(4-nitropyrrolidin-3-yl)-5-chloropyrroles **140, 141** and hexahydrodipyrrolo[3,4-*b*:3',4'-*d*]pyridin-5(1*H*)-ones **142** by the reaction of 4-(2-nitroethenyl)-5-chloropyrrole-3-carboxylates **139** and *N*-methylazomethynylide **A**.

The cyclocondensations of 4-formyl-5-chloropyrrole-3-carboxylates **42, 44** are of particular synthetic importance, which are realized with the participation of a formyl group atom and a chlorine atom. Their interaction with thioglycolic acid or ethyl thioglycolate in EtOH in the presence of EtONa at room temperature produced the corresponding thieno[2,3-*b*]pyrrole-2-carboxylic acids or thieno[2,3-*b*]pyrrole-2,4-dicarboxylates **143**. Instead, cyclocondensation with thioglycolic acid under reflux in the K_2CO_3-DMF system is accompanied by decarboxylation and leads to the formation of thieno[2,3-*b*]pyrrole-4-carboxylates **144**. Hydrolysis of carboxylates **143** and **144** with LiOH afforded thieno[2,3-*b*]pyrrole-2,4-dicarboxylic acids **145** and thieno[2,3-*b*]pyrrole-4-carboxylic acids **146**, respectively (**Scheme 43**).[40]



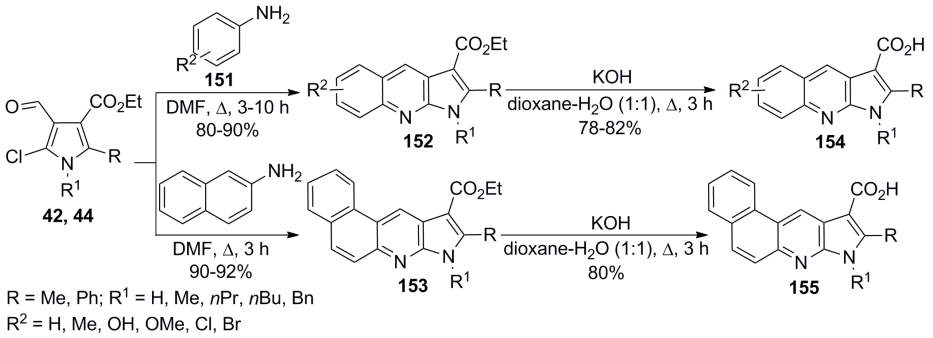
Scheme 43. Synthesis of thieno[2,3-*b*]pyrroles **143-146** by condensation of 4-formyl-5-chloropyrrole-3-carboxylates **42, 44** with thioglycolic acid or ethyl thioglycolate.

The authors of article[41] described the synthesis of polycyclic compounds based on ethyl 1-benzyl-2-phenyl-4-formyl-5-chloro-1*H*-pyrrole-3-carboxylate **44**. In particular, pyrrolo[3,4-*d*]pyridazinones **148** were obtained by selective cyclocondensation with hydrazines **147**, 5-phenylthieno[2,3-*b*]pyrrole-2,4-dicarboxylate **143** with mercaptoacetate, and pyrrolobenz[1,4]oxazepine, pyrrolobenzo[1,4]thiazepine and pyrrolobenzo[1,4]diazepine **150** with the corresponding *ortho*-substituted anilines (**Scheme 44**).



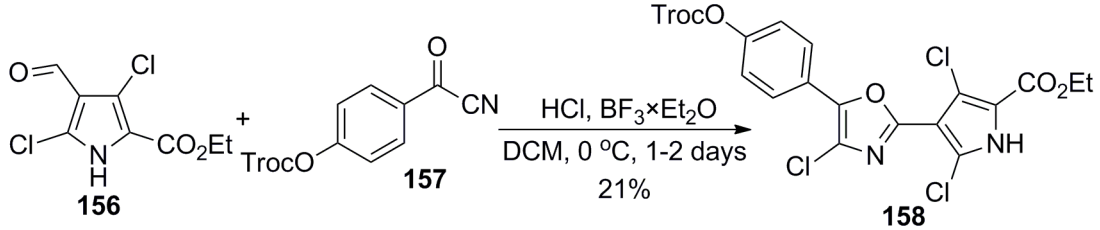
Scheme 44. Synthesis of pyrrolo[3,4-*d*]pyridazinones **148**, thieno[2,3-*b*]pyrrole **143** and pyrrolobenz[1,4](oxa-, thia-)diazepines **150** by condensation of ethyl 1-benzyl-2-phenyl-4-formyl-5-chloro-1*H*-pyrrole-3-carboxylate **44** with hydrazines **147**, ethyl mercaptoacetate and *ortho*-substituted anilines **149**.

Cyclocondensation of 4-formyl-5-chloropyrrole-3-carboxylates **42, 44** with anilines **151** or β-naphthylamine was used to synthesize a series of ethyl pyrrolo[2,3-*b*]quinoline-3-carboxylates **152** or their benzo[*f*]analogues **153** which have moderate fluorescent properties. Basic hydrolysis of carboxylates **152, 153** produced the corresponding carboxylic acids **154, 155** (**Scheme 45**).[69]



Scheme 45. Synthesis of ethyl pyrrolo[2,3-*b*]quinoline-3-carboxylates **152** or their benzo[*f*]analogues **153** by cyclocondensation of 4-formyl-5-chloropyrrole-3-carboxylates **42, 44** with anilines **151** or β-naphthylamine.

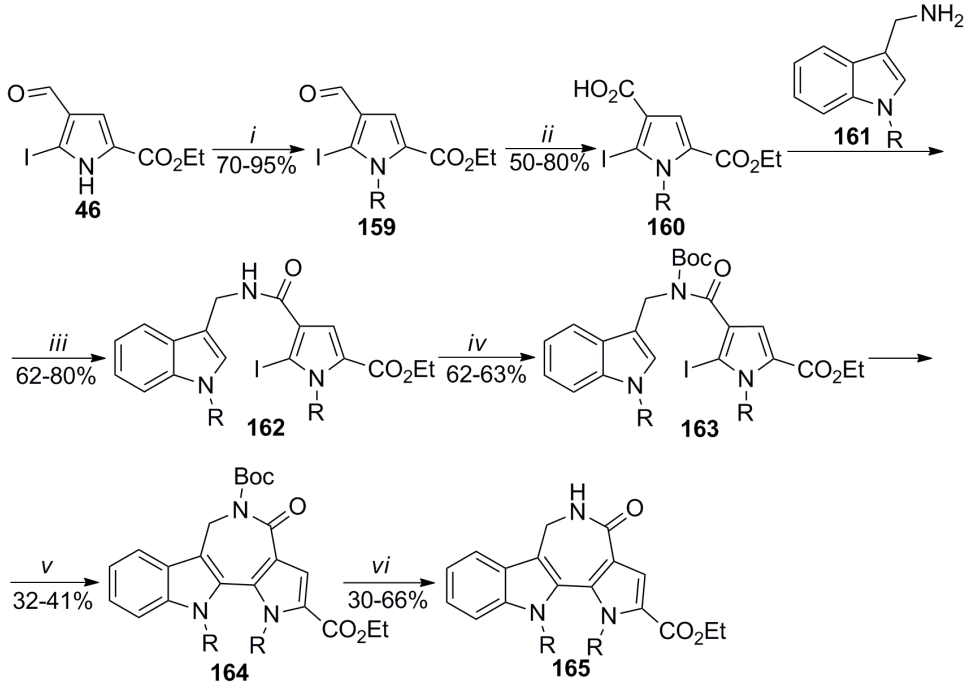
A three-component reaction of ethyl 3,5-dichloro-4-formyl-1*H*-pyrrole-2-carboxylate **156**, aryl cyanide **157** and HCl was used to synthesize oxazolylpyrrole **158** which can serve as a precursor for the preparation of the isomer of the phorbazole A alkaloid (**Scheme 46**).[70]



Scheme 46. Synthesis of oxazolylpyrrole **158** by three-component reaction of ethyl 3,5-dichloro-4-formyl-1*H*-pyrrole-2-carboxylate **156**, aryl cyanide **157** and HCl.

The authors[42] used ethyl 5-iodo-4-formyl-1*H*-pyrrole-2-carboxylate **46** for the synthesis of a tetracyclic system with a pyrrolo[2′,3′:5,6]azepino[4,3-*b*]indol-4(11*H*)-one core **165** which is structurally related to paullones, the protein kinase

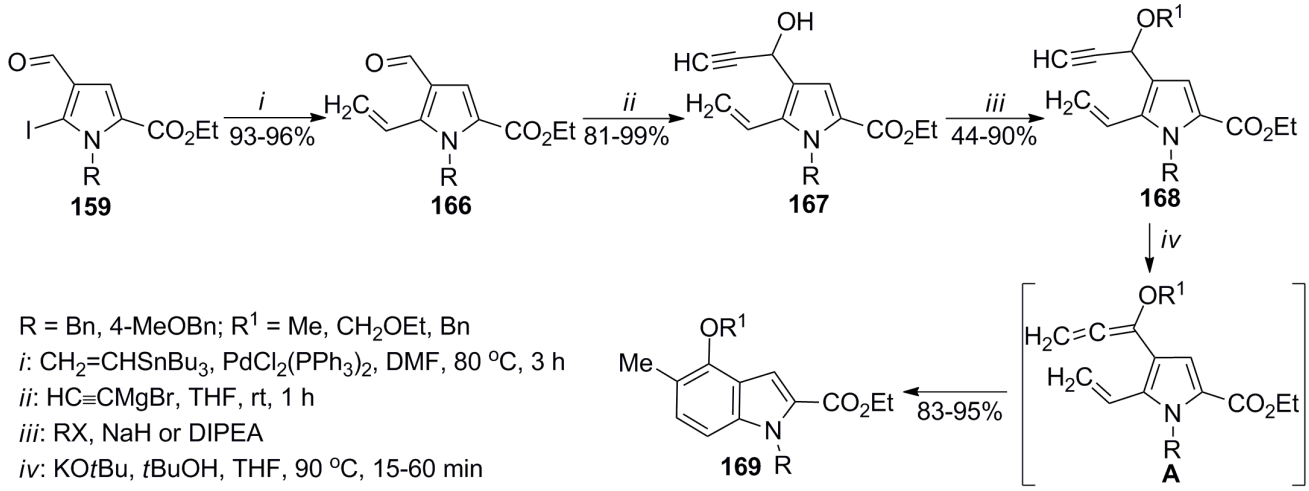
inhibitors. The developed protocol included the preparation of *N*-alkylpyrroles **159**, their oxidation to acids **160**, which were introduced into condensation with indole-3-methylamines to form amide conjugates **162**. The subsequent intramolecular Pd-catalyzed Heck reaction of their *N*-Boc-protected derivatives **163** resulted in the formation of the azepine skeleton of compounds **164**, which were readily converted into the target compounds **165** (**Scheme 47**).



R = CH_2OEt, $CH_2OCH_2CH_2SiMe_3$, CH_2OCH_2Ph
i: RCl, NaH, DMF, rt, 2 h
ii: $KMnO_4$, Me_2CO, H_2O, rt, 5.5 h
iii: 1. EDCI×HCl, DMAP, DCM, 0 °C, 4 h. 2. rt, 19 h
iv: Boc_2O, DMAP, MeCN, rt, 21 h
v: $Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, 135 °C, 30 min
vi: CF_3COOH, DCM, rt, 1 h

Scheme 47. Synthesis of pyrrolo[2′,3′:5,6]azepino[4,3-*b*]indol-4(11*H*)-ones **165** from ethyl 5-iodo-4-formyl-1*H*-pyrrole-2-carboxylate **46**.

The spectrum of synthetic applications of 5-iodo-4-formyl-1*H*-pyrrole-2-carboxylates **159** was extended to the preparation of indole-2-carboxylates **169**. The method proposed in work[71] included stages of Pd-catalyzed cross-coupling with the formation of 5-vinyl-substituted pyrroles **166**, their sequential transformation into propargylic alcohols **167** and ethers **168**. The electrocyclic reaction of the latter in the presence of *t*-BuOK via intermediate 2-vinyl-3-alenylpyrroles **A** led to the formation of the benzene ring of the target indoles **169** (**Scheme 48**).

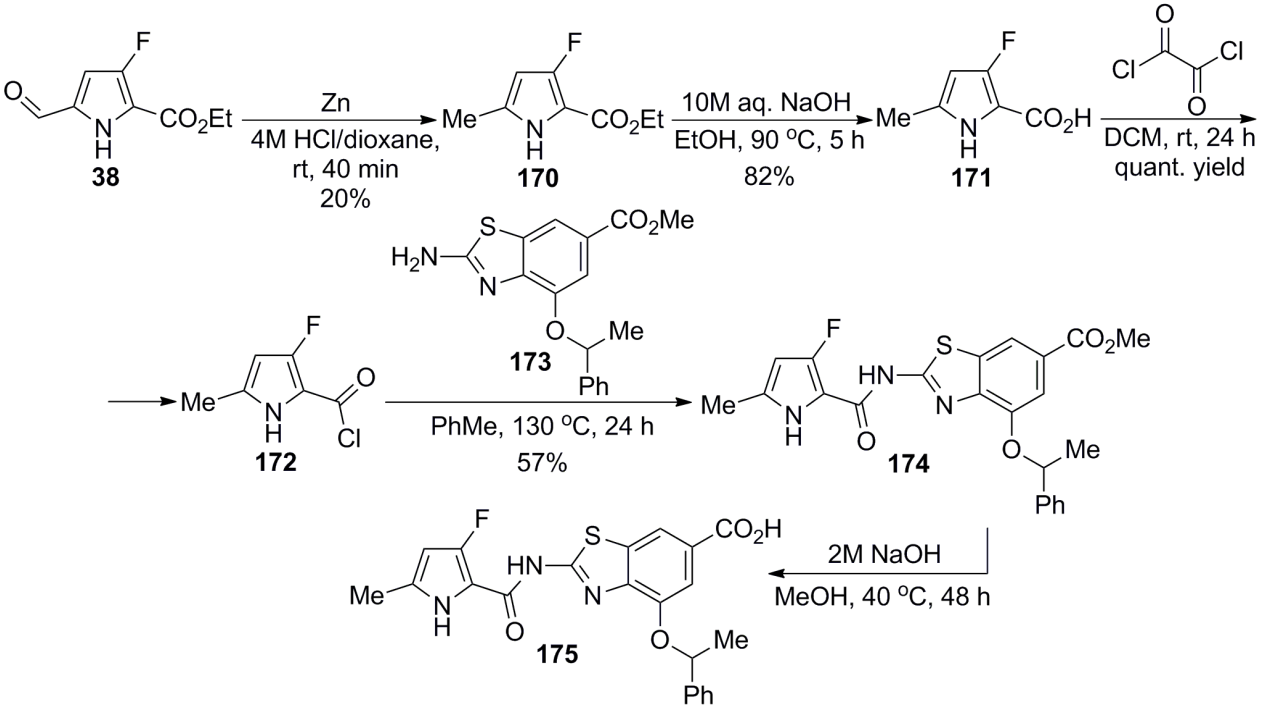


R = Bn, 4-MeOBn; R^1 = Me, CH_2OEt, Bn
i: CH_2=CHSnBu_3, $PdCl_2(PPh_3)_2$, DMF, 80 °C, 3 h
ii: HC≡CMgBr, THF, rt, 1 h
iii: RX, NaH or DIPEA
iv: KO*t*Bu, *t*BuOH, THF, 90 °C, 15-60 min

Scheme 48. 5-Iodo-4-formyl-1*H*-pyrrole-2-carboxylates **159** in the synthesis of indole-2-carboxylates **169**.

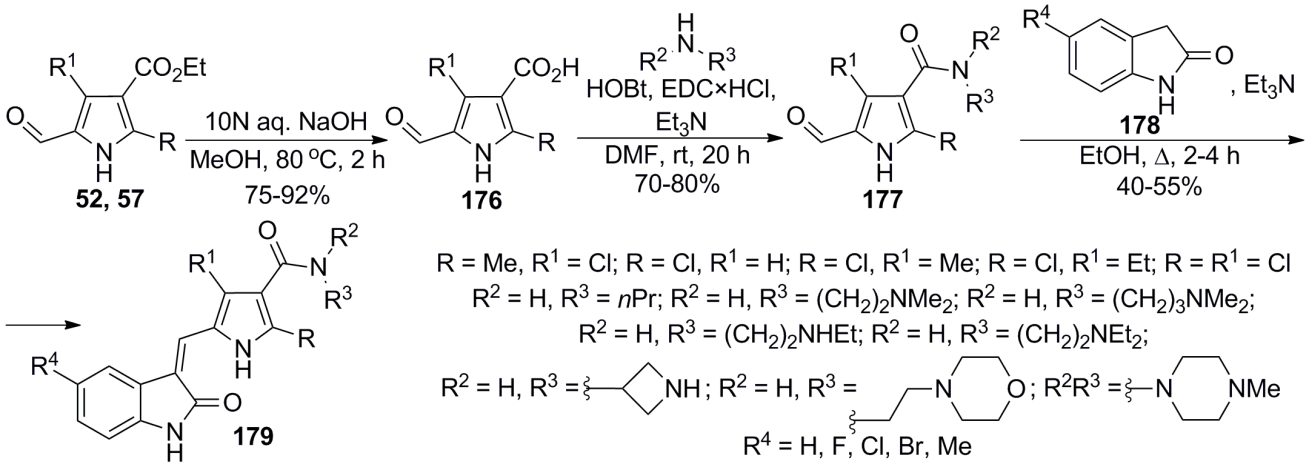
3.3. Chemical transformations of halogen-containing 5-formylpyrroles

Ethyl 3-fluoro-5-formylpyrrole-2-carboxylate **38** found use as a starting substrate for the synthetic design of a nanomolar inhibitor of bacterial DNA gyrase B **175**. The scheme of its structural modification included Clemmensen reduction to ethyl 5-methyl-3-fluoropyrrole-2-carboxylate **170**, which was converted stepwise to acid **171** and chloride **172** that was used for the acylation of 2-aminobenzo[*d*]thiazole-6-carboxylate **173**. The resulting methyl 2-(5-methyl-3-fluoro-1*H*-pyrrole-2-carboxamido)-4-(1-phenylethoxy)benzo[*d*]thiazole-6-carboxylate **174** was hydrolyzed to the target product **175** (**Scheme 49**).[38]



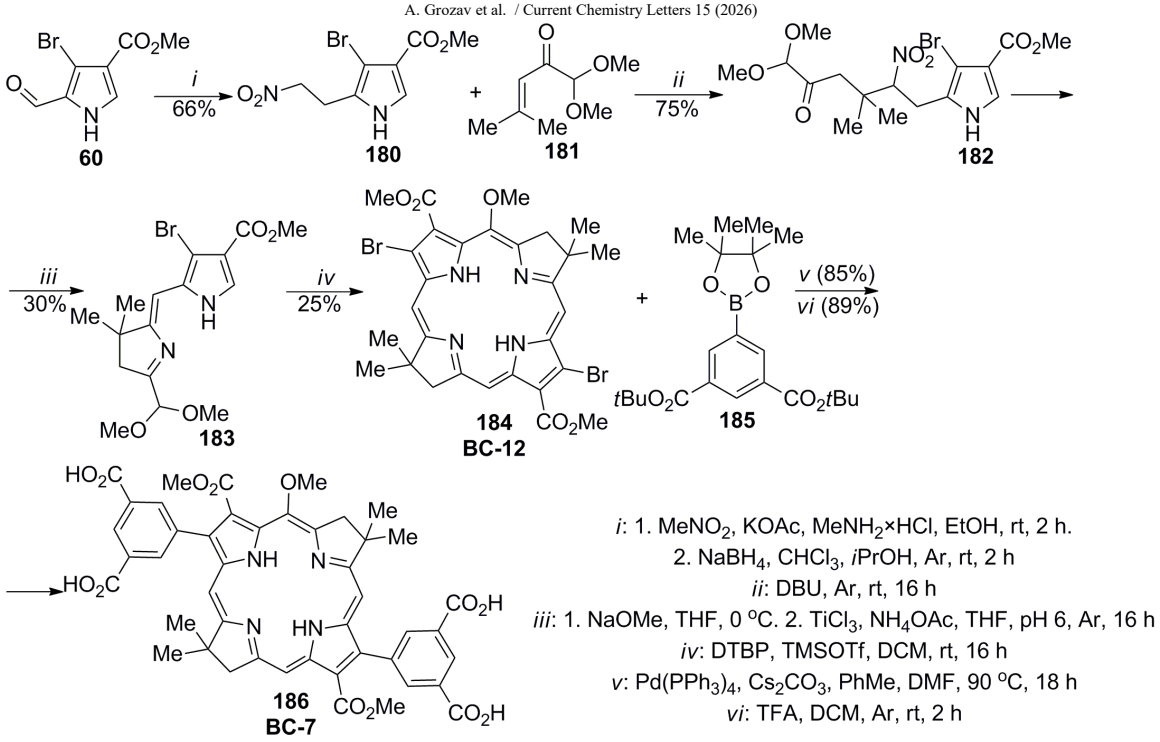
Scheme 49. Structural modification of ethyl 3-fluoro-5-formylpyrrole-2-carboxylate **38** to 2-(5-methyl-3-fluoro-1*H*-pyrrole-2-carboxamido)-4-(1-phenylethoxy)benzo[*d*]thiazole-6-carboxylic acid **175**.

Mono- and dichlorosubstituted formylpyrrolecarboxylates **52, 57** proved to be convenient templates for the synthesis of 3-substituted indolin-2-ones **179** with antitumor activity. The acids **176** obtained as a result of their hydrolysis were converted into the corresponding amides **177**. The latter were introduced into the Knoevenagel condensation with 5-substituted indolin-2-ones **178** to obtain compounds of the target structures **179**. It should be noted that the presence of a chlorine atom in the pyrrole nucleus was crucial for reducing cardiotoxicity (**Scheme 50**).[43]



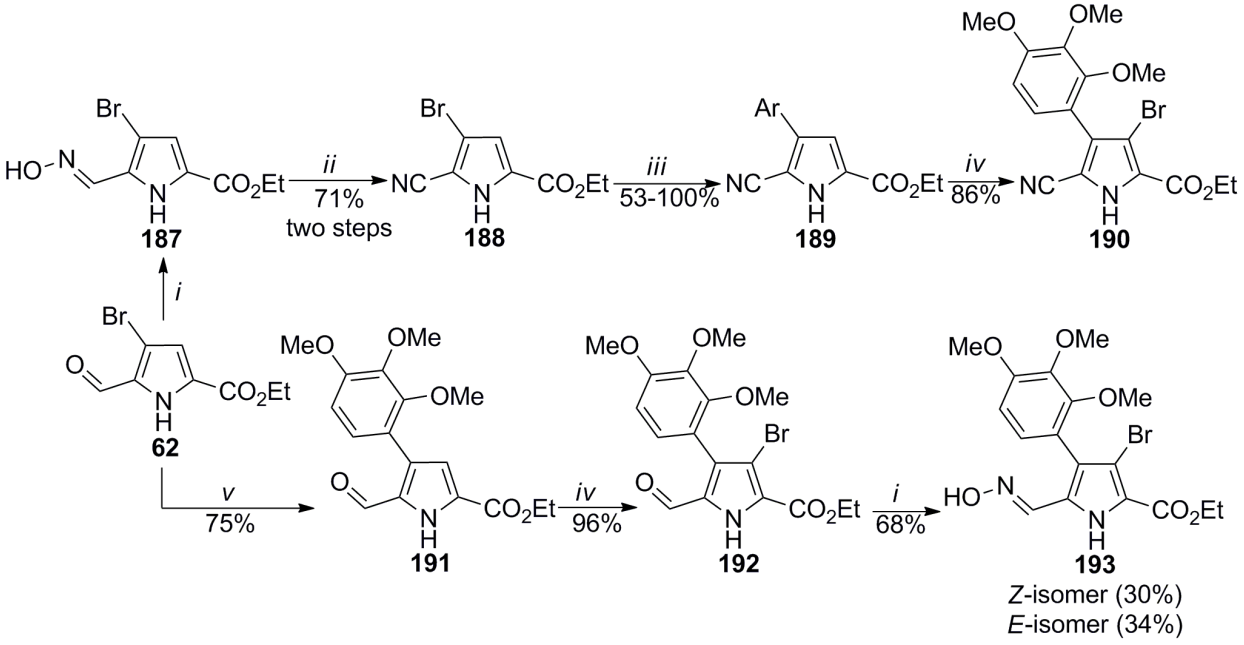
Scheme 50. Synthesis of 3-substituted indolin-2-ones **179** from chlorine-containing formylpyrrolecarboxylates **52, 57**.

A convenient synthetic route for the preparation of bacteriochlorins was developed based on methyl 4-bromo-5-formylpyrrole-3-carboxylate **60** that was sequentially converted to 4-bromo-5-nitroethylpyrrole-3-carboxylate **180**. Its subsequent Michael addition to 1,1-dimethoxy-4-methyl-3-penten-2-one **181** led to product **182**, which reductive cyclization resulted in the formation of [(3,4-dihydro-2H-pyrrol-2-ylidene)methyl]-1*H*-pyrrole-3-carboxylate **183**. Cyclodimerization of the latter gave bacteriochlorin **BC-12 184**, which was transformed into bacteriochlorin **BC-7 186** by Suzuki-Miyaura cross-coupling with boronopinacolate **185** (**Scheme 51**).[44]



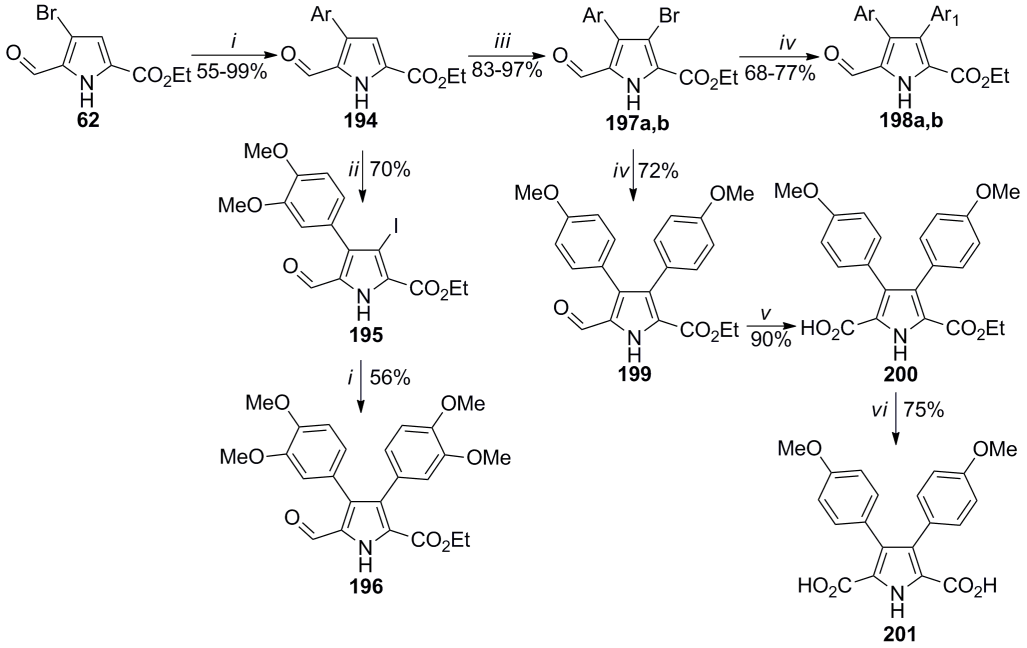
Scheme 51. Methyl 4-bromo-5-formylpyrrole-3-carboxylate **60** in the synthesis of bacteriochlorins **BC-12 184** and **BC-7 186**.

The authors of work[72] proposed a strategy for the construction of asymmetric structurally related 2,3,4,5-tetrasubstituted pyrroles **190, 192** and **193** based on ethyl 4-bromo-5-formylpyrrole-2-carboxylate **62**. It included variations of different sequences of steps of oximation of the aldehyde group, Suzuki-Miyaura cross-coupling, and bromination of the pyrrole ring (**Scheme 52**).



Scheme 52. Synthesis of 2,3,4,5-tetrasubstituted pyrroles **190, 192** and **193** by stepwise transformations of ethyl 4-bromo-5-formylpyrrole-2-carboxylate **62**.

Ethyl 4-bromo-5-formylpyrrole-2-carboxylate **62** proved to be an effective substrate for the preparation of diaryl-substituted pyrroles **196** and **201**, as well as their diindole analogues, which, respectively, found use as precursors in the synthesis of natural products, i.e. Gupton group lamellarin G trimethyl ether[73] and polycitone A, polycitone B, and polycitrine A.[45] The approach to the synthesis of precursor **196** included a sequence of arylation (compound **194**), iodination (compound **195**), and arylation (compound **196**) steps. The synthesis of precursor **201** involved the stages of bromination (compound **197**), arylation (compound **199**), oxidation (compound **200**), and hydrolysis (compound **201**) (**Scheme 53**).

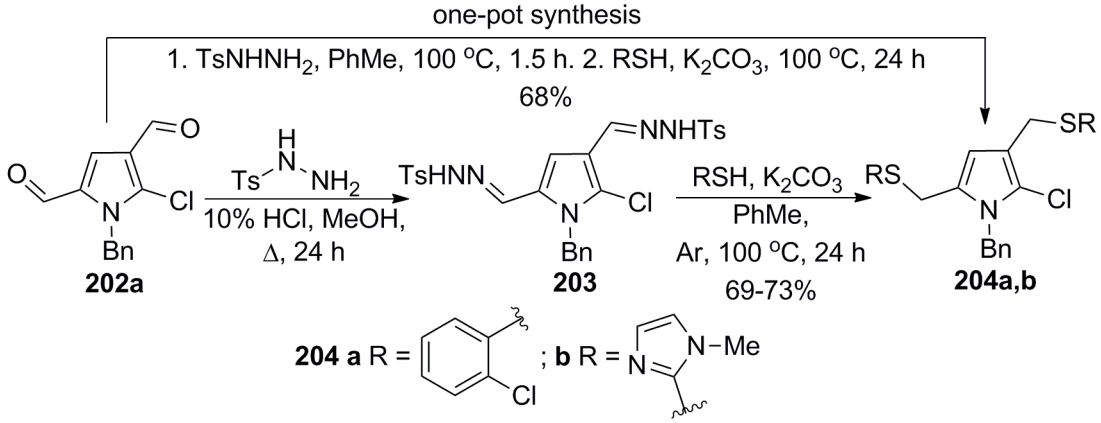


194 Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-HOC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-$MeSC_6H_4$, 4-$F_3COC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, benzo[3,4]dioxolyl, *N*-phenylsulfonyl-3-indolyl
197 a Ar = 4-MeC_6H_4, **b** Ar = 4-$MeOC_6H_4$
198 a Ar = 4-MeC_6H_4, Ar^1 = 4-$MeOC_6H_4$; **b** Ar = 4-$MeOC_6H_4$, Ar^1 = 4-MeC_6H_4;
i: $ArBF_3K$ or $ArB(OH)_2$, $Pd(PPh_3)_4$ or PdDPPF, DABCO, PhMe, EtOH, MW, 110 °C, 2 h
ii: 1. KOH, DMF, rt, 30 min. 2. I_2, rt, 24 h
iii: 1. KOH, DMF, rt, 15 min. 2. NBS, rt, 24 h
iv: Ar^1BF_3K, PdDPPF, DABCO, PhMe, EtOH, MW, 110 °C, 2 h
v: 1. NaH_2PO_4, $NaClO_2$, DMSO, H_2O, 60 °C, 2 h. 2. 6M HCl
vi: KOH, EtOH, H_2O, Δ, 24 h. 2. 6M HCl to pH = 2

Scheme 53. Synthesis of precursors **196** and **201** to natural compounds from ethyl 4-bromo-5-formylpyrrole-2-carboxylate **62**.

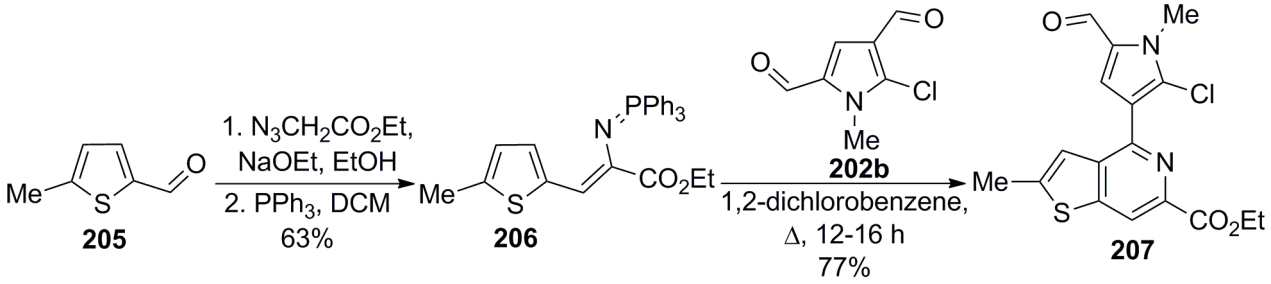
3.4. Chemical transformations of halogen-containing diformylpyrroles

The reaction of pyrrolo(2,4-di-*N*-tosylhydrazone) **203**, obtained from 1-benzyl-5-chloro-1*H*-pyrrole-2,4-dicarbaldehyde **202a** and *p*-toluenesulfonylhydrazide, in the absence of metal catalysts proceeds with the formation of pyrrole-containing thioethers **204a,b**. In addition, using dialdehyde **204a** as an example, a one-pot synthesis option was implemented without isolating the intermediate dihydrazone **203** (**Scheme 54**).[74]



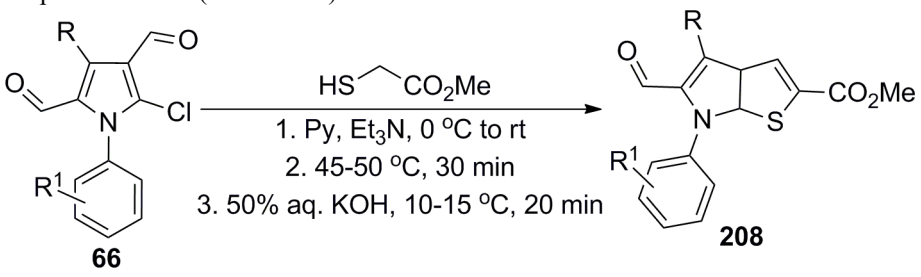
Scheme 54. Metal-free synthesis of pyrrole-containing thioethers **204** by the interaction of pyrrolo(2,4-di-*N*-tosylhydrazone) **203** with thiols.

The cyclocondensation of 1-methyl-5-chloro-1*H*-pyrrole-2,4-dicarbaldehyde **202b** with iminophosphorane **206** is characterized by marked regioselectivity and is realized only with the participation of the formyl group at position 4 of the pyrrole nucleus, leading to ethyl 4-(1-methyl-2-chloro-5-formyl-1*H*-pyrrol-3-yl)-2-methylthieno[3,2-*c*]pyridine-6-carboxylate **207** (**Scheme 55**).[75]



Scheme 55. Synthesis of ethyl 4-(1-methyl-2-chloro-5-formyl-1*H*-pyrrol-3-yl)-2-methylthieno[3,2-*c*]pyridine-6-carboxylate **207** by cyclocondensation of iminophosphorane **206** with 1-methyl-5-chloro-1*H*-pyrrole-2,4-dicarbaldehyde **202b**.

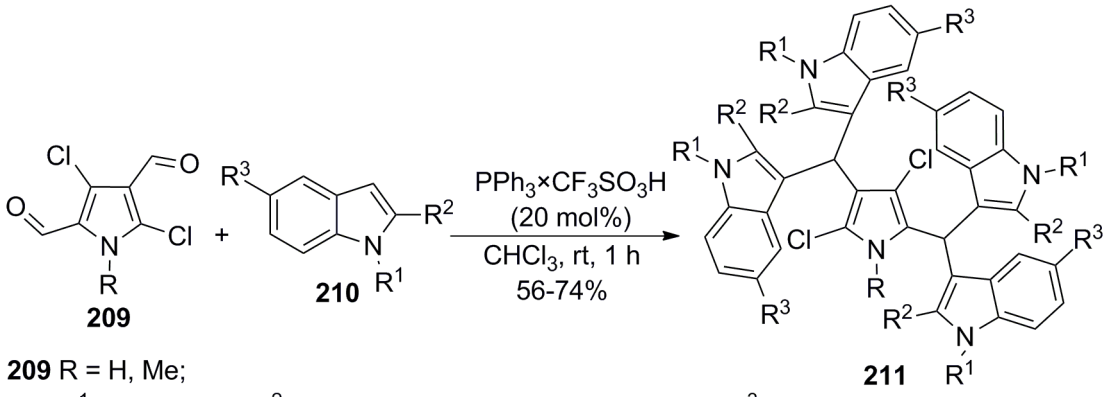
The base-mediated cyclocondensation of *N*-arylpyrrole-2,4-dicarbaldehydes **66** with methyl mercaptoacetate proved to be productive for the synthesis of thieno[2,3-*b*]pyrroles **208** functionalized with formyl group in the pyrrole ring and with ester group in the thiophene nucleus (**Scheme 56**).[76]



R = Ph, R^1 = H, 4-F, 4-Cl, Br; R = thiophen-2-yl, R^1 = 3-Cl-4-F;

Scheme 56. Synthesis of thieno[2,3-*b*]pyrroles **208** by condensation of *N*-arylpyrrole-2,4-dicarbaldehydes **66** with methyl mercaptoacetate.

Heteroaryl di(diindolyl)methanes **211**, promising nucleic acid detectors, were synthesized by the triphenylphosphonium triflate ($PPh_3 \cdot CF_3SO_3H$) catalyzed reaction of 3,5-dichloropyrrole-2,4-dicarbalaldehydes **209** with indoles **210** (**Scheme 57**).[77]

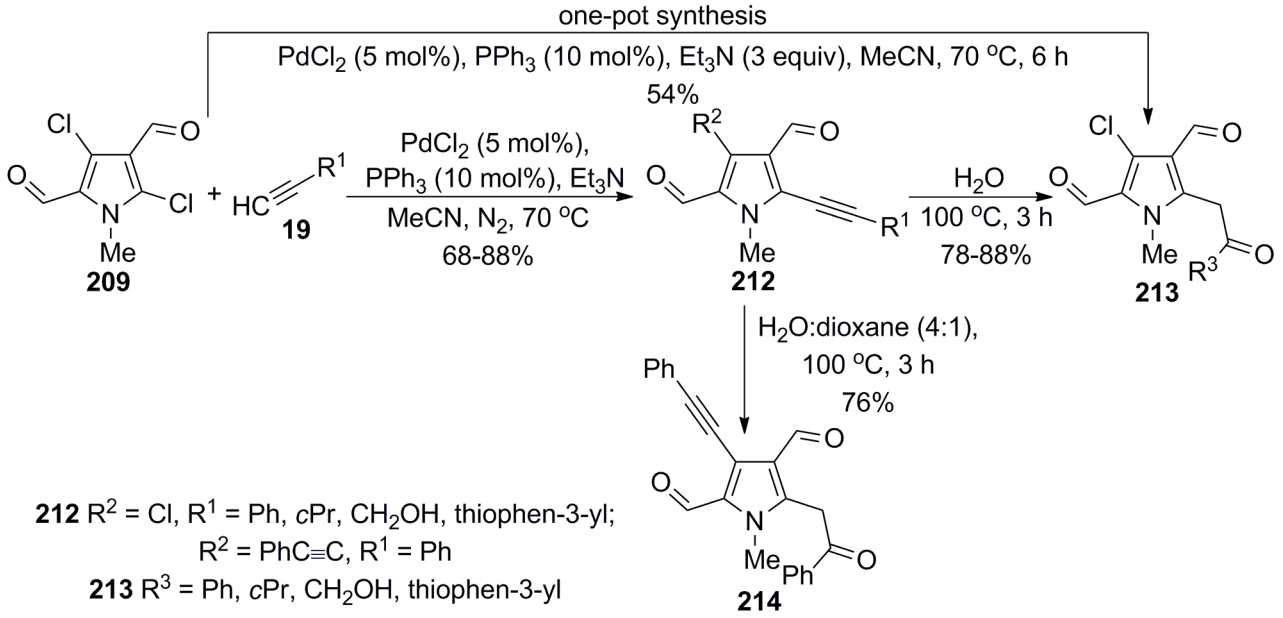


209 R = H, Me;

210 R^1 = H, Me, Bn; R^2 = H, Me, Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$; R^3 = H, Br

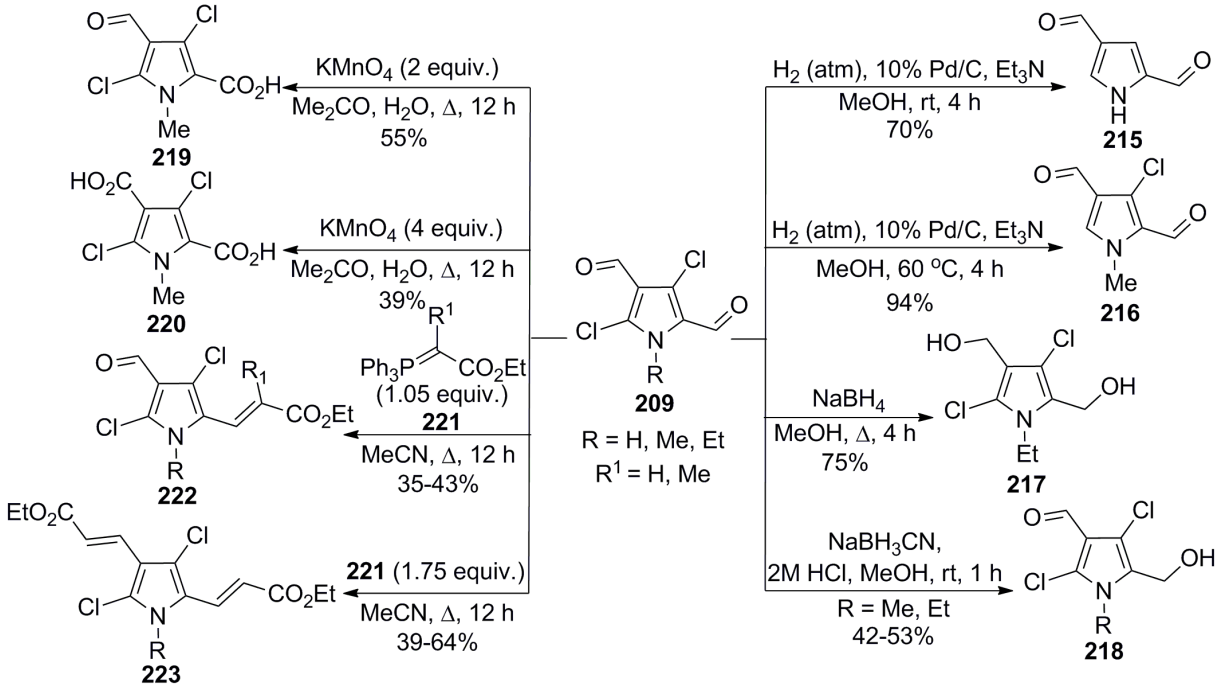
Scheme 57. Synthesis of heteroaryl(diindolyl)methanes **211** by the interaction of 3,5-dichloropyrrole-2,4-dicarbaldehydes **209** with indoles **210**.

3,5-Dichloro-1-methyl-1*H*-pyrrole-2,4-dicarbaldehyde **209** under Sonogashira reaction conditions reacts with terminal alkynes **19** to form mono- and dialkynyl-substituted derivatives **212**. It was found that 5-alkynyl-3-chloropyrrole-2,4-dicarbaldehydes **212**, when boiled in water for 3 h, gave 5-(2-oxo-2-phenylethyl)-3-chloro-1*H*-pyrrole-2,4-dicarbaldehydes **213** which can also be obtained by a one-pot synthesis from dialdehydes **209**. It is characteristic that the hydration of 1-methyl-3,5-bis(phenylethynyl)-1*H*-pyrrole-2,4-dicarbaldehyde **212** under similar reaction conditions is realized only via the 5-alkynyl fragment and leads only to the product **214** (**Scheme 58**).[78]



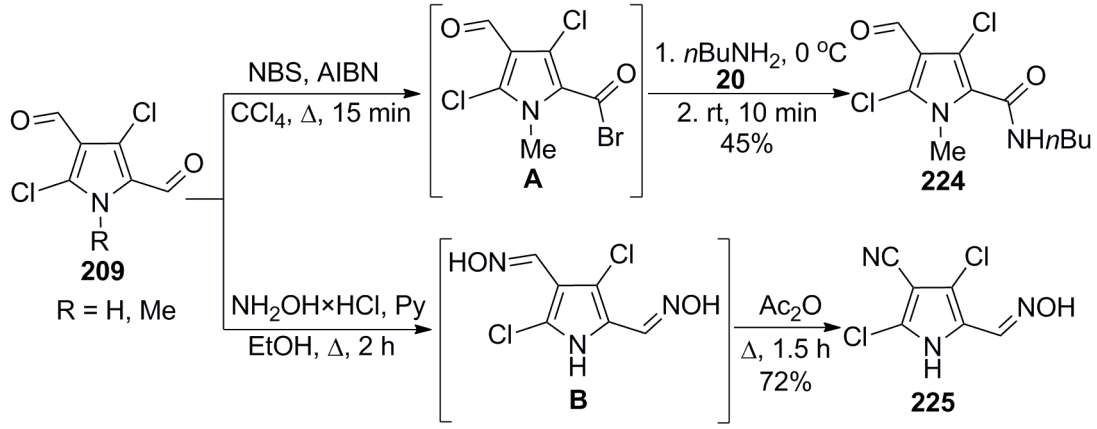
Scheme 58. Synthesis of 5-(2-oxo-2-phenylethyl)-3-chloro(phenylethynyl)-1*H*-pyrrole-2,4-dicarbaldehydes **213** and **214** from 3,5-dichloro-1-methyl-1*H*-pyrrole-2,4-dicarbaldehyde **209**.

3,5-Dichloropyrrole-2,4-dicarboxaldehydes **209** as highly functionalized polyelectrophilic systems have proven to be convenient model objects for studying the chemo- and regioselectivity of reduction, oxidation, and Wittig reactions.[79] For instance, catalytic hydrogenation of 3,5-dichloro-1*H*-pyrrole-2,4-dicarboxaldehyde **209** with hydrogen over Pd/C resulted in complete dechlorination, leading to 1*H*-pyrrole-2,4-dicarboxaldehyde **215**. Instead, 1-methyl-substituted pyrrole **209** underwent selective dehalogenation at C-5 under similar conditions to form 3-chloro derivative **216**. The process of reduction of pyrroles **209** with $NaBH_4$ extends to both aldehyde groups and results in diol **217**. At the same time, selective reduction of the 2-formyl group of **209** is observed under the action of $NaBH_3CN$ at pH 3-4, with the formation of monohydroxymethylpyrrolecarboxaldehydes **218**. Selective oxidation of the 2-formyl group of 1-methyl-substituted pyrrole **209** is observed under the action of 2 equiv. $KMnO_4$, and 4-formylpyrrole-2-carboxylic acid **219** can be obtained. In turn, the use of 4 equiv. $KMnO_4$ is accompanied by the oxidation of both aldehyde groups to dicarboxylic acid **220**. In the Wittig reaction of diformylpyrroles **209**, 1.05 equiv. of phosphorane **221** gave 2-alkenyl derivatives **222**, and 1.75 equiv. led to 2,5-dialkenyl adducts **223** (**Scheme 59**).



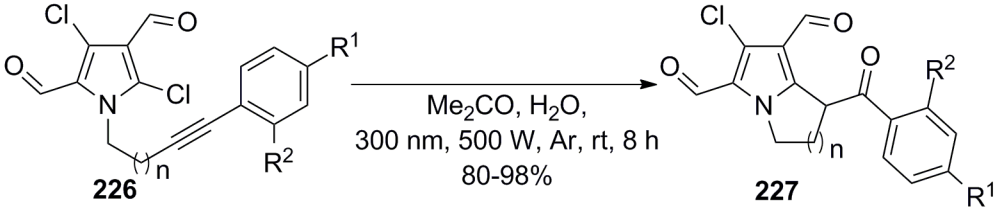
Scheme 59. Synthesis of functionalized pyrroles **215-220, 222, 223** by reduction, oxidation, and Wittig reactions of 3,5-dichloropyrrole-2,4-dicarboxaldehydes **209**.

The synthetic function of 3,5-dichloro-1-methylpyrrole-2,4-dicarboxaldehyde **209** was extended both to the reaction of selective radical bromination of the 2-formyl group, which formed the basis of the one-pot synthesis of amide **224** via intermediate bromide **A**, and to the formation of 4-cyano-2-aldoxime **225** via intermediate bisoxime **B** (**Scheme 60**).[79]



Scheme 60. One-pot synthesis of amide **224** and cyanooxime **225** from 3,5-dichloro-1*H*-pyrrole-2,4-dicarboxaldehyde **209**.

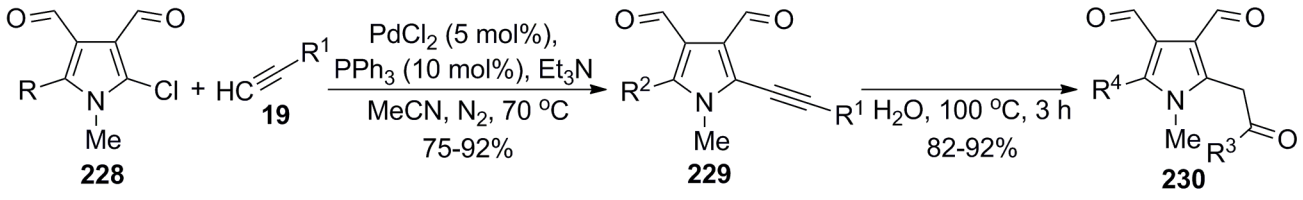
The one-pot synthesis of benzoyl-substituted pyrrolysines and indolysines **227** was realized by a two-step transformation of *N*-(ω-phenylalkynyl)-2-chloropyrrole-3-carbaldehydes **226**, which included photoinduced cyclization with chlorine atom transfer and subsequent photohydrolysis (**Scheme 61**).[80]



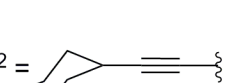
n = 1, $R^1 = R^2 = H$; R^1 = Me, R^2 = H; R^1 = MeO, R^2 = H; R^1 = Cl, R^2 = H;
n = 2, R^1 = MeO, R^2 = H; R^1 = Cl, R^2 = H; R^1 = H, $R^2 = CO_2Me$;

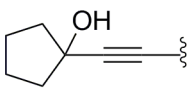
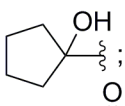
Scheme 61. One-pot synthesis of benzoyl-substituted pyrrolizines and indolizines **227** from *N*-(ω-phenylalkynyl)-2-chloropyrrole-3-carbaldehydes **226**.

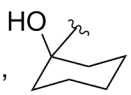
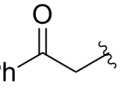
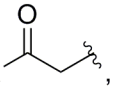
The Sonogashira reaction of chloroaldehydes **228** with terminal alkynes **19** produced 2-alkynylpyrrole-3,4-dialdehydes **229**, the subsequent regioselective hydration of which was used to synthesize 2-oxomethyl derivatives **230** in high yields (**Scheme 62**).[78]

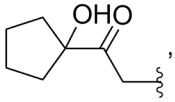
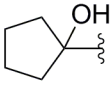


228 R = H, Cl

229 R^2 = H, R^1 = Ph, *c*Pr, thiophen-3-yl, ; R^2 = PhC≡C, R^1 = Ph; R^2 =  , R^1 = *c*Hex;

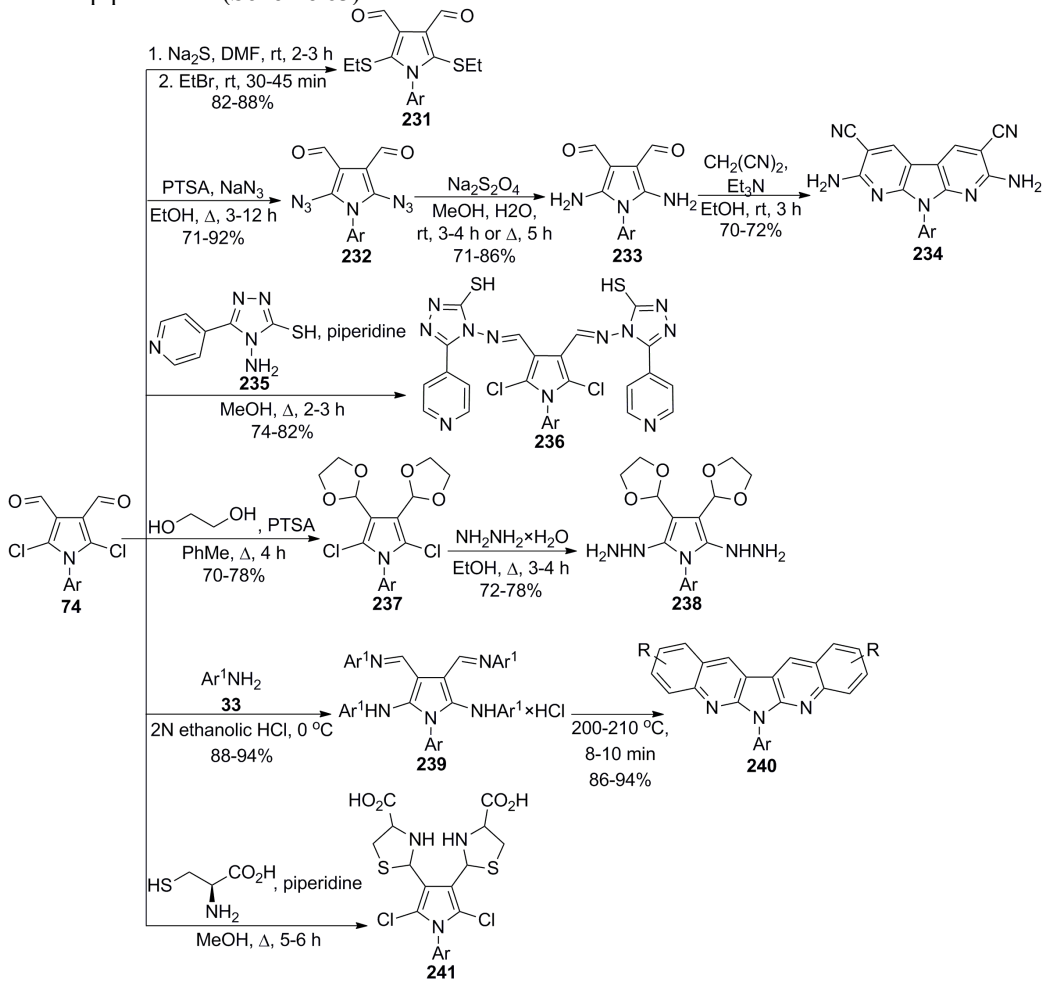
R^2 =  , R^1 =  ; R^2 = Cl, R^1 = Ph, *n*Bu

230 R^4 = H, R^3 = Ph, *c*Pr, thiophen-3-yl,  ; R^4 = Ph  , R^3 = Ph; R^4 = *c*Hex  , R^3 = *c*Hex;

R^4 =  , R^3 =  ; R^4 = Cl, R^3 = Ph, *n*Bu

Scheme 62. Synthesis of 2-oxomethyl-substituted pyrrole-3,4-dicarbaldehydes **230** from 2-chloro- and 2,5-dichloro-1-methyl-1*H*-pyrrole-2,4-dicarbaldehydes **228**.

The synthetic potential of 2,5-dichloropyrrole-3,4-dicarbaldehydes **74** was largely revealed by examples of the preparation of their functionalized and condensed derivatives which are of interest as potential antimicrobial agents. For instance, treatment of pyrroles **74** with Na_2S in DMF and ethyl bromide produced a series of symmetrical thioethers **231**.[50] The corresponding diazides **232** were synthesized by nucleophilic substitution of chlorine atoms, and their reduction yielded 2,5-diaminopyrrole-3,4-dicarbaldehydes **233**. The latter, upon condensation with malononitrile, formed pyrrolo[2,3-*b*:5,4-*b*']dipyridine-3,6-dicarbonitriles **234**.[51,52] The condensation of pyrrole-3,4-dicarbaldehydes **74** with amino-1,2,4-triazole **235** in the presence of a catalytic amount of piperidine in MeOH produced a series of heterocyclic azomethines **236**.[53] Treatment of dicarbaldehydes **74** with ethylene glycol in the presence of PTSA led to dioxolane derivatives **237**, which upon reaction with hydrazine hydrate gave the corresponding 2,5-dihydrazinylpyrroles **238**.[81] The condensation of 2,5-dichloropyrrole-3,4-dicarbaldehyde **74** with excess anilines **33** proceeds easily under mild reaction conditions, forming interesting tetrasubstituted derivatives **239**, which under thermolysis conditions give polycyclic products **240**.[82] A series of *bis*-thiazolidine derivatives **241** were synthesized by cyclocondensation of pyrroles **74** with *L*-cysteine in the presence of catalytic amounts of piperidine[83] (**Scheme 63**).



231 Ar = Ph, 2-ClC_6H_4, 3-$MeOC_6H_4$, 3-ClC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4
232-233 Ar = Ph, 2-ClC_6H_4, 3-$MeOC_6H_4$, 3-ClC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,4-$(Me)_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 3,5-$Cl_2C_6H_3$
234 Ar = 2-ClC_6H_4, 3-$MeOC_6H_4$
236 Ar = Ph, 3-ClC_6H_4, 3-$NO_2C_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4
237 Ar = Ph, 3-ClC_6H_4, 3-$OMeC_6H_4$, 4-ClC_6H_4
238 R = 3-ClC_6H_4, 4-ClC_6H_4
239 Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4; Ar^1 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4
240 Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4; R = Me, MeO, Cl
241 Ar = Ph, 3-$NO_2C_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4

Scheme 63. Synthesis of functionalized and condensed pyrroles **231-234, 236-241** from 2,5-dichloropyrrole-3,4-dicarbaldehydes **74** using nucleophilic substitution, condensation and cyclocondensation reactions.

4. Conclusions

Analysis, systematization, and generalization of literature sources demonstrated that multicomponent one-pot approaches to their preparation have become widespread in recent years, along with halogenation or formylation of the pyrrole nucleus as traditional methods for the synthesis of halogenated formyl- and diformylpyrroles. These functional pyrrole derivatives,

due to the presence of several electrophilic centers, are highly reactive structures, characterized by powerful synthetic potential, especially in Pd-catalyzed cross-coupling reactions, and are valuable templates for the construction of analogues of natural compounds and potential bioactive substances.

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