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Substituted pyrroles derived from ketones: application prospects and advances in synthesis

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The review addresses the applications of pyrroles and compounds based on them in pharmaceutics and various branches of technology in which pyrrole plays a key role. The emphasis is put on the studies that were not covered in the previous reviews. The second part of the review summarizes the published data of the last 15 years on the synthesis of pyrroles from widely encountered carbonyl compounds, which were chosen because of ready availability and the possibility of varying the substituents. This type of systematization is proposed for the first time.
The bibliography includes 199 references.
Keywords: ketones, ketoximes, monocarbonyl compounds, dicarbonyl compounds, acetylene, activated acetylene, pyrrole, substituted pyrroles.

Contents

1. Introduction

Pyrroles and their derivatives have been studied for more than a century in a variety of aspects, including methods of synthesis and diverse applications. The results of these studies are covered fairly comprehensively in monographs[1–5] that have already become classic and in reviews.[6–15]

After the appearance of the latest publications summarizing various issues of the structure, synthesis, reactivity and applications of pyrroles, quite a number of new studies appeared in this field, including numerous reviews (references to some recent reviews are given).[16–22] This attests to ever increasing interest in the extensive use of pyrrole derivatives in both medicinal chemistry and the chemistry of novel materials. Therefore, methods for the construction of pyrrole ring from readily available and cheap reactants come to the forefront. Most of recent reviews are focused either on applications of pyrrole derivatives in particular high-technology industry branches: as biologically active compounds,[16,17,19–21] ligands for metal complexes for various applications, parts of electronic systems, *etc*., or on particular methods of assembly of various classes of pyrrole systems.[18,22]

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The present review addresses the application of pyrroles and pyrrole-based compounds in pharmaceutics and various branches of technology in which pyrrole plays a key role, with the focus being placed on the studies that have not been included in the reviews mentioned above. The second part of the review integrates the results published over the last 15 years on the development and application of various approaches to pyrrole synthesis from widely encountered carbonyl compounds. This type of systematization has not been proposed before. Carbonyl compounds were chosen because of their ready availability and the possibility of varying the substituents. The latter may be challenging, as different applications bring about different requirements to the substituents. That is why this review is not arranged in the usual manner starting with the synthesis, which is followed by applications, but is arranged in the opposite order, since the fields of application dictate which substituents need to be introduced. This conceptually changes the subordination of goals.

Analysis of the most recent data indicates that together with improvement of the traditional methods for pyrrole synthesis, there is search for original, industrially applicable reactions that would allow the preparation of pyrroles from available starting compounds. In particular, the reaction of ketones (*via* ketoximes) with acetylene in the KOH/DMSO superbasic system, known as the Trofimov reaction, and intramolecular cyclization of carbonyl compounds are being actively studied.

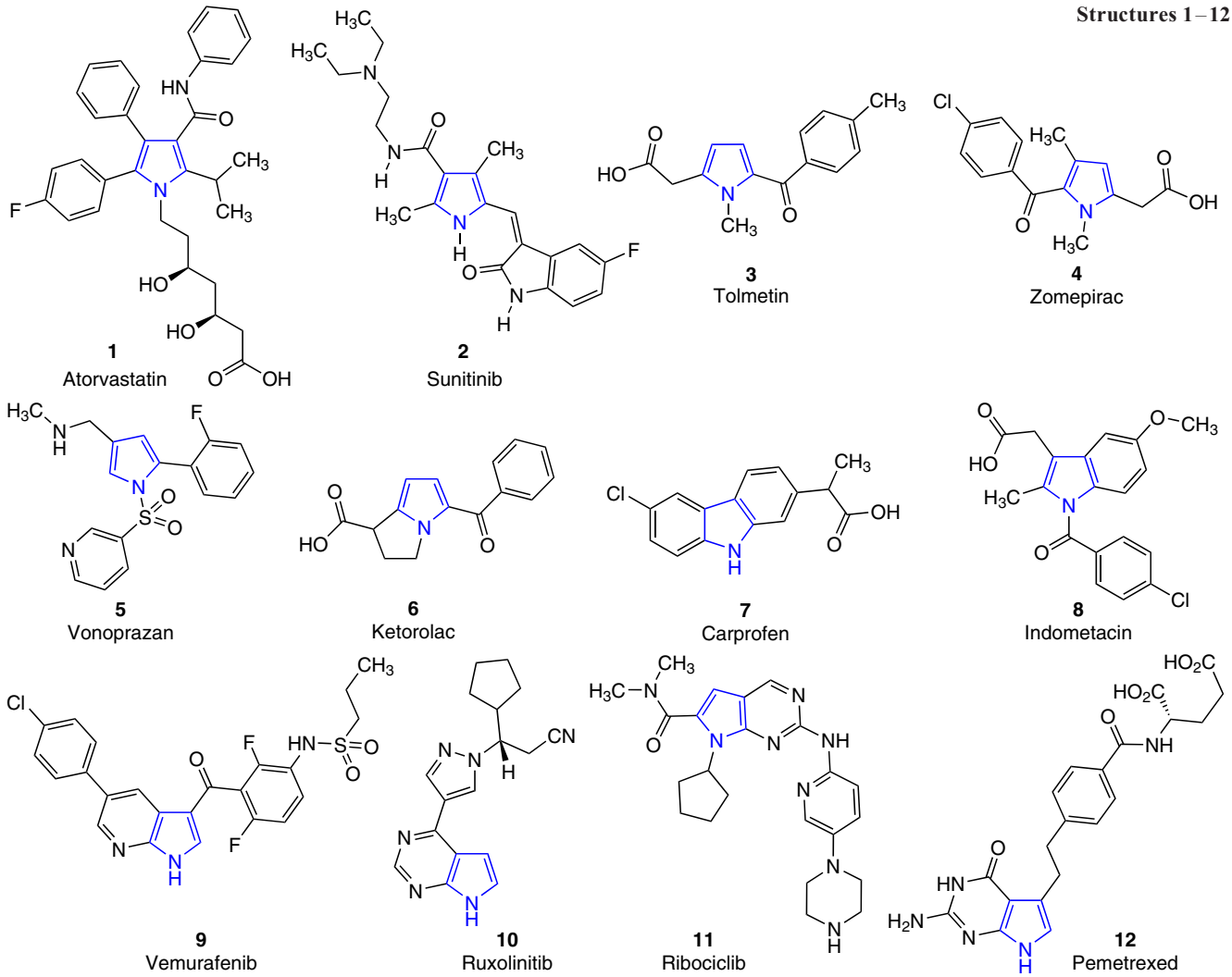
2. Modern pyrrole-based medicinal agents

The antihyperlipidemic drug atorvastatin **1**,[23] which is used to reduce the cholesterol level in blood and, hence, to decrease the cardiovascular risk, is currently one of the best selling drugs on the pharmaceutical market all over the world. Combinations of atorvastatin with acetylsalicylic acid are used to combat the SARS-Cov-2 infection.[24] Sunitinib **2**, effective for the treatment of the renal cell cancer and stromal tumours,[25] and tolmetin **3**[26] and zomepirac **4**,[27] which possess anti-inflammatory, antipyretic, and analgesic properties and are widely used to treat rheumatoid arthritis, are other well-known pyrrole-based drug.

More examples of pyrrole-based drugs include vonoprazan **5**, a potassium-competitive blocker of hydrochloric acid secretion used for the therapy of acid-dependent diseases of gastrointestinal tract;[28] ketorolac **6**, a non-steroidal anti-inflammatory analgesic drug used to treat rheumatoid arthritis, post-surgery pain, osteoarthritis, menstrual disorders and spondylitis;[29] and carprofen **7**, effective for the therapy of arthritis (currently, only in animals),[30] in which a pyrrole ring is annulated with two benzene rings. Indometacin **8**, derivative of indolylacetic acid, has anti-inflammatory, analgesic and antipyretic activities.[31]

A number of anticancer drugs have been developed on the basis of pyrroles fused with nitrogen heterocycles. They are used, in particular, for the therapy of late stages of melanoma (vemurafenib **9**),[32] myelofibrosis (ruxolinitib **10**),[33] breast

Structures 1–12



cancer (ribociclib **11**),[34] and non-small cells lung cancer (pemetrexed) **12**,[35,36] sold under the brand name Alimta.

3. Biological potential of natural and synthetic pyrrole derivatives

The previous Section deals with pyrrole derivatives that have already been approved as medicinal agents. However, researchers throughout the world continue investigation of the biological activity of new pyrrole compounds and known compounds in relation to new targets. This Section summarizes the information about pyrroles that are at various phases of preclinical and clinical trials and demonstrates that the appearance of conceptually new medicinal agents based on pyrrole derivatives may be expected in the near future.

3.1. Antimicrobial and fungicidal activity

Today, tuberculosis is a highly serious menace to human health. It was also noticed that tuberculosis pathology in immunocompromised patients is often accompanied by various fungal infections. This is why the development of new antimicrobial drugs, including tuberculostatic agents, and also fungicidal drugs is the focus of attention of scientists throughout the world.

Since 1998, when 1-[(1,5-bis(4-chlorophenyl)pyrrol-3-yl)-methyl]-4-methylpiperazine (BM 212) (compound **13**), a 1,5-diarylpyrrole derivative, was found[37] to exhibit a strong inhibitory activity against both *Mycobacterium tuberculosis* (MBT) and some drug-resistant nontuberculous mycobacteria, analogues of this compound have been actively investigated as anti-tuberculosis drugs. Among the extensive series of 1,2-diarylpyrroles with various substituents in positions 1 and 5 of the pyrrole ring, there are compounds that are much more active against MBT than BM 212, isoniazid, streptomycin or rifampicin.[38,39] One of these compounds (compound **14**) has a minimum inhibitory concentration (MIC) of 0.4 μg mL^{-1} (it is lower than MICs of BM 212 or streptomycin) and a protective index of 160, which exceeds this value for BM 212, isoniazid or streptomycin.[39]

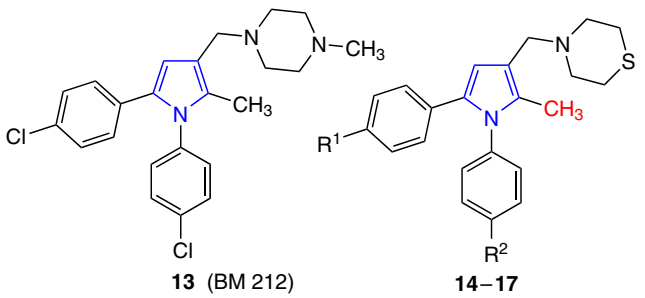
The effect of lipophilicity of substituents on the antituberculosis activity was evaluated for 15 new compounds with various substituents in the pyrrole and benzene rings.[40] It was found that higher activity is inherent in lipophilic pyrroles. The most active derivatives in this series are characterized by MICs ranging from 0.125 to 0.5 μg mL^{-1} and protective indices of 64–256 (compounds **15**, **16**). The search for active tuberculostatics in this series was continued, and one more highly active compound with MIC = 0.25 μg mL^{-1} and a protective index of more than 256 was discovered in 2006 (compound **17**).[41]

A number of analogues of compound BM 212 containing an ethyl group instead of methyl in position 2 of the pyrrole ring (compounds **18**) also proved to be good tuberculostatic agents. Most active among these derivatives is 2-ethyl-1-(4-fluorophenyl)-3-(thiomorpholin-4-yl)methyl-5-(4-methylphenyl)pyrrole (**18**, R^1 = Me, R^2 = 4-F), which has the same MIC as the methyl analogue, compound **14** (0.25 μg mL^{-1}), but a markedly higher protective index (>512), because of the low cytotoxicity exceeding 128 mg mL^{-1}.[42] This compound is also very active against MTB $H_{37}Rv$ and rifampicin-resistant MTB strains; the minimum inhibitory concentration of this compound is 0.25 μg mL^{-1} for both strains.

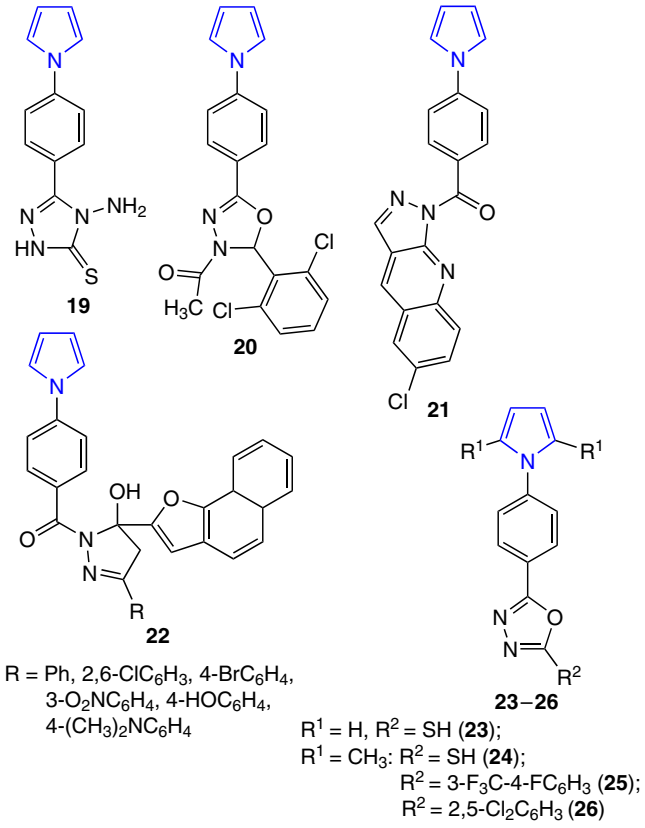
Joshi *et al.*[43–48] prepared a series of compounds **19**–**23**, in which the pyrrole ring is linked to various heterocycles (oxadiazole, triazole, pyrazolo[3,4-*b*]quinoline, naphtha[2,1-*b*]-furan, thiadiazole) through a phenyl bridge; the compounds exhibited good antituberculosis and antimicrobial properties.[43–48] In particular, pyrrolyloxadiazoles **24**–**26** showed a high antimicrobial activity (MIC = 1–4 mg mL^{-1}); some of them suppress the *Mycobacterium tuberculosis* $H_{37}Rv$ strain in a concentration of 1–2 mg mL^{-1}.[44]

Hybrid molecules with an inverted sequence of the rings, that is, directly linked pyrrole and thiadiazole rings with aryl substituents, inhibit *Mycobacterium tuberculosis* $H_{37}Rv$ less efficiently: out of 20 studied thiadiazoles, only three

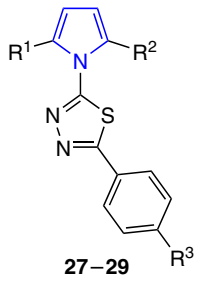
Structures 13–18



Structures 19–26

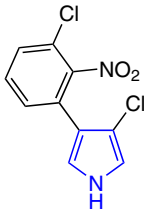


Structures 27–32

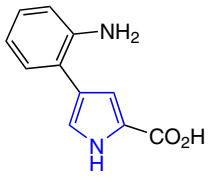


27–29

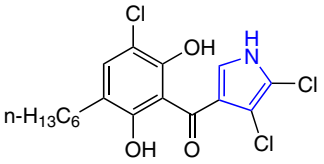
$R^1 = R^2 = H$, $R^3 = OCH_3$ (**27**);
$R^1 = R^2 = CH_3$, $R^3 = OCH_3$ (**28**);
$R^1–R^2 = CH_3$, $R^3 = NO_2$ (**29**)



30
Pyrrolnitrin



31
Banegasine



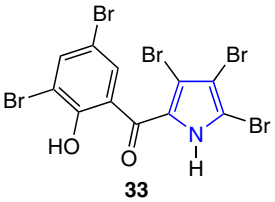
32
Celastramycin A

compounds are characterized by MIC = 12.5 (structures **27**–**29**).[43]

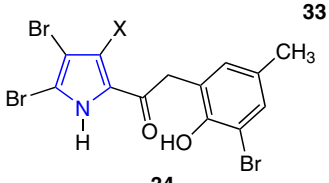
The antimicrobial activity is inherent in not only synthetic, but also natural pyrrole-based compounds. For example, the well-known antibiotics pyrrolnitrin **30** and banegasine **31**, which were isolated from the *Aristabacter necator* animal bacteria, efficiently inhibit the growth of *Mycobacterium smegmatis* [MIC > 0.5 μg mL^{-1} (**30**) and 0.3 μg mL^{-1} (**31**)]. When these compounds are used together, a synergistic increase in the activity is observed (for a **30**+**31** mixture, MIC = 0.075 μg mL^{-1}). The antibiotic celastramycin A **32**, which is a dichloropyrrole derivative, possesses a broad range of antimycobacterial activity (MIC = 0.05–3.1 μg mL^{-1} against *Mycobacterium smegmatis*, *Mycobacterium aurum*, *Mycobacterium vaccae* and *Mycobacterium fortuitum*).[49]

3,4,5,3′,5′-Pentabromo-2-(2′-hydroxybenzoyl)pyrrole **33** is a synthetic analogue of pyrrolomycin highly active against a number of gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus agalactiae*, *Listeria monocytogenes*, *Bacillus subtilis*): MIC values are in the range from 0.002 to 0.097 mg L^{-1} for all of the tested strains.[50] The introduction of the keto or methylene spacer between the phenyl group and the pyrrole ring in compound **33** (*e.g.*, compounds **34** and **35**) decreases the antibacterial activity against *Escherichia coli* and *Bacillus subtilis*.[51,52]

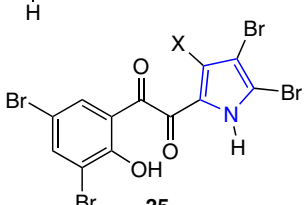
Structures 33–35



33



34

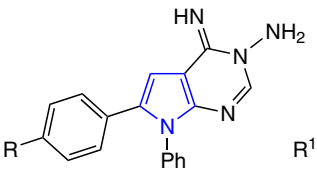


35

X = H, Br

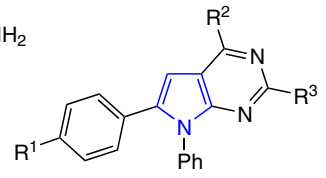
Study of the antimicrobial activities of a number of pyrrolopyrimidines against a variety of gram-positive and gram-negative bacteria and fungi revealed compounds **36** and **38**, which inhibit *Staphylococcus aureus* much more efficiently (MIC = 0.31 mg mL^{-1}) than ampicillin (MIC = 0.62 mg mL^{-1}), and compounds **37**, **39** and **40**, exhibiting antifungal activity against *Candida albicans* (MIC = 0.31–0.62 mg mL^{-1}) exceeding the activity of fluconazole (MIC = 1.5 mg mL^{-1}).[53]

Structures 36–40



36, **37**

R = Br, Cl (**36**);
R = H, CH_3, F (**37**)



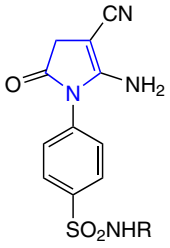
38–40

R^1 = F, R^2 = $NHNH_2$, R^3 = H (**38**);
R^1 = H, R^2 = $NHNH_2$, R^3 = H (**39**);
R^1 = CH_3, R^2 = NH_2, R^3 = NH_2 (**40**)

The fungicidal activity of some pyrroles **41**–**44** and pyrrolo[2,3-*d*]pyrimidines **45** containing a sulfonamide group against *Aspergillus ochraceus*, *Penicillium chrysogenum*, *Aspergillus fleavus* and *Candida albicans* is close to the activity of the known fungicide mycostatine (84.2–89.5%).[54]

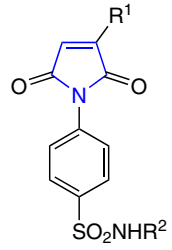
A series of 2,5-bis(guanidinoaryl)-*N*-methylpyrroles with pronounced antifungal properties have been synthesized.[55] Among them, mention should be made of pyrrole **46** (R^1 = 2-Cl, R^2 = H), which shows activity comparable with that of fluconazole. Meanwhile, compound **46** (R^1 = 2-CH_3, R^2 = H) is more active against most of tested strains than fluconazole.

Structures 41–46



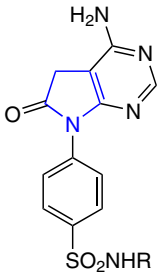
41

R is 2-pyridinyl



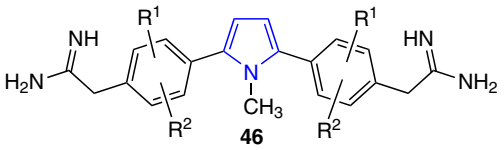
42–44

42: R^1 = CN,
R^2 is 2-pyridinyl;
43: R^1 = $COCH_3$,
R^2 is 2-pyridinyl;
44: R^1 = $COCH_3$,
R^2 = 2-(4-CH_3-pyridinyl)



45

R is 2-pyrimidinyl



46

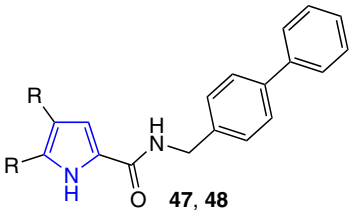
R^1 = H, 2-CH_3, 2-OCH_3, 2-Cl, 3-CF_3, 4-F, 4-Cl;
R^2 = H, 4-F

3.2. Anticarcinogenic activity

Cancer is one of the most serious health problems in the world, being the second most frequent cause of death. Therefore, search for new efficient anticarcinogenic agents is continuously in progress. The recent advances in the application of highly active and selective cytotoxic molecules containing a pyrrole ring showed good prospects of further research along this line.

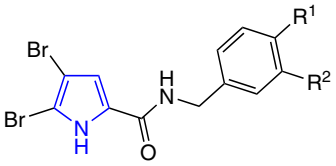
Thus 30 analogues of the natural alkaloid oroidin have been synthesized and screened for the activity against 20 cancer cell lines. As a result, a number of promising cytotoxic compounds

Structures 47–59



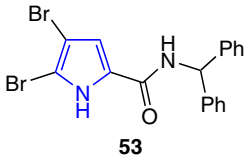
47, **48**

R = H (**47**), Br (**48**)

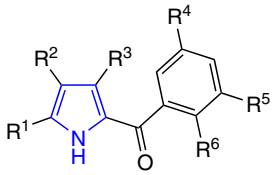


49–52

$R^1 = R^2 = H$ (**49**);
$R^1 = Cl$; $R^2 = H$ (**50**);
$R^1 = R^2 = Cl$ (**51**);
$R^1 = OH$; $R^2 = H$ (**52**)



53



54–59

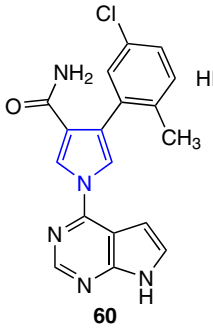
$R^1 = R^2 = R^4 = R^5 = Cl$, $R^3 = H$, $R^6 = OH$ (**54**);
$R^1 = R^2 = R^3 = R^4 = R^5 = Br$, $R^6 = OH$ (**55**);
$R^1 = H$, $R^2 = NO_2$, $R^3 = H$, $R^4 = R^5 = Cl$, $R^6 = OH$ (**56**);
$R^1 = NO_2$, $R^2 = Cl$, $R^3 = H$, $R^4 = R^5 = Cl$, $R^6 = OH$ (**57**);
$R^1 = NO_2$, $R^2 = Br$, $R^3 = H$, $R^4 = R^5 = Cl$, $R^6 = OH$ (**58**);
$R^1 = R^2 = Cl$, $R^3 = NO_2$, $R^4 = R^5 = Cl$, $R^6 = OH$ (**59**)

were identified, particularly pyrroles **47**–**53**. Compounds of this class, especially pyrrole **48**, are most efficient for the treatment of colon cancer.[56]

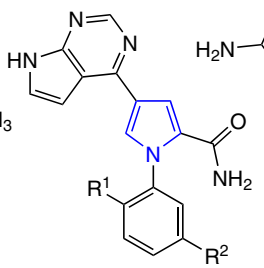
It is known that apart from antimicrobial activity, polyhalo-substituted natural antibiotic pyrrolomycin **54** and its pentabrominated analogue **55**, show anticarcinogenic properties. The introduction of the nitro group into various positions of the pyrrole ring in **54** enhances the anticarcinogenic activity: compounds **56**–**59** (particularly compounds **56** and **59**) effectively inhibit the growth of colon cancer (HCT116) and breast cancer (MCF 7) cells and, what is more important, they are less toxic against normal epithelial cells (hTERT RPE-1) than natural pyrrolomycins.[57]

Pyrrolecarboxamide derivatives **60**–**67** exhibit good antiproliferative activity and low cytotoxicity against target cells. Among these compounds, most promising is pyrrole **64**, a potent JAK2 inhibitor suitable for oral administration, which efficiently inhibits the tumour growth in the SET-2 ovarian tumour xenograft model.[58]

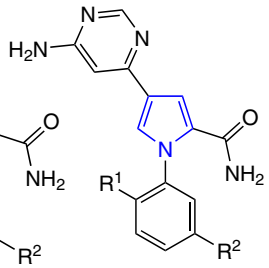
Structures 60–67



60



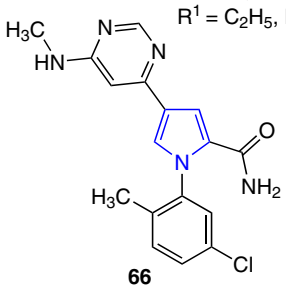
61–63



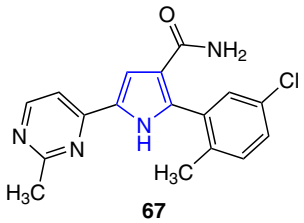
64, **65**

$R^1 = CH_3$, $R^2 = Cl$ (**61**);
$R^1 = Br$, $R^2 = Cl$ (**62**);
$R^1 = C_2H_5$, $R^2 = Cl$ (**63**)

$R^1 = CH_3$, $R^2 = Cl$ (**64**);
$R^1 = C_2H_5$, $R^2 = Cl$ (**65**)



66

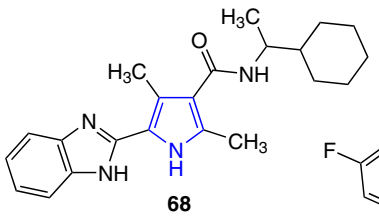


67

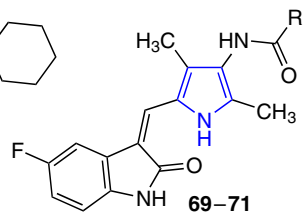
Benzimidazole-substituted 2,4-dimethylpyrrole-3-carboxamide **68** efficiently (62.46%) inhibits the growth of MDA-MB-435 melanoma cells in the concentration of 10 μM.[59]

Some sunitinib analogues, for example indolin-2-ones **69**–**71**, have an excellent anticancer activity (in *in vitro* assays). Studies carried out *in vivo* demonstrated that the most active compound **71** considerably inhibits the tumour growth in the HT-29 colon adenocarcinoma and NCI-H460 non-small cell lung cancer xenografts without causing a significant loss of body weight. The same compound effectively inhibits various types of kinases (enzymes catalyzing the transfer of the phosphate group from the ATP molecule to various substrates) such as VEGFR-2, VEGFR-3, FLT3, Ret and PDGFR-b.[60]

Structures 68–71



68

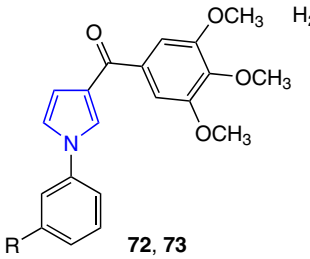


69–71

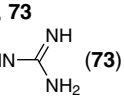
R = $(CH_2)_2N(CH_3)_2$ (**69**),
4-CH_3-(1-piperazinyl) (**70**),
$(CH_2)_2$-(1-piperazinyl)-CH_3-4 (**71**)

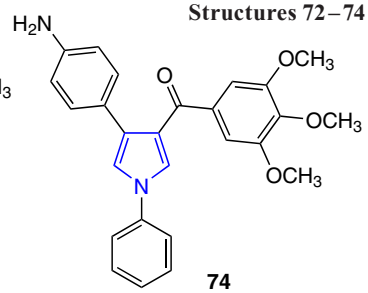
Silvestri and co-workers[61] obtained a series of 1-aryl-3-aroylpyrroles as potential anticancer agents. In the authors' opinion, the N-phenyl substituent and the trimethoxyphenylcarbonyl moiety are necessary to attain a potent inhibition of tubulin polymerization, binding of colchicine to tubulin and cancer cell growth. Indeed, studies demonstrated that pyrroles **72** and **73** can efficiently inhibit tubulin polymerization and cancer cell growth and have a potential for inhibiting the Hedgehog signalling pathway. Later, the range of potentially anticancer 1-aryl-3-aroylpyrroles was expanded by inclusion of representatives with various substituents in positions 1 and 4 of the benzene rings.[62] All of the synthesized compounds **72**–**74** can inhibit, to some extent, tubulin polymerization, binding of

Structures 72–74



72, **73**

R = NH_2 (**72**),  (**73**)



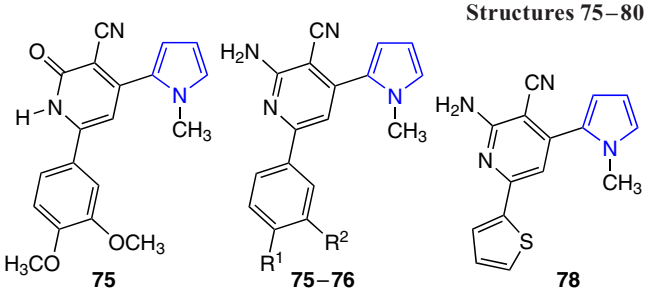
74

colchicine to tubulin and cancer cell growth. The most active pyrrole **74** can be considered as the lead compound for the development of a drug for the treatment of chronic myeloid leukemia patients.

The anticarcinogenic properties of a number of pyrrolylpyridines, including bi-, tri and tetracyclic compounds have been studied; all of the compounds were found to exhibit some anticancer activity.[63] 2-Aminopyridine-3-carbonitrile derivatives **76**–**78**, especially compound **77**, were most efficient among this series. Furthermore, compounds **75** and **77** showed a clear-cut antioxidant activity.

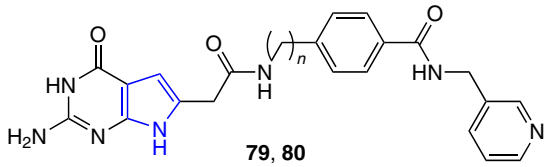
2-Amino-4-oxo-6-substituted pyrrolo[2,3-*d*]pyrimidines **79** and **80** show a considerable antiproliferative activity against a number of cancer cell lines, including nasopharyngeal epidermoid carcinoma (KB), lung cancer (A549) and hepatocellular carcinoma (HepG2). Compound **80**, which is most active among them, can be considered as the lead structure for the subsequent structure optimization.[64]

Structures 75–80



75 **75–76** **78**

$R^1 = R^2 = H$ (**76**);
$R^1 = R^2 = OCH_3$ (**77**)

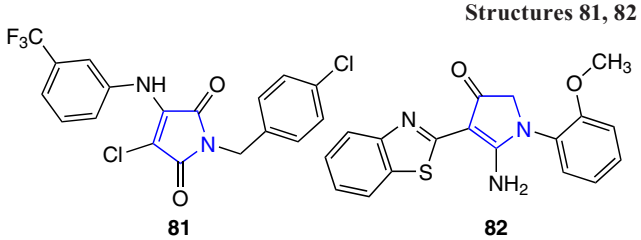


79, **80**

n = 0 (**79**), 1 (**80**)

It was proposed[65] that pyrrole derivatives, 1*H*-pyrrole-2,5-dione **81** and 3*H*-pyrrol-3-one **82**, which possess anti-inflammatory, apoptotic and antitumor activities, can be used as competitive inhibitors of EGFR and VEGFR and as antioxidants.

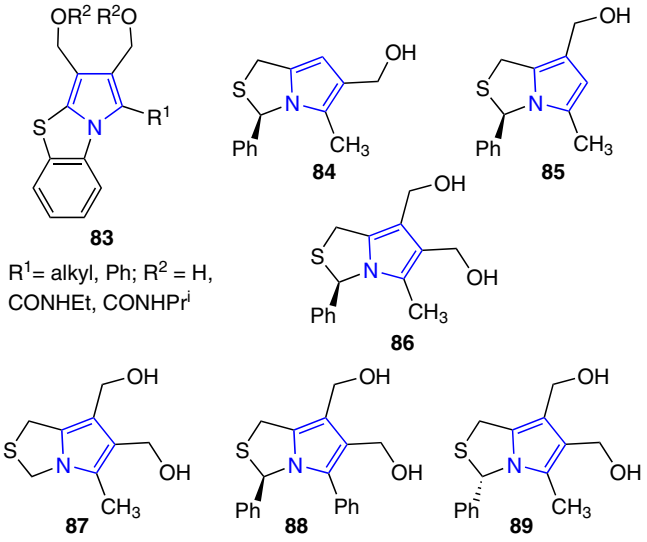
Structures 81, 82



81 **82**

Soares *et al.*[66] investigated the activity of a few hydroxymethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **83**–**89** against breast cancer (MCF7) and established the effect of substituents on their efficiency.[66] (3*R*)-6,7-Bis(hydroxymethyl)-5-methyl-3-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **86** was chosen as the lead compound owing to its high activity (IC_{50} = 1.0 μM). The results of studying the activity *in vitro* showed that a phenyl group at C(3) and a methyl group at C(5) in the pyrrolothiazole system are necessary for attaining a high efficiency. The enantiomer of pyrrolothiazole **86**, (3S)-6,7-bis(hydroxymethyl)-5-methyl-3-phenyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **89**, proved to be the compound of choice in this series (IC_{50} = 0.5 μM).

Structures 83–89



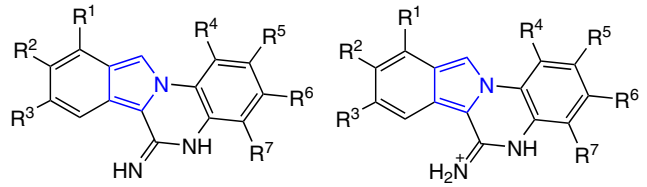
83

R^1= alkyl, Ph; R^2 = H, CONHEt, CONHPr^i

84 **85** **86** **87** **88** **89**

Water-soluble isoindoloquinoxaline imines **90** and corresponding acetates **91**, containing a pyrrole ring in the molecule, have anti-proliferative activity against 60 human cancer cell lines, with the activity of some of them being manifested at a nanomolar level.[67] Compounds with substituents in positions 3 and 8 and/or 9 are especially efficient in impairing cell cycle progression and inducing apoptosis in cancer cells. These effects are associated with disruption of tubulin polymerization at pharmacologically significant concentrations of the test compounds. In addition, impaired DNA topoisomerase function and telomere architecture were found in the cells treated with pyrroles **90** and **91** in micromolar concentrations.

Structures 90, 91



90 **91**

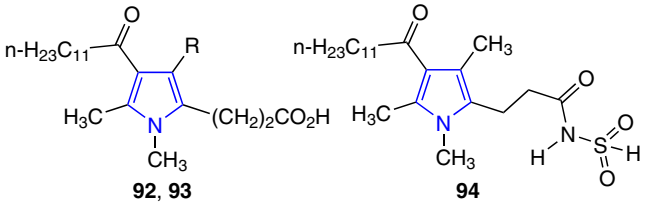
R^1 = H, F; R^2, R^3 = H, CH_3, OCH_3; R^4 = H, OCH_3; R^5 = H, CH_3, OCH_3, Cl; R^6 = H, CH_3, OCH_3, OH, Cl; R^7 = H, CH_3, OCH_3

Recent studies considering the prospects of using pyrrole derivatives as inhibitors of tyrosine kinase receptors, cytochrome P450, NF–Y and ICB2 interactions, hypoxia-inducible factors, modulators of Bcl-2 family members and microtubule polymerization-targeting agents are considered in reviews.[68,69]

3.3. Anti-inflammatory activity

It was shown that 3-(4-dodecanoyl-1,3,5-trimethylpyrrol-2-yl)-propionic acid **92** is a submicromolar inhibitor (IC_{50} = 0.14 μM) of microsomal prostaglandin E2 synthase 1 (mPGES-1),[70] which is an enzyme induced in inflammatory processes. Changes in the structure of this lead compound have only a minor effect on its inhibitory properties. In the presence of a detergent, Triton X-100, the inhibitory activity of pyrroles disappears. For example, pyrroles **93** and **94**, which show activity with IC_{50} concentrations from 0.1 to 1 μM, became completely inert even in a much higher concentration (10 μM) when 0.1% detergent

Structures 92–94



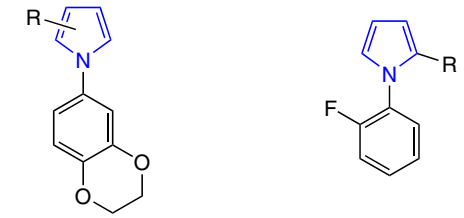
92, **93** **94**

R = CH_3 (**92**), Ph (**93**)

was added. Thus, compounds **92**–**94** are prostaglandin inhibitors and, hence, potential anti-inflammatory agents.

Pyrrolecarboxylic acids **95**–**100** (especially compounds **96** and **100**) possess [71] higher anti-inflammatory activity *in vivo* and *in vitro* than the known anti-inflammatory agent ibuprofen, the action of which is due to inhibition of prostaglandin synthesis. For example, the inhibitory activity of pyrrole **96** (IC_{50} = 5.8 μM) is 17 times as high as that of ibuprofen. Similarly, pyrrole **100** with a potential anti-3α-HSD enzymatic activity (IC_{50} = 34 μM) inhibits carrageenan-induced edema more efficiently than ibuprofen does. In addition, its activity is retained for more than four hours, whereas the activity of ibuprofen rapidly decreases. According to preliminary data on COX-1 and COX-2 enzyme inhibition *in vitro*, pyrroles **99** and **100** have moderate selectivity to COX-2 (COX-2/COX-1 = 3.2 and 4.4 for pyrroles **99** and **100**, respectively).

Structures 95–100



95–**97** **98**–**100**

R = 2-$COCO_2H$ (**95**), 2-CH_2CO_2H (**96**), 3-CH_2CO_2H (**97**)

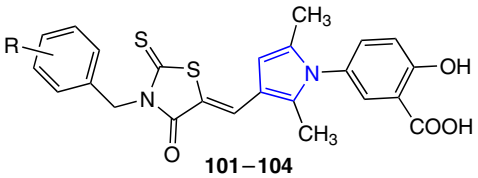
R = CH_2CO_2H (**98**), $COCO_2H$ (**99**); Ac (**100**)

3.4. Antiviral activity

The acquired immunodeficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV) and is a global health care problem. Therefore, the search for new antiviral agents, including those based on the pyrrole ring, is constantly in progress. The pyrrole ring is present in a few compounds possessing antiretroviral activity (*e.g.*, remdesivir). A recent review [72] covers publications (from 2015 to 2020) that describe pyrrole derivatives with anti-HIV activity as new potential drugs for the treatment of AIDS.

It was shown that 3-substituted *N*-(3-carboxy-4-hydroxy) phenyl-2,5-dimethylpyrroles **101**–**103** efficiently inhibit

Structures 101–104



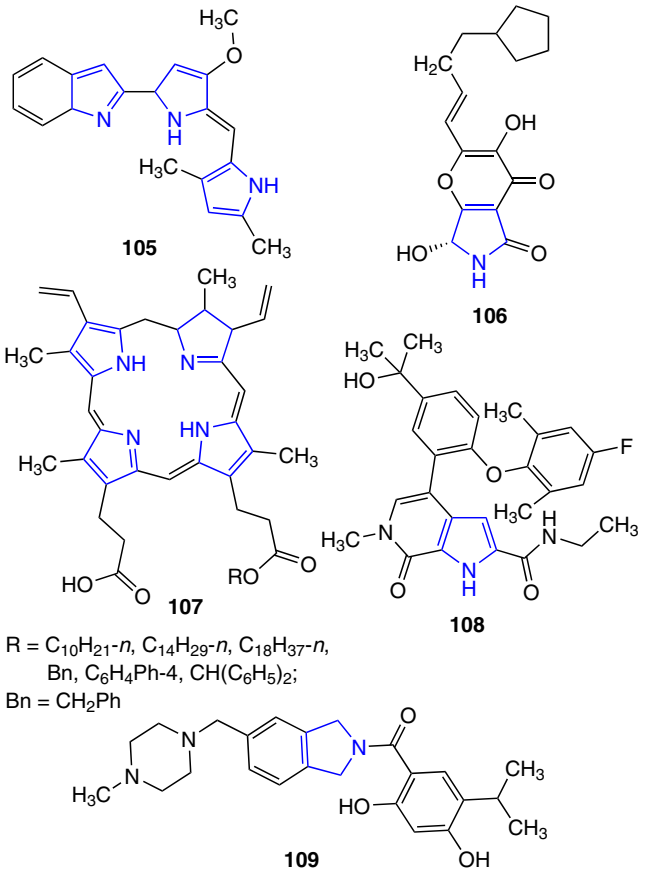
101–**104**

R = 4-CO_2CH_3 (**101**), 4-Bu^t (**102**), 3-CO_2CH_3 (**103**), 2-CF_3 (**104**)

(IC_{50} = 1.8–2.6 μM) the formation of the HIV-1 gp41 recombinant antigen and suppress the replication of HIV-1 in MT-2 cells (EC_{50} = 0.3–1.5 μM).[73] In addition, they are equally efficient against both T20-sensitive and -resistant strains. Later, one more compound of this class, pyrrole **104**, was obtained. Compound **104** showed a good inhibitory activity against infection with primary and drug-resistant HIV-1 strains, including X4, R5, and X4R5 strains with EC_{50} from 2.03 to 6.85 μM.[74]

The coronavirus (COVID-19) pandemic caused by the new SARS-CoV-2 virus has become a real problem for the whole world. According to published data, the SARS-CoV-2 main protease is an attractive target for the drugs that prevent virus replication and transcription. The *in vivo* screening of more than 136 antiviral agents in the cells resulted in the identification of structures **105**–**109** effective against SARS-CoV-2.[75–79]

Structures 105–109



105 **106** **107** **108**

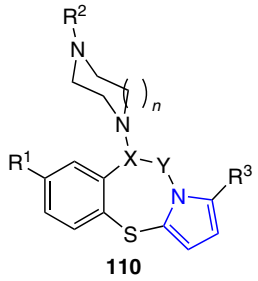
R = $C_{10}H_{21}$-*n*, $C_{14}H_{29}$-*n*, $C_{18}H_{37}$-*n*, Bn, C_6H_4Ph-4, $CH(C_6H_5)_2$;
Bn = CH_2Ph

109

3.5. Antipsychotic activity

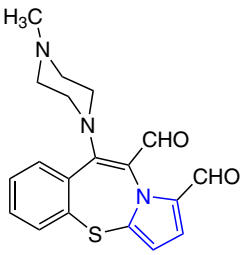
A study of a group of pyrrolo[1,3]benzothiazepines **110** and **111** showed that they are serotonin and dopamine receptor antagonists.[80] Using the molecular modelling approach, the authors generated a series of novel potential atypical antiphychotic agents, among which compound **112** was most promising; this was confirmed by pharmacological and biochemical assays carried out *in vivo*. This compound is active in a dose of 1.1 mg kg^{-1}, which is 100 times lower than the dose that causes catalepsy (ED_{50} > 90 mg kg^{-1}); it slightly increases the serum level of prolactin and counteracts the cognitive impairment induced by phencyclidine. The pharmacological profile of compound **112** is better than those of clozapine and olanzapine.

Structures 110–112

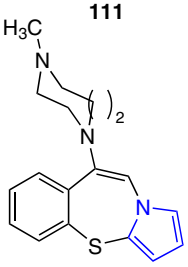


110

R^1 = H, Cl, F, Br; R^2 = CH_3, 2-(oxoimidazolidinyl)ethyl; R^3 = H, CHO, CH_2OH, CH_2OPr^i, CH_2=NOH; X–Y = CH–CH_2, C=CH



111



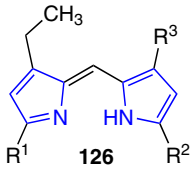
112

3.6. Antimalarial activity

Bromopyrrole alkaloids **113**–**125**, isolated from sea sponges, are efficient against protozoan microorganisms that cause dangerous or lethal (such as malaria) human diseases.[81] In particular, alkaloids **120** and **122** are promising as trypanocidal and antileishmanial agents with narrow therapeutic windows, while alkaloids **114** and **117** can serve as antimalarial agents (active against the *Plasmodium falciparum* strain) with low toxicity for mammals. In addition, it was shown that bromopyrrolohomoarginin **123** efficiently inhibits the *Pf*FabZ enzyme.

Synthetic prodiginines **126** have a moderate or high antimalarial activity against the multidrug-resistant *Plasmodium falciparum* strain.[82]

Structures 126



126

R^1 = Ph, 2-Pyr, 2-indolyl, 2-Fu, 2-Th; Pyr is pyrrolyl, Fu is furyl, Th is thienyl
R^2 = H, CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}, *n*-$C_{11}H_{23}$, *n*-$C_{16}H_{33}$, 4-$XC_6H_4CH_2$ (X = F, Cl, Br), 2,4-$X_2C_6H_3CH_2$ (X = F, Cl);
R^3 = H, CH_3, $CH_2CH(CH_3)_2$, *n*-C_3H_7, *n*-C_4H_9, *n*-C_6H_{13}, *n*-C_8H_{17}, 4-$ClC_6H_4CH_2$, 4-$FC_6H_4CH_2$, 3-$FC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 2,4-$Cl_2C_6H_3CH_2$, 2,4-$F_2C_6H_3CH_2$

3.7. Insecticidal activity

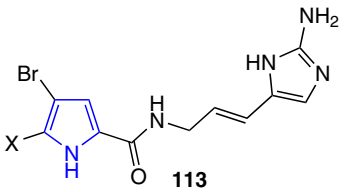
Pyrrole derivatives are also widely studied as agents for the control of agricultural pests. In particular, some commercial pesticides contain pyrrole rings in the molecules (*e.g.*, compounds **127**–**131**).[83]

Pyrroles **132**–**135** possess insecticidal activity against cotton leafworm *Spodoptera Littoralis* (boisduval scale),[84] a dangerous polyphagous moth, which is becoming increasingly difficult to control because of its resistance to chemical and biological insecticides.

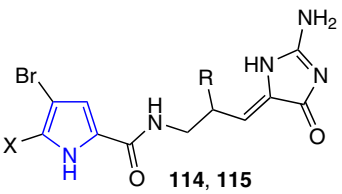
Arylpyrroles **136**–**140** are potent inhibitors of *Eimeria tenella* (Et) PKG (cGMP-dependent protein kinase) with a broad range of action for the prevention and treatment of coccidiosis in poultry.[85]

Thus, the above analysis of published data indicates that the main requirement to pyrroles incorporated in biological systems can be formulated as a 'multiple variability' of substituents. The systems substituted at the carbon atom (including inaccessible classic pyrroles functionalized only in position 3, with the α-positions being vacant) and the systems substituted at the nitrogen atoms are both required. The substituents often contain functional groups either directly bound to the pyrrole ring or located in the side chains of substituents. Pyrroles annulated

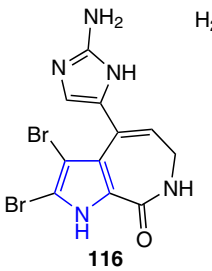
Structures 113–125



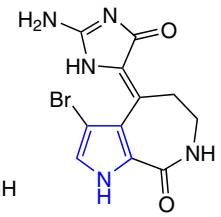
113
Hymenidin
X = H, Br



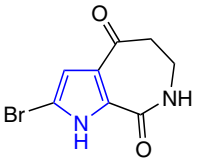
114, **115**
Dispacamide **B**: R = H (**114**);
Dispacamide **D**: R = OH (**115**)



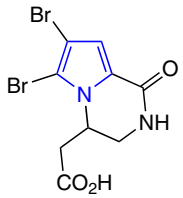
116
Stevensine



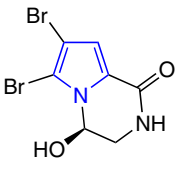
117
Spongiacidin B



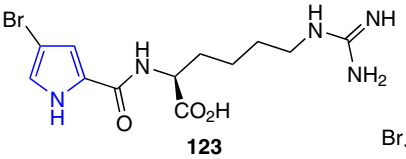
118
Bromoaldisin



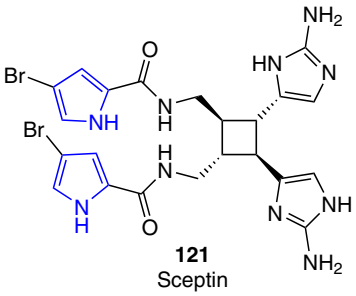
119
Longamide A



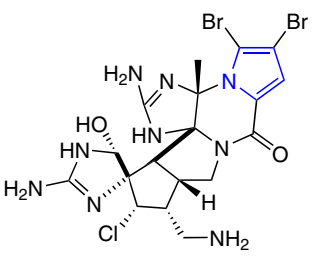
120
Longamide B



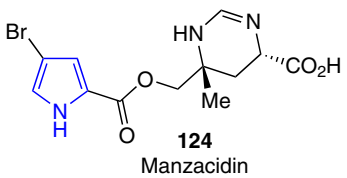
123
Bromopyrrolohomoarginin



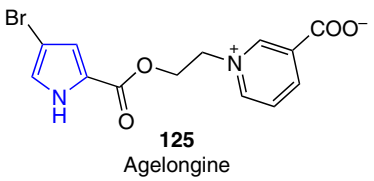
121
Sceptin



122
Dibromopalau 'amine'

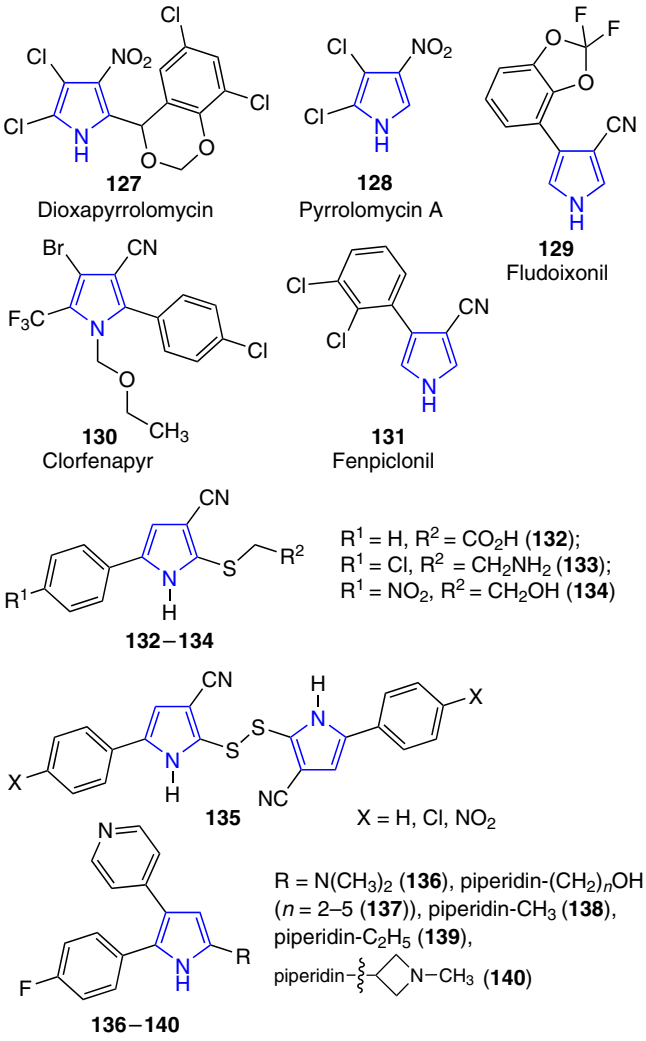


124
Manzacidin



125
Agelongine

Structures 127–140



with other heterocycles are widely encountered, which is most likely attributable to the rigidity of the skeleton of these systems and the lack of possibility of spatial rearrangements of molecules, which are often necessary for better interaction with the target. It is clear that creation of these extensive and diverse libraries of pyrroles requires either multistep synthesis or convenient synthons that enable easy variation of substituents or direct assembly of substituted pyrroles

4. Pyrroles in high-technology materials

The history of organic electronics started in 1980 when the IBM company prepared polypyrrole.[86] It is no surprise that the molecule that opened the age of organic electronics is still studied as one of the most important and significant ones.

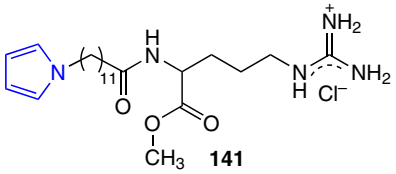
The development of reliable robotic and intelligent devices mimicking the multifunctional organs of living things requires the appearance of new biomimetic structures and artificial muscles. Glucose — gelatine nanofibre scaffolds coated with polypyrrole films using first chemical and then electrochemical polymerization are perfectly suited for the future technological applications such as artificial muscles, batteries and intelligent membranes.[87]

Solar batteries in which one of the components is a pyrrole-containing compound are more efficient and stable than their analogues containing no pyrrole ring.[88–91]

A minor amount of pyrrole additive passivates perovskite films and provides solar cells with enhanced efficiency and stability.[92]

In recent years, pyrroles (*e.g.*, compound **141**) have been becoming key components of nanostructured materials[93] and organic semiconductors.[94]

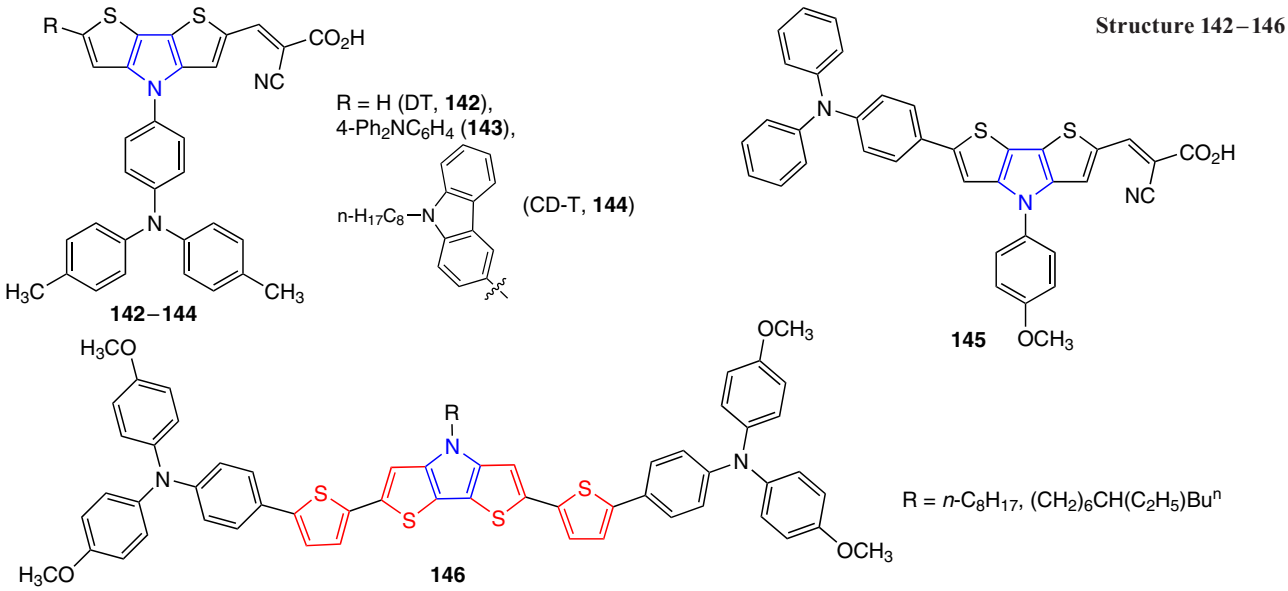
Structure 141



New push — pull organic dyes (structures **142**–**145**) suitable for the design of solar cells with enhanced photoelectric characteristics were obtained on the basis of dithieno[3,2-*b*:2′,3′-*d*]pyrroles.[95]

p-Type organic semiconductors based on dithieno[3,2-*b*:2′,3′-*d*]pyrroles **146** possessing excellent film-forming properties and the ability to quench photoluminescence provide a more than 20% charge transport efficiency in perovskite solar

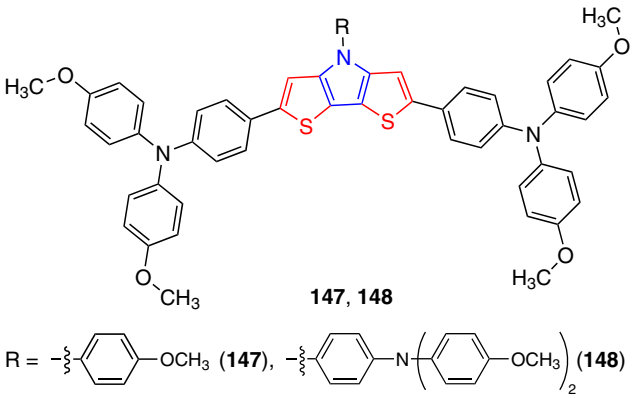
Structure 142–146



cells.[96] Their modification by elongation of the π-conjugation chain and *N*-alkylation enables fine tuning of the HOMO energy levels, charge mobility, solubility and charge-forming characteristics.

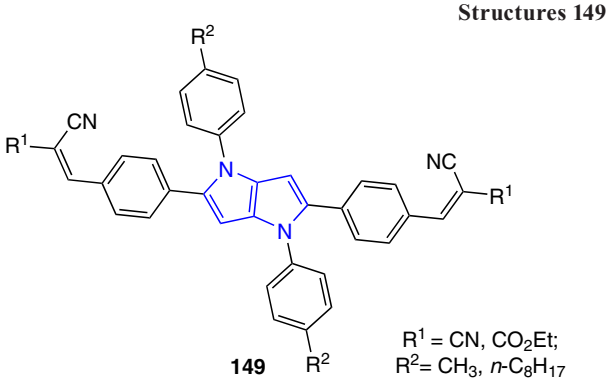
Owing to good π-conjugation, dithienopyrroles **147** and **148** are important organic photovoltaic materials.[97]

Structures 147, 148



Low-molecular-weight acceptor–donor–acceptor pyrrolo[3,2-*b*]pyrroles **149** have a high thermal stability and appropriate HOMO–LUMO energy levels, which makes them suitable as electron donors in bulk heterojunction organic solar cells.[98]

Structures 149

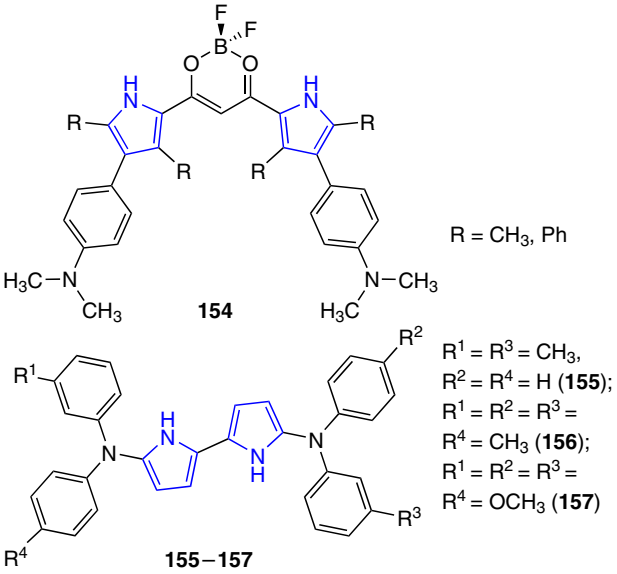


The development of organic optoelectronics requires compounds with suitable combinations of photophysical and electronic properties. These properties are inherent in heteropentalenes **150**–**153**.[99] The most important feature of these dyes is strong solvatofluorochromism, which makes them valuable as probes sensitive to environmental conditions.

The introduction of electron-donating *N*,*N*-dimethylaminophenyl groups into dipyrrolyl diketone BF_2 complexes **154** gave rise to remarkable fluorescence properties.[100] The observed multiple fluorescence sensitivity of these compounds to the solvent polarity, anion binding and protonation attests to high promise of these compounds as molecular logic gates.

Compounds based on 2,2-bipyrrole (structures **155**–**157**) also possess excellent optoelectronic properties.[101]

Structures 154–157

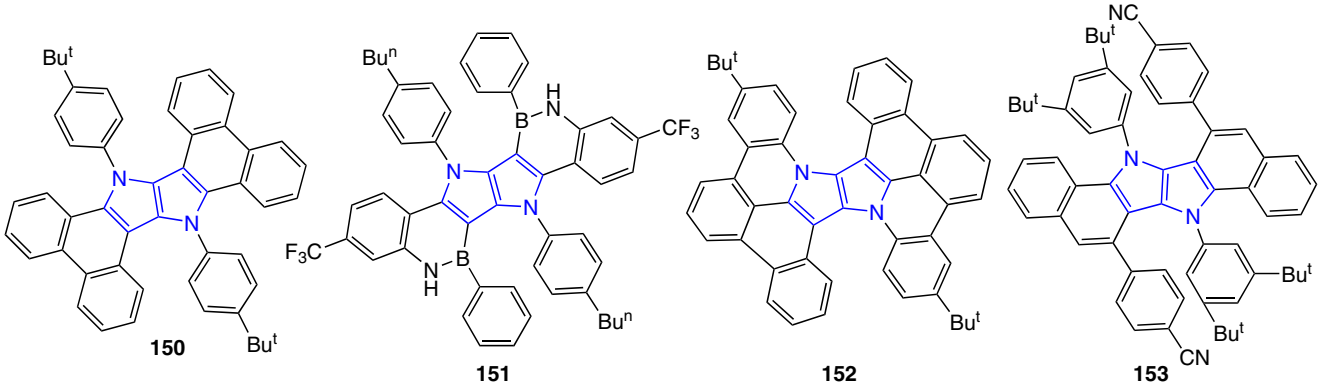


Substituted pyrroles are used for the assembly of fluorescence dyes of the difluoroboradiazaindacene (BODIPY) type, which find numerous applications as laser media, markers, fluorescent biolabels, chemosensors, intensity limiters of hard laser radiation, photosensitizers in photodynamic therapy, DNA intercalators and so on.[102–104]

The photophysical and electrochemical properties of BODIPY fluorophores are most strongly affected by π-conjugated substituents both in the *meso*-position of the boradiazaindacene skeleton and in the pyrrole rings.[105] Compounds with these substituents show absorption and fluorescence in the red spectral range with high quantum yields, excellent luminescent properties and good ion sensing properties, and they can accomplish balanced electron transfer in materials.

Recent reviews[106,107] present a detailed discussion of the photophysical properties of a broad range of materials based on π-conjugated BODIPY, which can be used in organic light-emitting diodes, nonlinear optical devices, sensors, charge

Structures 150–153

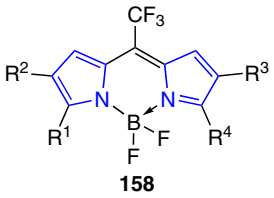


transfer materials, electron transport materials and perovskite solar cells and also as ultrafast charge transfer materials.

For imparting the desired properties to BODIPY fluorophores, functionalization of the *meso*-, α- and β-positions and the B(III) centre is widely used. This is done by introducing substituents with different electronic properties, varying the length of the chain of conjugation and adding appropriate spacers or p-linkers.[108–114]

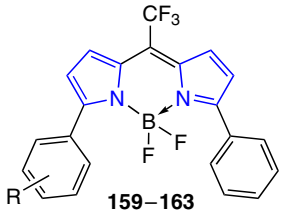
Dyes **158** exhibiting fluorescence in the long-wavelength range (626–698 nm) with a high quantum yield (0.84–0.99) are synthesized by introducing a CF_3 group into the *meso*-position of BODIPY fluorophores containing aryl and heteroaryl substituents in positions C(3) and C(5) of the boradiazaindacene skeleton.[115]

Structures 158–163



158

$R^1 = R^4$ = Ph, 4-substituted Ph, 2-Th; $R^2 = R^3$ = H, Ph



159–163

R = 4-N$(CH_3)_2$ (**159**), 3-NH_2 (**160**), 4-NH_2 (**161**), 4-$NHCOCH_3$ (**162**), 3-$NHCOCH_3$ (**163**)

Among compounds of this class, there are potential sensors responsive to pH of the medium and promising for tumour imaging, evaluation of potential pharmaceutical agents and detection of the main metal cations in soft tissues. For example, BODIPY **159** with a 2,5-dimethylaminophenyl substituent in position 3, which fluoresces at ⩾ 695 nm, or BODIPY **160**–**163** with 3(4)-amino- and acetamidophenyl substituents are potential pH sensors.[116]

The fluorescence of dyes **160** and **161** and symmetrical derivatives **164** and **165** is sensitive to the presence of aromatic non-polar hydrocarbons; therefore, they (in particular, compound **164**) can be used to detect minor amounts of benzenes and similar compounds in various materials, *e.g.*, in a fuel.[117,118]

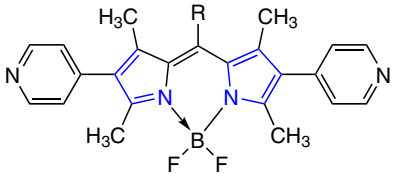
Fluorescent sensor **166** is able to efficiently detect lysosomes in malignant cells. Its low toxicity and high selectivity to lysosomes makes it possible to perform long-term intravital observation of cells. Owing to high fluorescence quantum yield, it is possible to minimize the background noises, which provides a reliable visualization of lysosomes.[119,120]

BODIPY-based fluorescent surfactant **167**, which shows photocytotoxicity against MCF-7 and HeLa cancer cells and can efficiently stain living cell membranes with long retention times, is promising for the targeted imaging and effective photodynamic therapy.[121]

Therapeutic properties were also found for BODIPY-based macrocycles.[122] For example, photostable platinum complex **168**, which absorbs in the near-IR range, is promising for the photodynamic therapy of cancer.

A number of intensely fluorescent complexes of platinum, palladium, ruthenium and iridium based on 3,5-dipyridyl BODIPY derivatives **169** are promising for the intracellular imaging by confocal microscopy.[123–125]

Structures 169

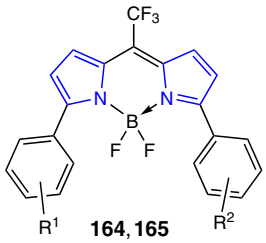


169

R = CH_3, Ph, 4-$F_3CC_6H_4$, 4-$O_2NC_6H_4$

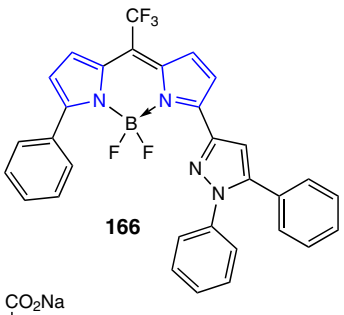
For example, palladium macrocycle **170** based on BODIPY **169**, which is highly active against brain cancer cells, is easily

Structures 164–168

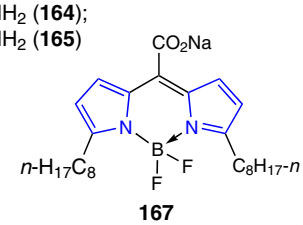


164, 165

$R^1 = R^2$ = 3-NH_2 (**164**);
$R^1 = R^2$ = 4-NH_2 (**165**)



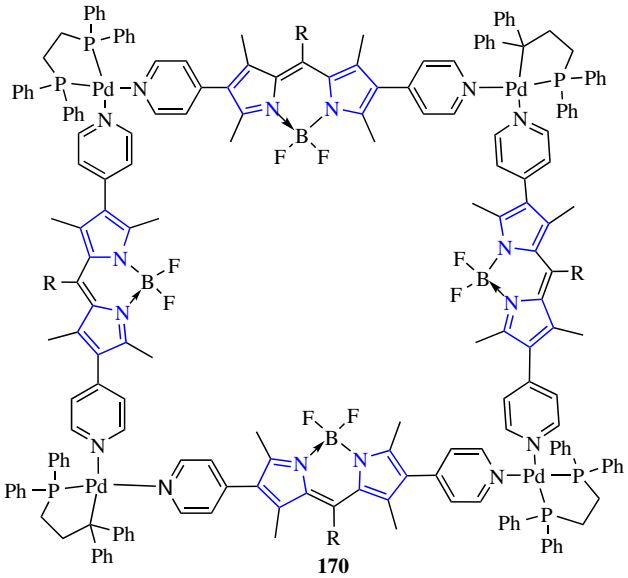
166



167

168

Structures 170

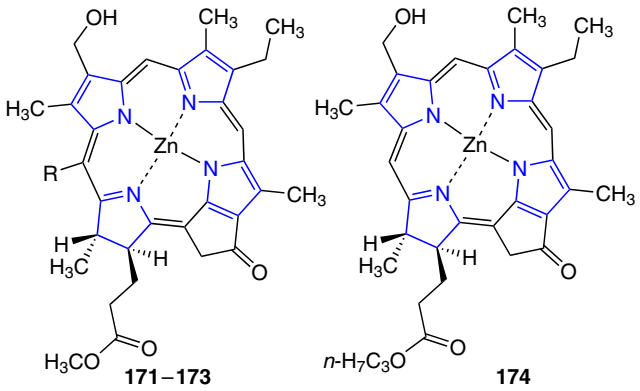


170

localized in the cytoplasm and on the plasmatic membrane; this can be visualized by confocal microscopy.[123]

A variety of pyrrole-containing porphyrins and metal porphyrins, in particular compounds **171**–**174**, are used for the production of colour pigments, semiconductors and catalysts and in medicine.[126, 127]

Structures 171–174



171–173 **174**

R = C≡CPh (**171**), Br (**172**), H (**173**)

As shown in the previous Section, a fundamentally important factor for the application of pyrroles is the possibility to vary the substituents. Of course, aromatic substituents that increase the chain of conjugation and, in some cases, contain electron-donating and/or electron-withdrawing groups (so-called push–pull systems) are, first of all, required for these compounds. In this regard, annulated systems are of most value, but due to a different factor: the possibility to avoid energy expenditure for the rotation of parts of the molecule around the σ-bonds.

Thus, pyrrole can actually be considered to be a privileged structure for fine organic synthesis and for the design of various compounds and materials. Among obvious benefits of pyrrole, note easy functionalization by diverse groups; this broad pallete of options for the decoration of the pyrrole core may provide almost any desirable properties. In the case of pyrrole-based pharmaceuticals, it is easy to select spatial factors and unique relative arrangement of functional groups, which makes the molecule suitable for a variety of targets and, as a consequence, endow the molecule with a broad range biological activity. In the case of design of electronic materials, significant issues include the electronic structure, aromaticity, involvement of substituents in electron conjugation and formation of annulated systems, which enables fine control over the physical properties of molecules.

Of course, with this diversity of possibilities, construction of a pyrrole ring with the widest set of possible substituents is a fundamentally important issue. The applicability of compounds as pharmaceutical drugs or material precursors directly depends on the compound availability, which imposes additional restrictions on the starting reactants that can be used for the design of pyrroles.

In the second part of the review (see Sections 5 and 6), we summarized the advances in the construction of the pyrrole ring from ketones and their simple derivatives. The use of ketones appears highly appropriate, since ketones are a widely encountered and easily accessible class of organic compounds, frequently used both in laboratory and in industry. This diversity of starting compound libraries provides easy synthesis of a wide range of functionalized pyrroles for advanced technologies.

5. Synthesis of pyrroles from ketones and functionalized ketones

Among methods for pyrrole synthesis based on ketones, an important position still belongs to classic reactions: condensation of aminoketones (Knorr synthesis) or haloketones (Hantzsch synthesis) with β-keto esters in ammonia or primary amines and the condensation of 1,4-dicarbonyl compounds with primary amines (Paal–Knorr synthesis). Studies devoted to the use of these reactions for the assembly of a pyrrole ring are considered in detail in recent reviews.[128–130] Simultaneously, new promising methods are also being developed, in particular the Trofimov reaction[131–135] and intramolecular cyclization of carbonyl compounds.

The methods for the pyrrole ring construction considered in the review are divided into two main groups, that is, reactions based on monocarbonyl (Section 5) and dicarbonyl (Section 6) compounds.

5.1. Synthesis of pyrroles from monocarbonyl compounds

5.1.1. Synthesis from ketones (*via* ketoximes) and acetylene or its synthetic equivalents

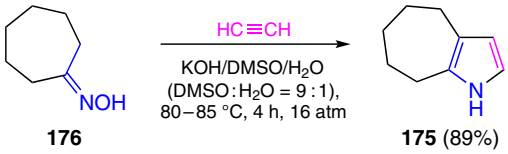
A new extensive area of pyrrole chemistry appeared in recent years, namely, pyrrole synthesis from ketones (*via* ketoximes) and acetylenes in superbasic systems consisting of an alkali metal hydroxide and DMSO (MOH/DMSO). This approach provides routes to a large series of substituted pyrroles that had been poorly accessible before, such as alkyl-, aryl and heteroarylpyrroles; pyrroles incorporated into polycyclic terpene and steroid systems; and especially *N*-vinylpyrroles, opening basically new opportunities for the introduction of functional substituents into the pyrrole ring and for preparation of new structural types, polypyrroles.

This reaction, known in the literature as the Trofimov reaction,[131–135] is being actively developed as a versatile tool for the targeted synthesis of pyrrole derivatives ranging from simple ones (which are often difficult to obtain) to complex functionalized pyrrole ensembles.

For example, a number of pyrrole precursors of BODIPY dyes that show intense red fluorescence were obtained using this reaction.[115–120]

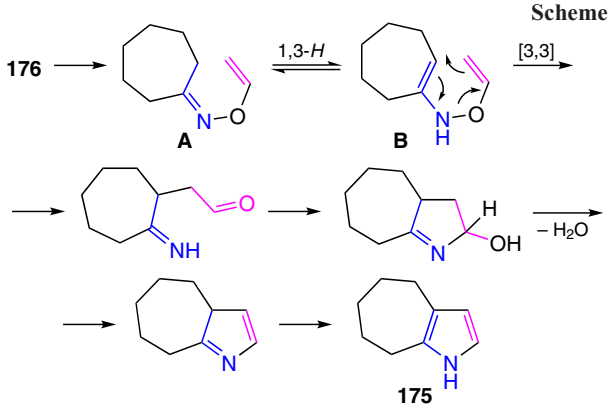
Conditions for the selective synthesis of one more compound of this type, 1,4,5,6,7,8-hexahydrocyclohepta[*b*]pyrrole **175**, from cycloheptanone oxime **176** and acetylene (Scheme 1) have recently been reported.[134]

Scheme 1



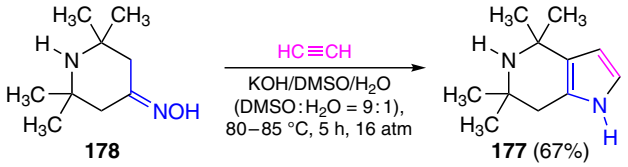
Probably, pyrrole **175** is formed according to the Trofimov reaction mechanism proposed previously and confirmed experimentally,[5] including 1,3-prototropic shift in *O*-vinyl oxime **A** and the subsequent 3,3-sigmaropic rearrangement of the resulting *O*-vinylalkenyl hydroxylamine **B** (Scheme 2).

Scheme 2



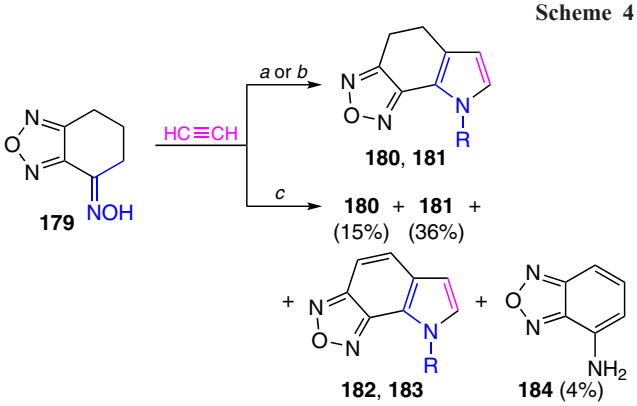
2,2,6,6-Tетрамethyltetrahydropyrrolo[3,2-*c*]pyridine **177**, precursor of pyrazolyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridine, was obtained from 2,2,6,6-tetramethylpiperidin-4-one oxime **178** and acetylene (Scheme 3).[137]

Scheme 3



The reaction of 6,7-dihydro-2,1,3-benzoxadiazol-4(5*H*)-one oxime **179** with acetylene in the KOH/DMSO system resulted in the synthesis of 1,2,5-oxadiazolo[3,4-*g*]dihydroindoles **180** and **181** (Scheme 4).[138,139] The selective formation of *NH*-indole **180** was attained by conducting the reaction under acetylene pressure of 12–15 atm (110 °C, 4 h) in the KOH/DMSO/H_2O system (DMSO:H_2O = 6:4) (see Scheme 4, conditions *a*). For the selective synthesis of *N*-vinyl-5,8-dihydro-4*H*-[1,2,5]-oxadiazolo[3,4-*g*]indole **181**, the content of water in the reaction mixture was reduced to 20%, while the reaction time was increased to 5 h (see Scheme 4, conditions *b*). The reaction performed in anhydrous DMSO afforded a mixture of products containing (as measured in the reaction mixture) dihydroindoles **180**, **181** and their fully aromatic derivatives **182**, **183** and benzodiazole-4-amine **184** (4% yield) (see Scheme 4, conditions *c*). The effect of addition of water on the overall reaction outcome deserves attention: indole **180** can be selectively

Scheme 4

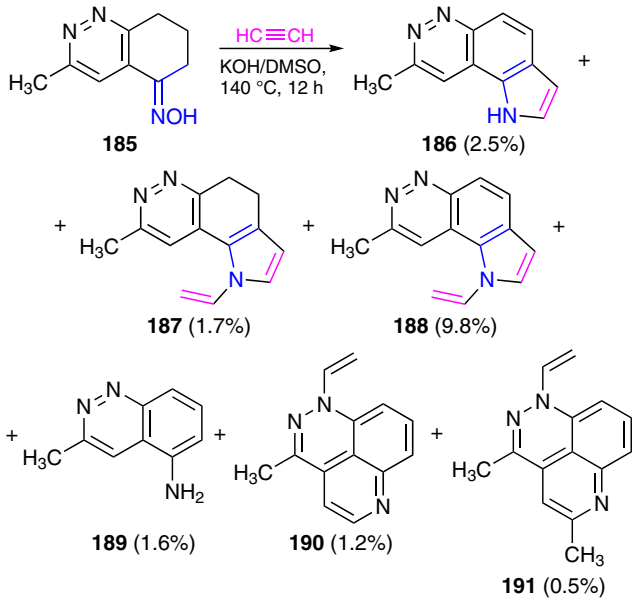


(*a*) KOH/DMSO/H_2O (DMSO:H_2O = 6:4), 110 °C, 4 h;
(*b*) KOH/DMSO/H_2O (DMSO:H_2O = 8:2), 110 °C, 5 h;
(*c*) KOH/DMSO, 110 °C, 4 h;
R = H (**180**, 39%), CH_2=CH_2 (**181**, 76%), H (**182,** 4%), CH_2=CH_2 (**183,** 10%)

obtained only in the presence of 40% H_2O in the reaction mixture. Even the selective synthesis of *N*-vinyl derivative **181** requires up to 20% H_2O. This is a new aspect for the Trofimov reaction, in which a minor amount of water (10% relative to the DMSO volume) is usually required to maintain the superbasic conditions.[5] Apart from promoting the annulation of oxime **179** with acetylene, the presence of water prevents aromatization of dihydro derivatives **180**, **181** and thus increases the reaction selectivity.

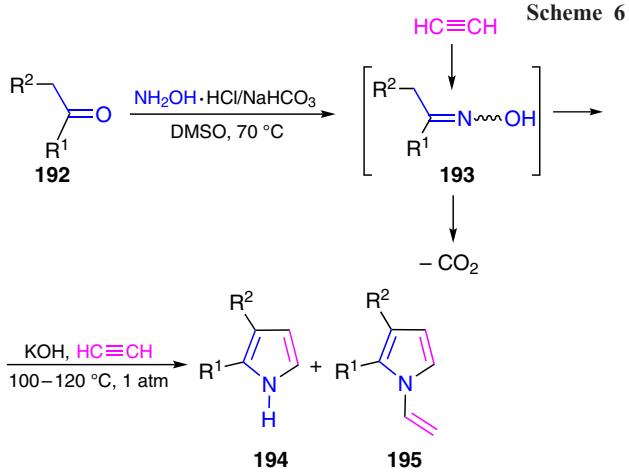
In the case of 3-methyl-7,8-dihydrocinnolin-5(6*H*)-one oxime **185**, the Trofimov reaction is accompanied by other transformations: apart from the formation of pyrrole **186** and *N*-vinylpyrroles **187** and **188**, reduction of the oxime group to the amine group (amine **189**) and formation of *N*-vinyl tricyclic compounds with a pyridazine ring **190** and **191** take place.[140] The reaction was carried out at 140 °C in a flow reactor (atmospheric pressure) for 12 h; the resulting compounds **186**–**191** were isolated by column chromatography (Scheme 5).

Scheme 5



In addition to the synthesis of pyrroles from ketoximes and acetylene, a new version of the Trofimov reaction, that is, one-pot assembly of pyrroles from ketones and acetylene, is also

Scheme 6

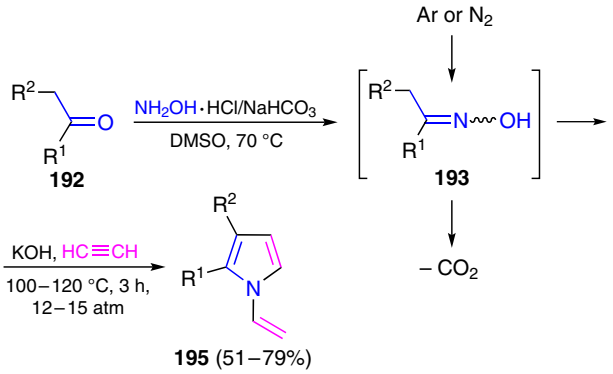


R^1 = CH_3, C_2H_5, Bu^t, Ph, 2-Th, 2-Fu; R^2 = H; R^1–R^2 = $(CH_2)_4$

widely used (Scheme 6).[141] In this case, alkyl, aryl and heteroaryl ketones **192** are treated with a mixture of $NH_2OH \cdot HCl/NaHCO_3$ at 70 °C to be converted to oximes **193**, which then react with acetylene at 100–120 °C to give 2- and 2,3-disubstituted *NH*- (**194**) and *N*-vinylpyrroles **195**, the contents of which in the reaction mixture depend on the nature of substituents in the pyrrole ring and amount to 3–85% for *NH*-pyrroles **194** and 6–87% for *N*-vinylpyrroles **195**. It is noteworthy that in the case of cyclohexanone oxime [**192**, R^1–R^2 = $(CH_2)_4$], the reaction proceeds selectively and affords the corresponding *N*-vinylpyrrole (in 71% isolated yield).

The reaction between the same reactants, but with the final step being conducted under acetylene pressure of 12–15 atm, results in the selective formation of *N*-vinylpyrroles **195** (Scheme 7).[142]

Scheme 7



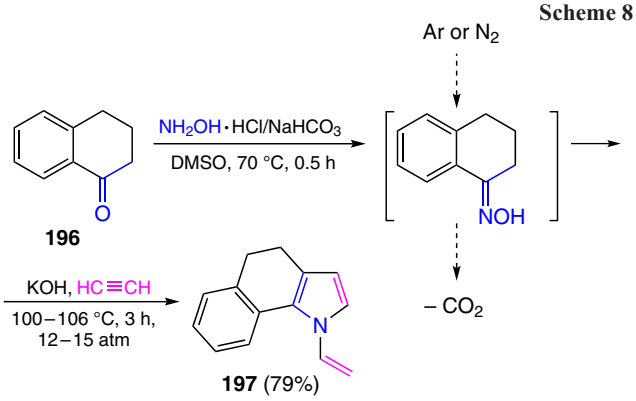
R^1 = CH_3, Ph, 2-Th; R^2 = H, CH_3; R^1–R^2 = $(CH_2)_4$

Under similar conditions, 1-tetralone **196** reacts with hydroxylamine hydrohloride and acetylene to furnish *N*-vinyl-4,5-dihydrobenzo[*g*]indole **197** (Scheme 8).

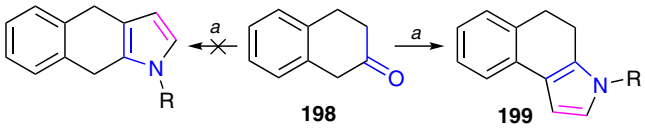
In the case of 2-tetralone **198**, which could be theoretically converted to a mixture of isomers, the reaction in the MOH/DMSO system affords only *NH*- (when NaOH is used) or *N*-vinyl-4,5-dihydrobenzo[*e*]indoles **199** (when KOH is used) (Scheme 9).[143]

The same research team[144] accomplished the selective one-pot synthesis of *N*-vinyl-4,5-dihydrobenzo[*g*]indole **197** from 1-tetralone **196** and acetylene in the $NH_2OH \cdot HCl/KOH/DMSO$ system without using an auxiliary base and, therefore, without the need to remove carbon dioxide from the reaction medium (Scheme 10). The yield of indole **197** purified by chromatography

Scheme 8



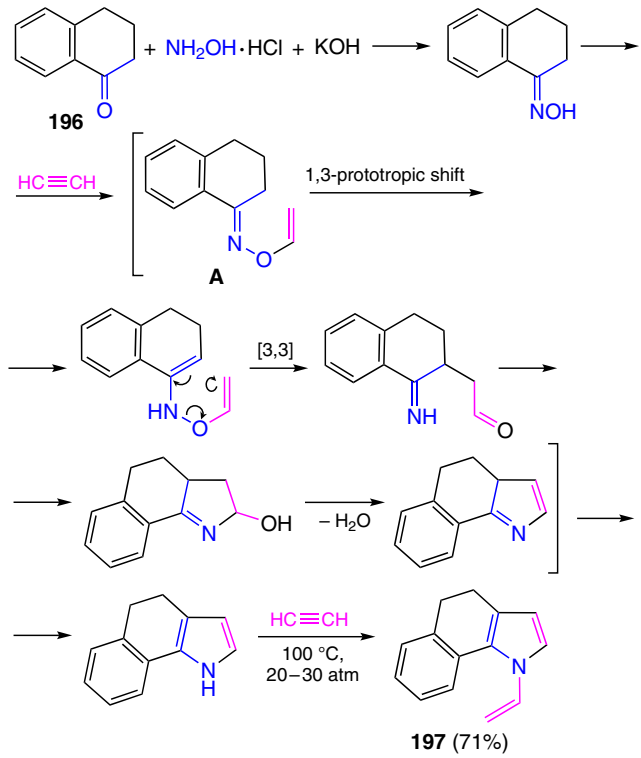
Scheme 9



(*a*) 1) $NH_2OH \cdot HCl/NaHCO_3$, DMSO, 70 °C, 30 min;
2) acetylene/MOH/DMSO, 90–110 °C, 1–3 h, 4–14 atm (M = Na, K);
R = H (41%), $CH{=}CH_2$ (75%)

was 71%. The reaction proceeds as a typical multicomponent process involving a number of consecutive and parallel reactions: the reaction of hydroxylamine chloride with KOH, oximation of ketone **196**, vinylation of the resulting oxime with acetylene followed by the domino conversion of *O*-vinyl oxime **A** to give intermediate *NH*-4,5-dihydrobenzo[*g*]indole and subsequent vinylation to give product **197**.

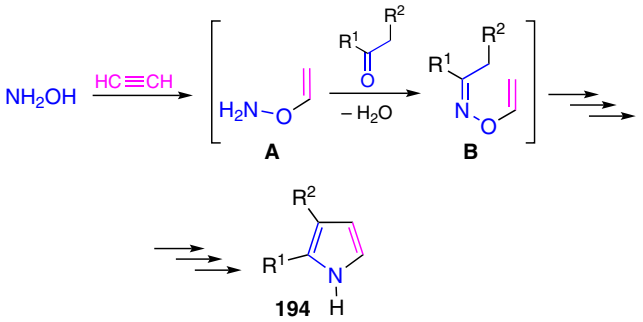
Scheme 10



The synthesis of *NH*- and *N*-vinylpyrroles directly from ketones and acetylene in the $NH_2OH \cdot HCl/KOH/DMSO$ system has a few significant advantages: the number of reactant

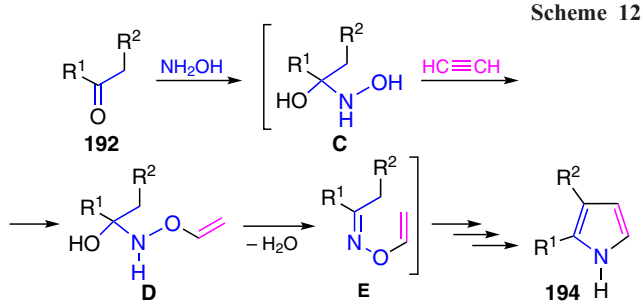
decreases, no auxiliary reactor for oximation in the presence of $NaHCO_3$ is required, no degassing of the reaction medium (CO_2 stripping) is needed and extraction of the target products from aqueous DMSO is facilitated due to salting-out effect of potassium chloride, which is formed during the oximation. These advantages are probably due to combination of the usual synthetic route (*via* vinylation of oxime) with two other parallel reactions that are not inherent in the synthesis using ready ketoximes (Scheme 11). One of these reactions is vinylation of hydroxylamine to give *O*-vinyl hydroxylamine **A**, which then oximates the ketone to afford *O*-vinyl oxime **B**, which is converted to pyrrole **194**.

Scheme 11



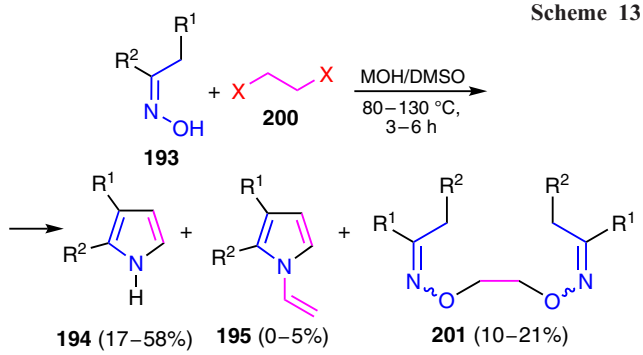
An alternative reaction pathway is trapping of the intermediate adduct of ketone and hydroxylamine **C** with acetylene to yield *O*-vinyl derivative **D**, which is subsequently dehydrated to give *O*-vinyl oxime **E** (Scheme 12). This trapping may be more preferable than vinylation of the ketoxime, as the hydroxyl group in this case is bound to nitrogen, which is less electronegative than oxygen in the ketoxime.

Scheme 12



The possibility of using dihaloethanes **200** as synthetic equivalents of acetylene in the Trofimov reaction was studied more than 30 years ago.[145–147] However, in this case, the reaction was accompanied by the formation of ketoxime diethers **201** (Scheme 13), which were difficult to separate from target pyrroles **194** and **195**. During separation of the reaction mixture,

Scheme 13

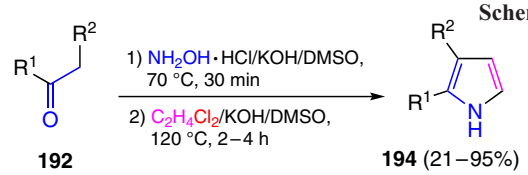


$R^1 = R^2 = H$, Alk; X = Cl, Br; M = Na, K

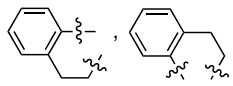
the yields of pyrroles markedly decreased. Therefore, despite certain success, these works were not further developed.

More recently, this method was advanced.[148,149] Ketoximes were replaced by ketones, and 1,2-dichloroethane was used as a synthetic analogue of acetylene. As a result, ketones **192** were selectively converted to pyrroles **194** (Scheme 14).

Scheme 14

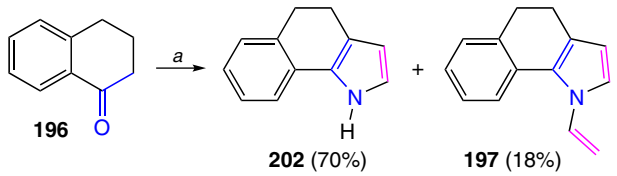


R^1 = CH_3, Bu^n, Ph, C_6H_4R-4 (R = CH_3O, Cl), 2-Naph, 2-Fu, 2-Th, 2-Py (Naph is naphthyl); R^2 = H, Pr^n;

$R^1–R^2$ = 

Under more drastic conditions (140 °C), the reaction may give *N*-vinyl derivatives, together with *NH*-pyrroles. For example, a mixture of pyrroles **202** and **197** in a total yield of 88% was obtained from 1-tetralone **196** and 1,2-dichloroethane (~ 4 : 1 ratio according to GLC) (Scheme 15).[150]

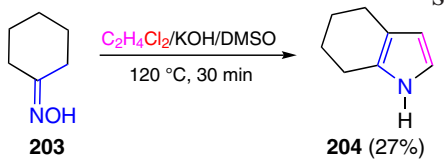
Scheme 15



(*a*) 1) NH_2OH·HCl/KOH/DMSO, 70 °C, 30 min;
2) $C_2H_4Cl_2$/KOH/DMSO, 140 °C, 3 h

Kritskaya *et al.*[151] were also able to selectively prepare 4,5,6,7-tetrahydroindole **203** from cyclohexanone oxime **204** and dichloroethane; however, the product yield was moderate (Scheme 16).

Scheme 16



Lately, calcium carbide has been often used as the source of acetylene.[152–154]

In particular, calcium carbide was utilized in the reaction with ketoximes **193**, which selectively afforded 2-arylpyrroles **194** (Scheme 17).[155] In the case of 4-methoxyacetophenone and propiophenone oximes, together with pyrroles **194**, their *N*-vinyl derivatives **195** are also formed in minor amounts (2–5%).

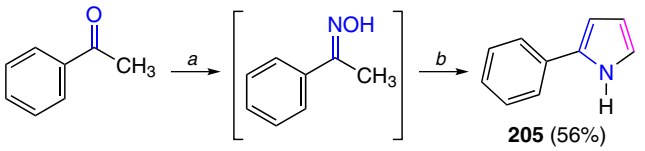
Scheme 17

R^1 = Ph, 4-R-C_6H_4 (R = CH_3, OCH_3, Cl, NPh_2, Ph), 1-Naph;
R^2 = H, CH_3

The same publication[155] describes a one-step method for the synthesis of 2-phenylpyrrole **205** from acetophenone and

calcium carbide. In this case, acetophenone oxime is formed *in situ* from the ketone and hydroxylamine in the presence of $NaHCO_3$ (Scheme 18).

Scheme 18



(*a*) $NH_2OH \cdot HCl/NaHCO_3$, DMSO, 60 °C, 4 h;
(*b*) CaC_2/KOH, 18-crown-6, 100 °C, 15 h

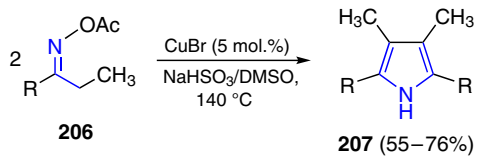
Thus, reactions of ketones (ketoximes) with acetylene in a superbasic system (Trofimov reaction) provides a facile route to *NH*- and *N*-vinylpyrroles. This reaction, based on cheap and readily available reactants (ketones and acetylene), proved to be a convenient tool for the construction of a pyrrole ring. Although in some cases this reaction gives a mixture of *NH*- and *N*-vinylpyrroles, the products can be easily isolated in a pure state (by separate extraction or flash chromatography).

5.1.2. Synthesis from *O*-acyl ketoximes

A recent series of studies[151,156–160] is devoted to the use of *O*-acyl ketoximes for the construction of a pyrrole ring. Usually reactions between these compounds occur in the presence of copper salts and include a single-electron transfer step.

For example, homocoupling of ketoximes **206** catalyzed by copper salts affords symmetrical pyrroles **207** (Scheme 19).[156]

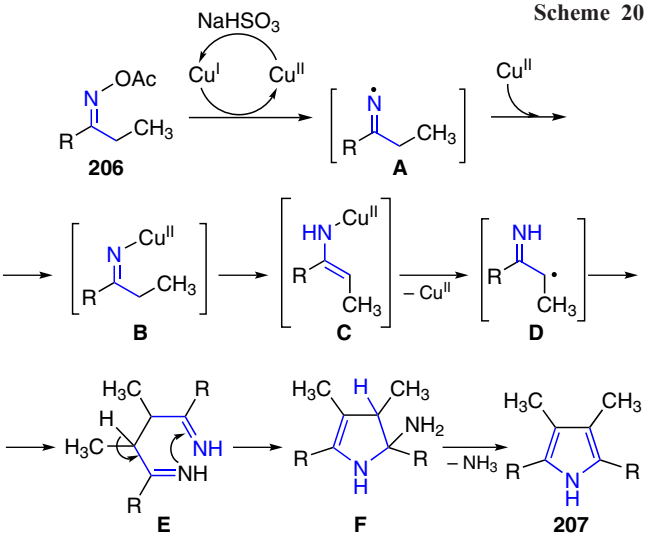
Scheme 19



R = C_6H_4R-4 (R = CH_3, C_2H_5, OCH_3, F, Cl, Br), $C_6H_3(CH_3)_2$-3,4

According to the authors' assumption, this reaction begins with a two-step reduction of ketoxime **206** with Cu^I (including a single-electron transfer step) to give imino-Cu^{II} complex **B** (Scheme 20), which is then converted into enamine **C** *via* tautomerization. Cleavage of the N–Cu^{II} bond in enamine **C** furnishes radical **D**. Dimerization of **D** gives diimine **E**, the intramolecular cyclization of which affords diamine **F**, and this is followed by elimination of an ammonia molecule.

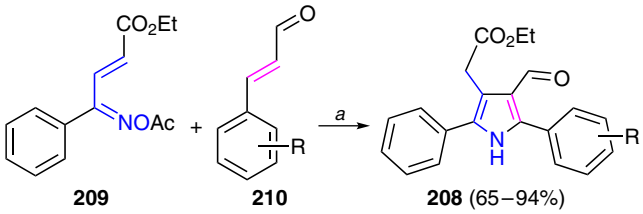
Scheme 20



It should be noted that the homocoupling of *O*-acyl ketoximes leads only to pyrroles with aromatic substituents, which reduces the applicability of this method.

Tetrasubstituted pyrroles **208** were obtained by regioselective [3+2]-cycloaddition of *O*-acyloxime **209** to α,β-unsaturated aldehydes **210** in the CuI/Pr^i_2NH system (Scheme 21).[157]

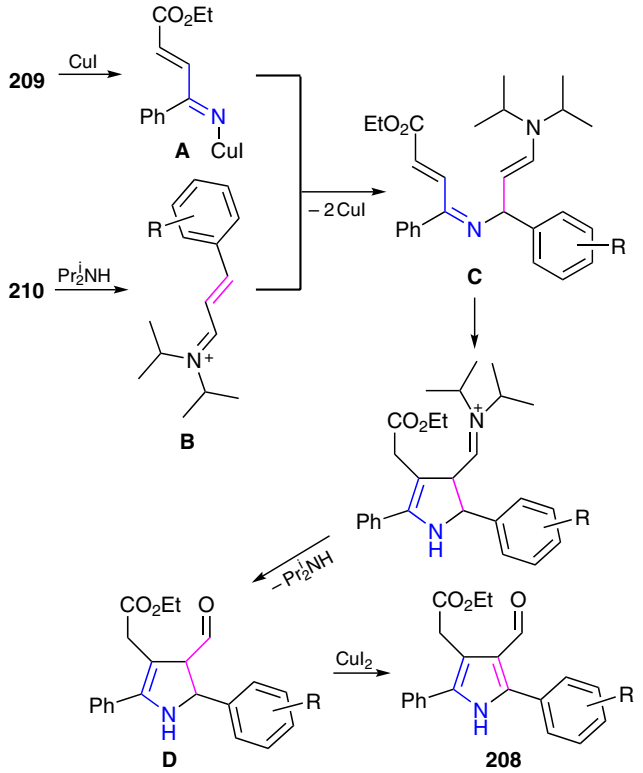
Scheme 21



(a) CuI (10 mol.%), Pr^i_2NH (20 mol.%), DCE, 140 °C, 24 h
(DCE is dichloroethane);
R = H, 4-CH_3, 3-OCH_3, 4-OCH_3, 4-$N(CH_3)_2$, 4-F, 4-Cl, 4-CF_3, 4-NO_2, 3-NO_2

The formation mechanism of pyrroles **208** includes the reaction of *O*-acyloxime **209** with CuI, the addition of the resulting intermediate **A** to the iminium ion **B** that has formed from enal and diisopropylamine, intramolecular cyclization of intermediate **C**, hydrolysis accompanied by elimination of diisopropylamine, and oxidation of dihydropyrrole **D** with CuI_2 (Scheme 22).

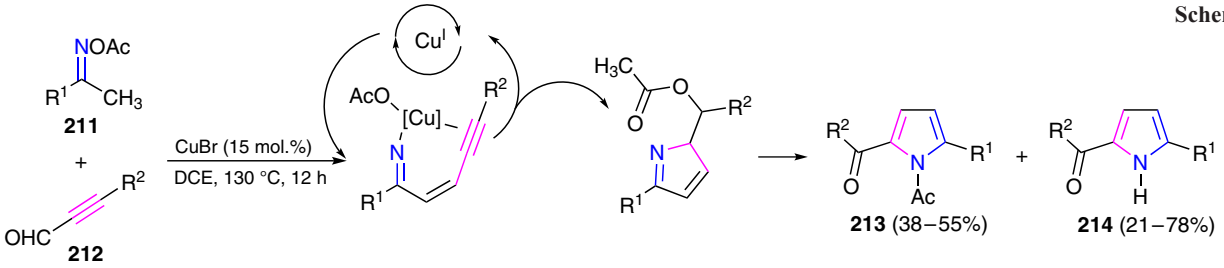
Scheme 22



The redox reaction of *O*-acyl ketoximes **211** with arylpropynals **212** resulted in the synthesis of 2-acyl-*N*-acyl-**213** and *NH*-pyrroles **214** with various aromatic substituents (Scheme 23).[158]

The CuCl-catalyzed reaction of *O*-acyl ketoximes **215** with dialkyl acetylenedicarboxylates **216** conducted under aerobic

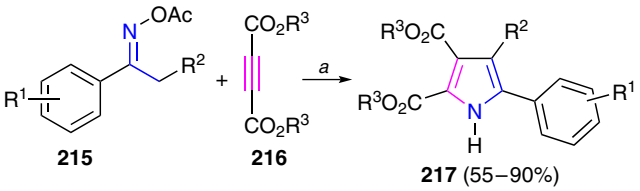
Scheme 23



R^1 = Ph, C_6H_4R-4 (R = CH_3, Bu^t, Bu^i, F, Cl, Br, OCH_3, OCF_3), C_6H_4R-3 (R = CH_3, F, Br, CF_3, OCH_3, OCF_3), C_6H_4R-2 (R = CH_3, F, Cl), $C_6H_3(CH_3)_2$-2,4, $C_6H_3(OCH_3)_2$-3,4, 2-Fu, 2-Th, 3-Th; R^2 = Ph, C_6H_4R-4 (R = CH_3, Bu^t, Bu^i, F, Cl, Br, OCH_3, OCF_3), C_6H_4R-3 (R = CH_3, F, Br, CF_3, OCH_3), C_6H_4R-2 (R = CH_3, F, Cl)

conditions affords tetrasubstituted pyrroles **217** (Scheme 24).[159] The authors did not explain the effect of oxygen on the reaction, but noted that oxygen markedly promoted the reaction.

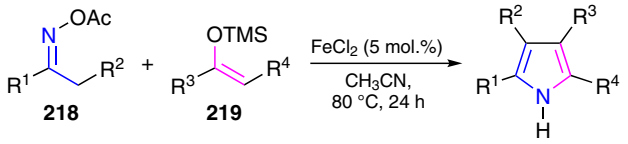
Scheme 24



(*a*) CuCl (10 mol.%), Na_2SO_3, DMSO, O_2, 120 °C, 12 h;
R^1 = H, CH_3, Bu^i, F, Cl, OCH_3; R^2 = H, CH_3; R^3 = CH_3, C_2H_5

The $FeCl_2$-catalyzed reaction of *O*-acyl ketoximes **218** with strong enol ethers **219** was used to prepare pyrroles **220** (Scheme 25).[160] In the opinion of the authors, the reaction involves the iminyl radical.

Scheme 25



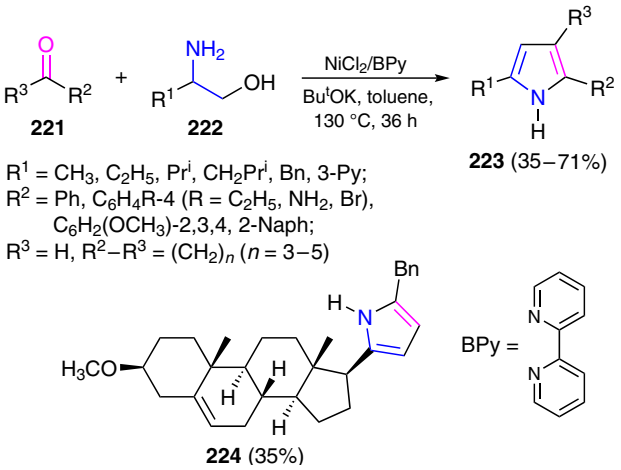
R^1 = Ph, C_6H_4R-4 (R = OCH_3, Br), C_6H_4Br-3, 2-Th;
R^2 = H_3, CO_2Et, Ph, Bn; R^3 = H, CH_3, Ph;
R^4 = Ph, CO_2Et, C_6H_4R-4 (R = OCH_3, Cl, CO_2CH_3, NO_2), 2-Fu, 2-Naph; TMS = $Si(CH_3)_3$

5.1.3. Synthesis by the reaction of ketones with amines

The reaction of ketones **221** with β-amino alcohols **222** catalyzed by nickel salts results in the formation of a broad range of 2,5- and 2,3,5-substituted *NH*-pyrroles **223**, including the most pharmacologically promising pyrrole **224** (Scheme 26).[161] This reaction smoothly proceeds for various amino alcohols such as 1-aminopropanol, methyl-, ethyl-, isopropyl, isobutyl- and benzyl-substituted β-amino alcohols and derivatives of amino acids (phenylalaninol and phenylglycinol). The range of applicable ketones includes aliphatic, particularly long-chain representatives, compounds containing a terminal double bond, and cycloaliphatic (cyclopentanone, cyclohexanone, cycloheptanone, 7-methoxytetralone), aromatic (acetophenones, 1- and 2-acetylnaphthalenes, 3-acetylpyridines) and steroidal (pregnenolone) derivatives.

The reaction proceeds *via* the formation of imines **A**, which are dehydrogenated (under the action of Ni) to give α-imino

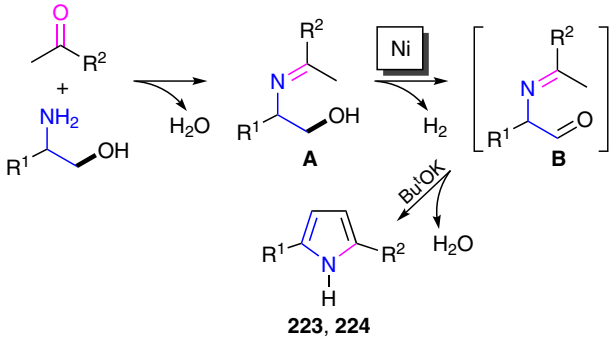
Scheme 26



R^1 = CH_3, C_2H_5, Pr^i, CH_2Pr^i, Bn, 3-Py;
R^2 = Ph, C_6H_4R-4 (R = C_2H_5, NH_2, Br), $C_6H_2(OCH_3)$-2,3,4, 2-Naph;
R^3 = H, R^2–R^3 = $(CH_2)_n$ (n = 3–5)

aldehyde **B**, which undergoes base-catalyzed intramolecular cyclization followed by dehydration to give the target product (Scheme 27). The presumptive reaction mechanism was confirmed by control experiments.

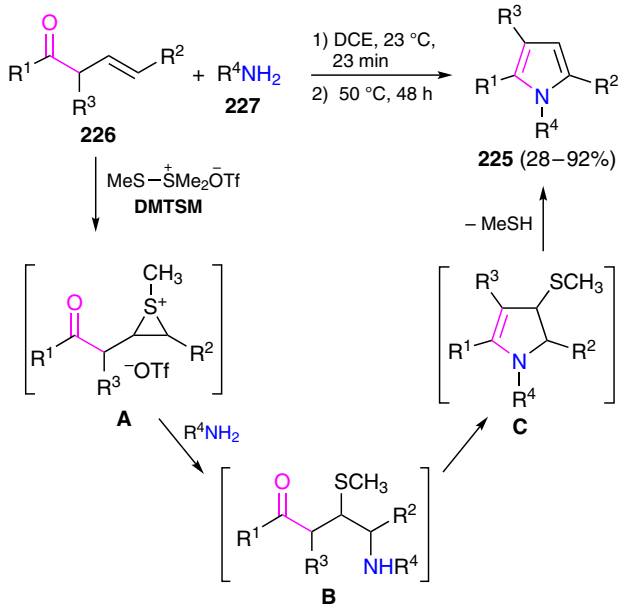
Scheme 27



Pyrroles **225** were obtained in good yields from allyl ketones **226** and amines **227** (Scheme 28).[162] The reaction includes C = C bond activation in allyl ketones with dimethyl(methylthio) sulfonium trifluoromethanesulfonate (DTMSM), the subsequent nucleophilic addition of primary amine to the episulfonium intermediate **A** accompanied by ring opening, intramolecular condensation of the resulting amino ketone **B** and aromatization of intermediate pyrroline **C**.

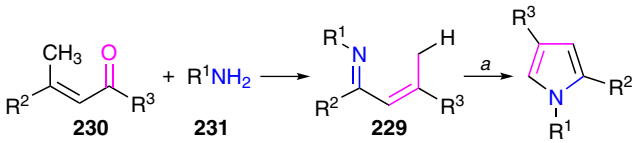
An atom-economical approach to the synthesis of 1,2,4-trisubstituted pyrroles **228** is based on palladium-catalyzed intramolecular amination of the $C(sp^3)$–H bond in 1-azadienes **229**, formed upon unsaturated ketones **230** and amines **231** (Scheme 29).[163]

Scheme 28



R^1 = $(CH_2)_6$, Ph, C_6H_4R-4 (R = CH_3, OCH_3, F, Br, I, CF_3), $C_6H_4CH_3$-2, 2-Fu, 2-Th, 2-Naph, 2-styryl; R^2 = R^3 = H, CH_3; Tf = CF_3SO_2

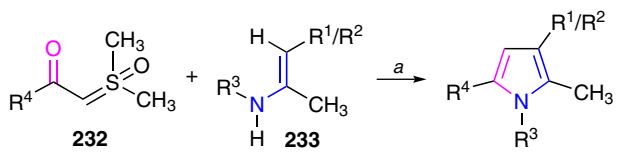
Scheme 29



(*a*) $Pd(OAc)_2$, TBAB, DMSO, 80 °C;
R^1 = Bu^t, Ph, C_6H_4R-4 (R = CH_3, OCH_3), $C_6H_4CH_3$-2;
R^1 = R^2 = Ph, C_6H_4R-4 (R = CH_3, OCH_3, Cl, Br), 2-Th;
TBAB = Bu_4Br^n

The reactions of acyl-substituted sulfoxonium ylides **232** with unsaturated amines **233** catalyzed by $[Ir(COD)Cl]_2$ and *p*-toluenesulfonic acid afford 2,3,5-substituted pyrroles **234** (Scheme 30).[164]

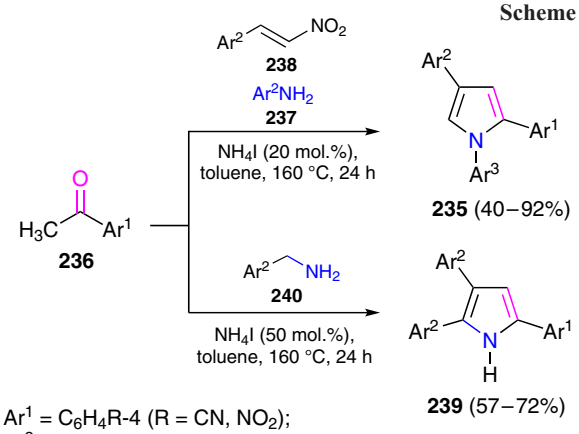
Scheme 30



(*a*) $[Ir(COD)Cl]_2$ (2 mol.%), *p*-TSA (10 mol.%), toluene, MW, 140 °C, 45 min;
R^1 = CO_2CH_3; R^2 = $CO_2C_2H_5$; R^3 = H, Bn, cyclo-C_4H_7, Cy, $(CH_2)_3$Ph, $CH_2C_6H_4$R-4 (R = Ph, OCH_3), $C_6H_4OCH_3$-4;
R^4 = Ph, C_6H_4R-4 (R = F, Cl, NO_2), C_6H_4R-2 (R = Br, OCH_3);
Cy is cyclohexyl

A number of polyaryl-substituted pyrroles **235** were obtained in high yields from aryl ketones **236**, anilines **237** and nitrostyrenes **238** in the presence of 20 mol.% NH_4I (Scheme 31).[165] The multicomponent reaction proceeds *via* the intermediate formation of the products of condensation of ketones with anilines. 2,3,5-Triarylpyrroles **239** can also be formed without using nitrovinylarenes by the reaction of aryl

Scheme 31

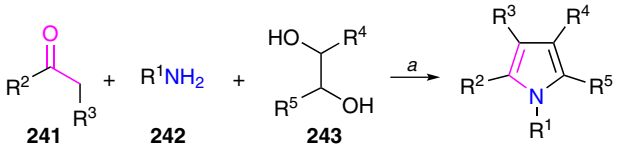


Ar^1 = C_6H_4R-4 (R = CN, NO_2);
Ar^2 = H, C_6H_4R-4 (R = CH_3, OCH_3, F, Cl, Br, CN), C_6H_4R-2 (R = CH_3, Cl, Br), $C_2H_3(CH_3)_2$-3,4;
Ar^3 = Ph, $C_6H_4CH_3$-4, C_6H_4Cl-2

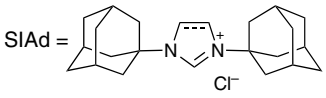
ketones **236** with two equivalents of benzylamines **240**. In the latter case, the amount of NH_4I was increased to 50 mol.%.

The three-component reaction of aryl methyl ketones **241** with various amines **242** and 1,2-diols **243** catalyzed by [Cu(NHC)] (NHC is *N*-heterocyclic carbene formed *in situ*) affords substituted pyrroles **244** (Scheme 32).[166]

Scheme 32

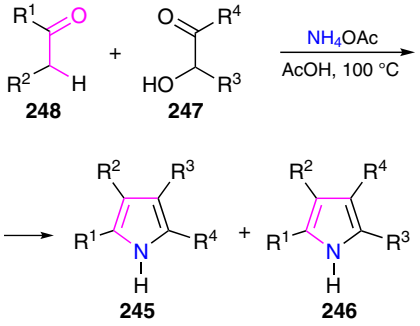


(a) CuBr–SIAd (4 mol.%), $LiOBu^t$ (25 mol.%), 140 °C, 24 h;
R^1 = $(CH_2)_2$Ph, $CH_2N(C_2H_5)_2$, $C_6H_4OCH_3$-4;
R^2 = Ph, $C_6H_4OCH_3$-4, 2-Naph; R^3, R^4 = H, CH_3;



An efficient method for the assembly of unsymmetrical tetraaryl-substituted pyrroles **245** and **246** by acid-promoted cross-dehydrative aromatization has been developed (Scheme 33).[167] In this synthesis, two monocarbonyl compounds, benzoin **247** and deoxybenzoin **248**, were used as substrates. Owing to the tautomerization capability of benzoin **247**, its reaction with deoxybenzoins containing two different substituents gave not only pyrroles **245**, but also their regioisomers **246**.

Scheme 33

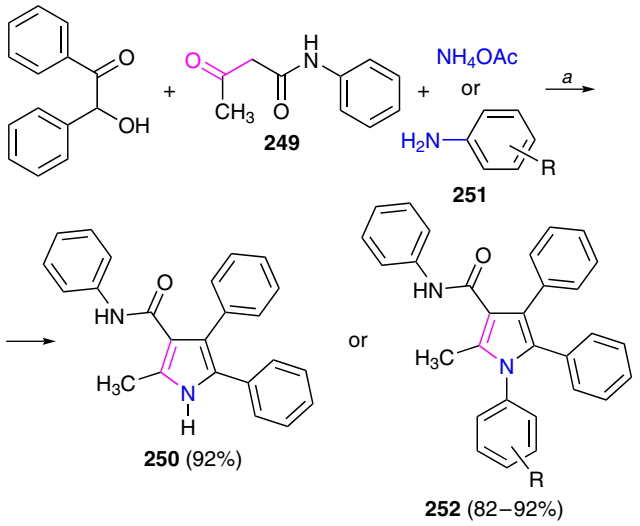


R^1 = $C_6H_4CH_3$-4, $C_6H_4OCH_3$-4, C_4H_2Br-2;
R^2 = C_6H_4R-4 (R = OCH_3, F, Bu^t);
R^3 = Ph;
R^4 = C_6H_4Cl-4

245 + **246** 95% (5:1); 89% (5:1); 46% (4:1)

The use of acetoacetanilide **249** as the carbonyl compound under the same conditions provided 2-methyl-1,4,5-triphenylpyrrole-3-carboxamide **250** (Scheme 34).[168] When anilines **251** were used in this reaction instead of ammonium acetate, pentasubstituted pyrrole-3-carboxamides **252** were obtained (see Scheme 34).

Scheme 34

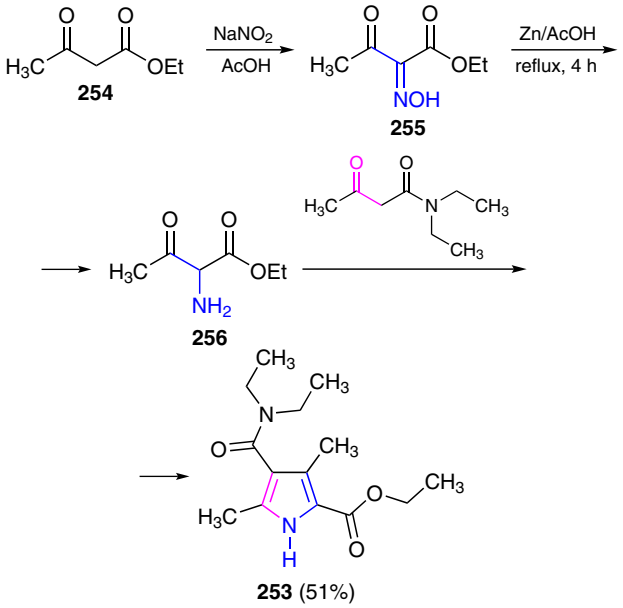


(*a*) CH_3CO_2H, 100 °C; R = CH_3, C_6H_4R-4 (R = F, Br, CN, OCH_3), $C_6H_4NO_2$-3, C_6H_4Cl-2

5.1.4. Knorr synthesis

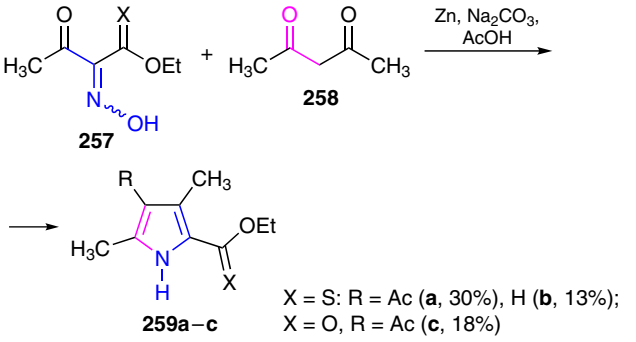
Pyrrole **253** was obtained from ethyl acetoacetate **254** by the Knorr reaction. The synthesis includes three preparative steps: (1) nitrosation of ethyl acetoacetate **254** with $NaNO_2$ in acetic acid, (2) reduction of oxime **255**, and (3) reaction of amine **256** formed *in situ* with *N*,*N*- diethylacetoacetamide (Scheme 35).[169]

Scheme 35



Similarly, oxime **257** and 2,4-pentanedione **258** were allowed to react to give pyrrole **259a** (Scheme 36).[170] The reaction was accompanied by the formation of deacylated pyrrole **259b** and ethyl pyrrole-2-carboxylic acid **259c**.

Scheme 36

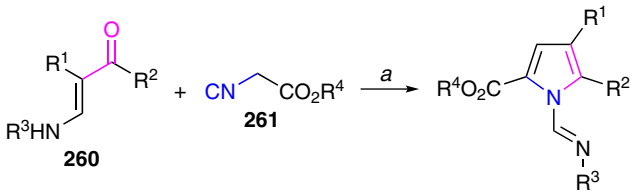


X = S: R = Ac (**a**, 30%), H (**b**, 13%);
X = O, R = Ac (**c**, 18%)

5.1.5. Synthesis from β-aminoenones

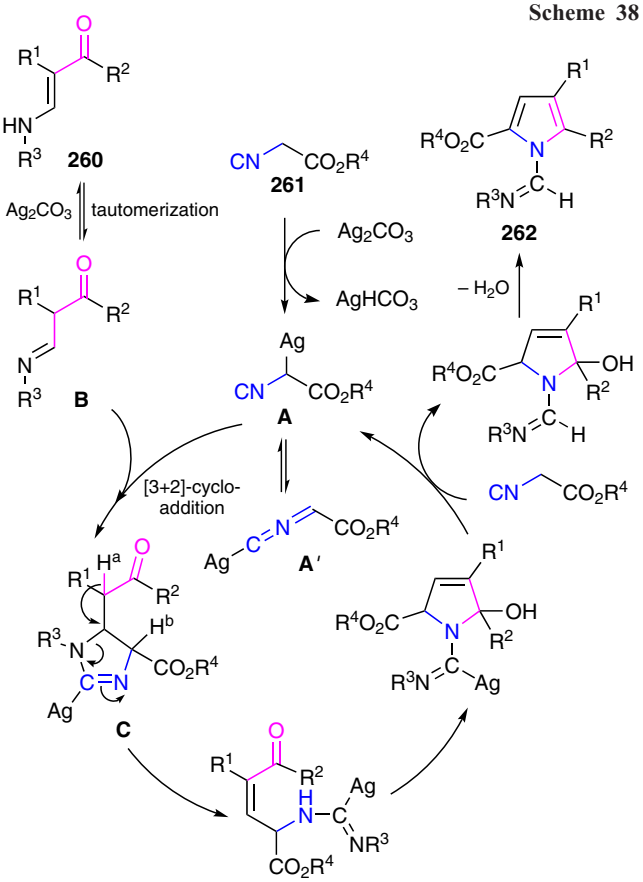
Fang *et al.*[171] described the cascade reaction of β-aminoenones **260** with isocyanoacetates **261** catalyzed by Ag_2CO_3 (10 mol.%) giving rise to functionalized pyrroles **262** (Scheme 37). This reaction can proceed for enaminones both containing electron-withdrawing and electron-donating substituents. When H_2O (5 mol.%) was added to the catalytic system, the yield of target pyrroles increases to 92%.

Scheme 37



(*a*) Ag_2CO_3 (10 mol.%), 1,4-dioxane, 80 °C, 6–24 h, N_2;
R^1 = CO_2R (R = CH_3, C_2H_5, Pr^n, C_5H_{11}, Bn, Ph); R^2 = CH_3, C_2H_5;
R^3 = Ph, C_6H_4R-4 (R = F, I, OCH_3), C_6H_4Br-2-CH_3-4, $C_6H_3Cl_2$-2,4, 1-Naph; R^4 = CH_3, C_2H_5

Scheme 38

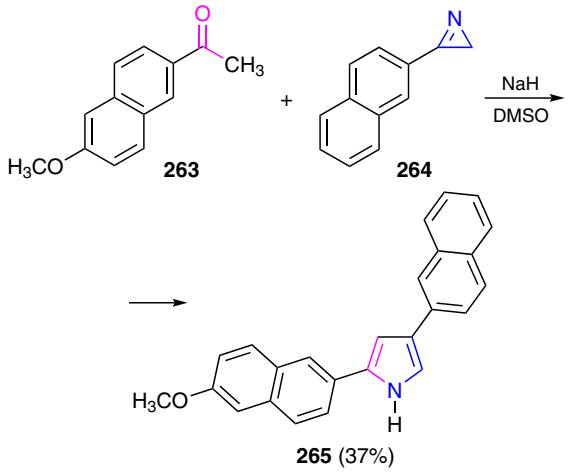


Relying on these results, the authors proposed a possible mechanism for the reaction (Scheme 38). Apparently, the first step is activation of isocyanoacetate **261** containing an acidic α-hydrogen atom with Ag_2CO_3 to give intermediate **A**. This intermediate reacts, in the form of tautomer **A′**, with the iminium tautomer **B** of aminoenone **260** to form 2-imidazoline **C**, which undergoes ring opening, cyclization and dehydration to be converted to the target pyrrole **262**.

5.1.6. Synthesis from ketones and azirines

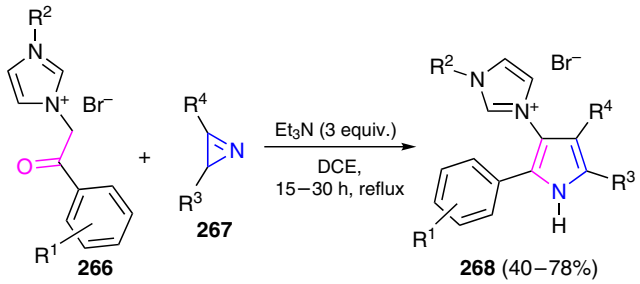
The reaction of ketone **263** with azirine **264** in the NaH/DMSO system furnishes pyrrole **265** (Scheme 39).[172]

Scheme 39



The domino reaction of imidazole derivatives of ketones **266** with 2*H*-azirines **267** provides a simple approach to pyrrole imidazolyl bromides **268** (Scheme 40).[173]

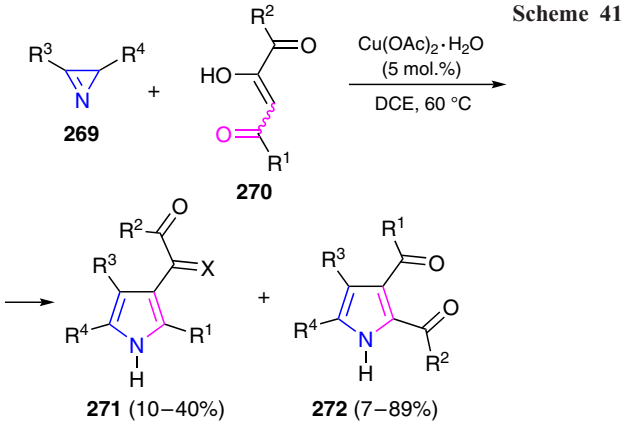
Scheme 40



R^1 = H, 4-OCH_3, 2,4-$(OCH_3)_2$, 4-NO_2, 3-NO_2, 3-Br, 4-Br, 4-F, 4-Cl;
R^2 = CH_3, Bn; R^3 = H, $CO_2C_2H_5$, Ph; R^4 = CH_3, Ph

2*H*-Azirines **269** were allowed to react with 1,2,4-tricarbonyl compounds **270** in the presence of $Cu(OAc)_2$, which gave 3-(1,2-dioxoethyl)- and 2,3-dicarbonylpyrroles **271** and **272** (Scheme 41).[174]

Scheme 41

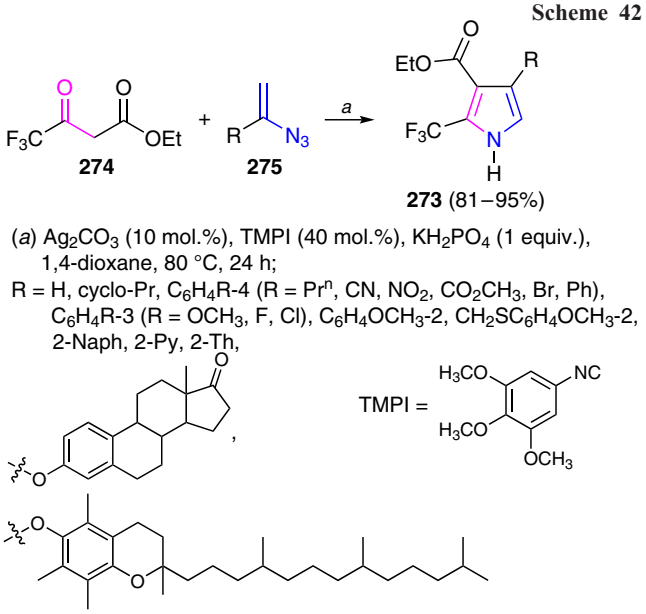


R^1 = CH_3, Ph, C_6H_4Br-2; R^2 = OCH_3, OC_2H_5;
R^3 = CH_3, Bu^t, Ph, C_6H_4R-4 (R = OCH_3, NO_2, Br), $C_6H_4NO_2$-3;
R^4 = H, $CO_2C_2H_5$, Ph

2-Trifluoromethyl-*NH*-pyrroles **273** were prepared by silver carbonate-catalyzed reaction of 4,4,4-trifluoro-3-oxobutanoate **274** with various alkyl, β-aryl and α-heteroaryl and α,β-disubstituted vinyl azides **275** (Scheme 42).[175] High pyrrole yields are attained when 3,4,5-trimethoxyphenyl isocyanide (TMPI) and KH_2PO_4 are added to the catalyst.

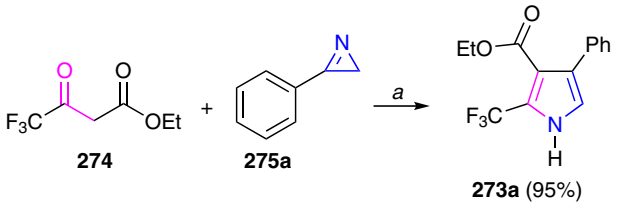
In this case, the pyrrole ring is constructed *via* the intermediate formation of 2*H*-azirines, which was confirmed by the synthesis of pyrrole **273a** (R = Ph) in a quantitative yield from 3-phenyl-2*H*-azirine **275a** and 4,4,4-trifluoro-3-oxobutanoate **274** (Scheme 43).[175]

Scheme 42



(*a*) Ag_2CO_3 (10 mol.%), TMPI (40 mol.%), KH_2PO_4 (1 equiv.), 1,4-dioxane, 80 °C, 24 h;
R = H, cyclo-Pr, C_6H_4R-4 (R = Pr^n, CN, NO_2, CO_2CH_3, Br, Ph), C_6H_4R-3 (R = OCH_3, F, Cl), $C_6H_4OCH_3$-2, $CH_2SC_6H_4OCH_3$-2, 2-Naph, 2-Py, 2-Th,

Scheme 43



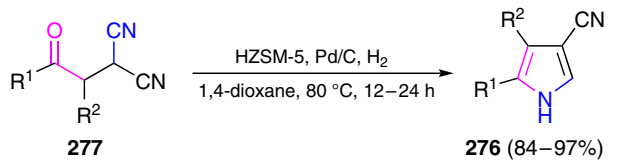
(*a*) Ag_2CO_3 (10 mol.%), TMPI (40 mol.%), KH_2PO_4 (1 equiv.), 1,4-dioxane, 80 °C, 24 h

5.1.7. Intramolecular cyclization of carbonyl-containing compounds

4,5-Substituted pyrrole-3-carbonitriles **276** are formed in a high yield upon hydrogenation of 2-(2-oxo-2-arylethyl)malononitriles **277** either catalyzed by HZSM-5 zeolite and Pd/C (Scheme 44),[176] or in the presence of acetic acid in a reactor filled with Pd/Al_2O_3.[177]

According to Chen *et al.*,[176] the reaction includes the formation of ketoimines **A**, which then cyclize (as aminoenone tautomers **B**) to give hydroxypyrrolines **C**, and acid-catalyzed dehydration of **C** (Scheme 45).

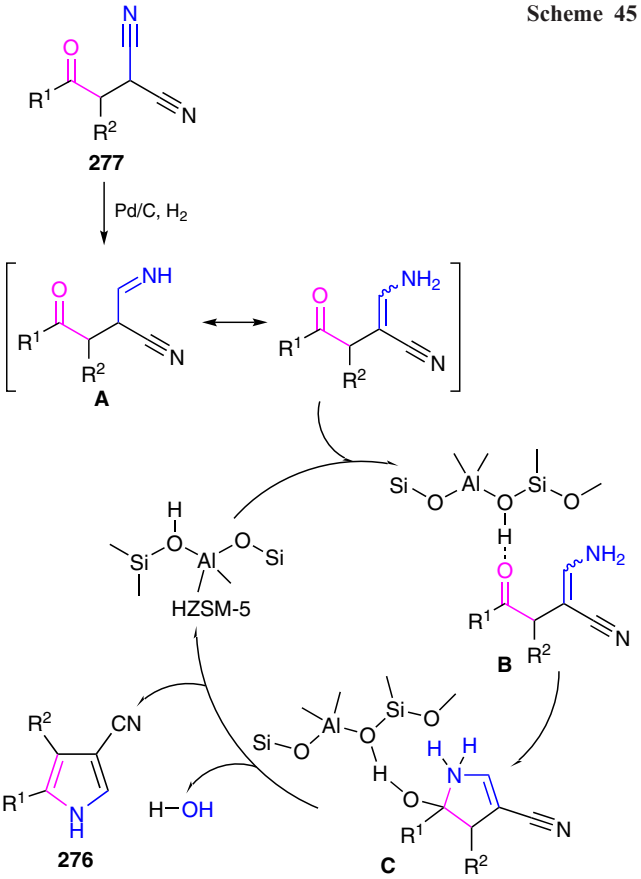
Scheme 44



277 **276** (84–97%)

R^1 = Ph, C_6H_4R-4 (R = F, Cl, OCH_3, CF_3), C_6H_4R-3 (R = F, Cl), $C_6H_4OCH_3$-2, $C_6H_3(OCH_3)_2$-3,4, 1-Naph, 2-Naph, 2-Fu;
R^2 = H, CH_3

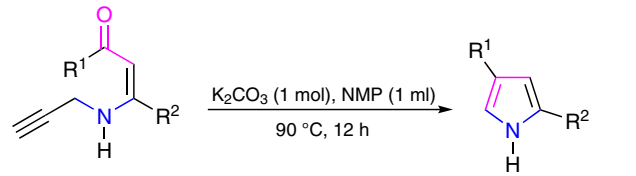
Scheme 45



In recent years, *N*-propargyl-β-aminoenones have been widely employed to prepare *N*-heterocyclic compounds. The main data concerning their conversion to substituted pyrroles are described in detail in recent reviews.[178,179]

The present review gives a few examples of application of these compounds for the formation of the pyrrole ring that were not included in the above reviews. Cheng *et al.*[180] described a base-catalyzed intramolecular cyclization of *N*-propargyl-β-aminoenones **278** to 2,4-disubstituted pyrroles **279** (Scheme 46).

Scheme 46

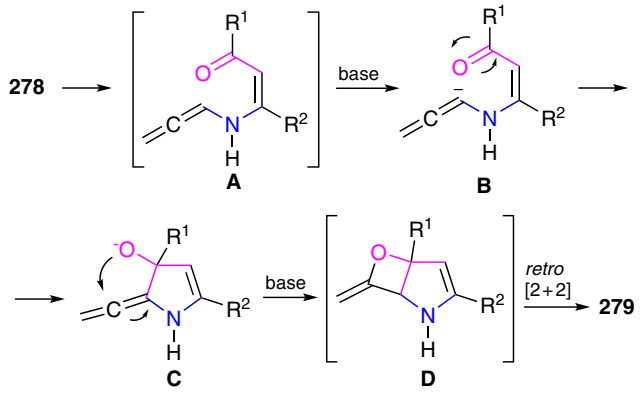


278 **279** (up to 93%)

R^1 = Ph, C_6H_4R-4 (R = CH_3, Bu^t, F, Cl, Br, CF_3), $C_6H_4OCH_3$-3, 2-Tol-, $C_6H_4Cl_2$-3,4, 2-Naph, 2-Th;
R^2 = C_6H_4R-4 (R = CH_3, OCH_3, F, Cl), 2-Tol, 3-Tol; Tol is tolyl

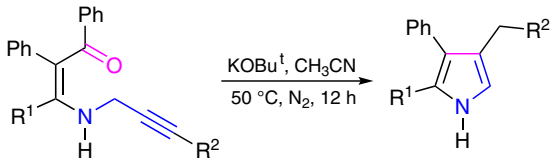
Presumably, the first step results in the formation of *N*-allenyl-β-aminoenones **A**, which then undergo deprotonation of the allene group to give anion **B**. The two subsequent intramolecular cyclizations (5-*exo-trig* involving the carbonyl group and giving alcoholate **C** and 4-*exo-dig* to give oxetane **D**) and stepwise retro-[2+2]-reaction complete the pyrrole ring assembly (Scheme 47).

Scheme 47



The base-catalyzed intramolecular cyclization of *N*-propargyl-β-aminoenones **280** gives rise to 2,3,4-trisubstituted pyrroles **281** in high yields (Scheme 48).[181]

Scheme 48

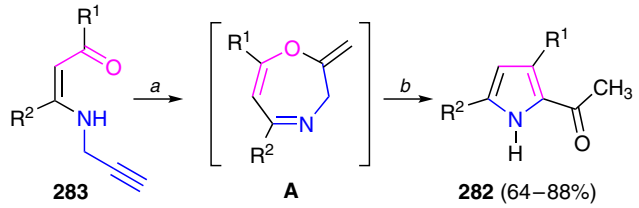


280 **281** (70–87%)

R^1 = CH_3, Ph, C_6H_4R-4 (R = OCH_3, F), C_6H_4F-3;
R^2 = CH_3, Ph, C_6H_4R-4 (R = CH_3, OCH_3, OCF_3, F, Cl, $CO_2C_2H_5$, Ac), C_6H_4R-3 (R = CH_3, F)

One-pot synthesis of 2-acetyl-*NH*-pyrroles **282** from *N*-propargyl-β-aminoenones **283** was performed by refluxing the starting compounds in CH_3OH in the presence of $ZnCl_2$.[182] The reaction proceeds *via* the intermediate formation of 1,4-oxazepines **A** (Scheme 49).

Scheme 49

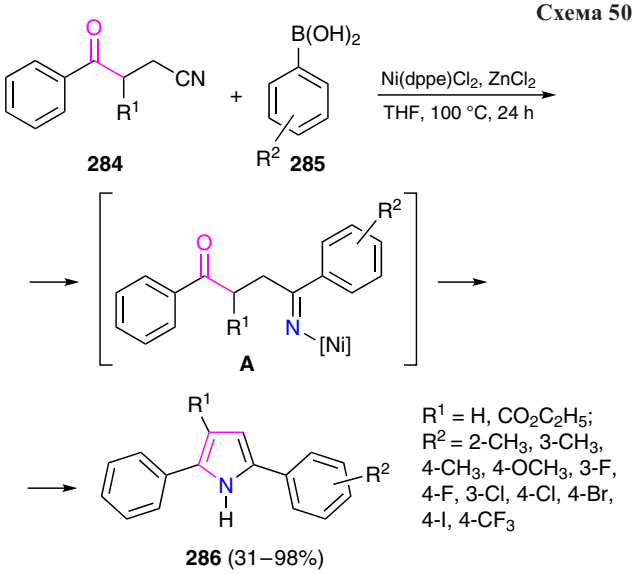


(*a*) $ZnCl_2$ (1 equiv.), $CHCl_3$, 61 °C;
(*b*) $ZnCl_2$ (1 equiv.), CH_3OH, 65 °C;
R^1 = Ph, C_6H_4R-4 (R = CH_3, Cl); R^2 = Ph, C_6H_4R-4 (R = CH_3, OCH_3, Cl, Br, CF_3, $N(CH_3)_2$), 2-Th

5.1.8. Miscellaneous reactions

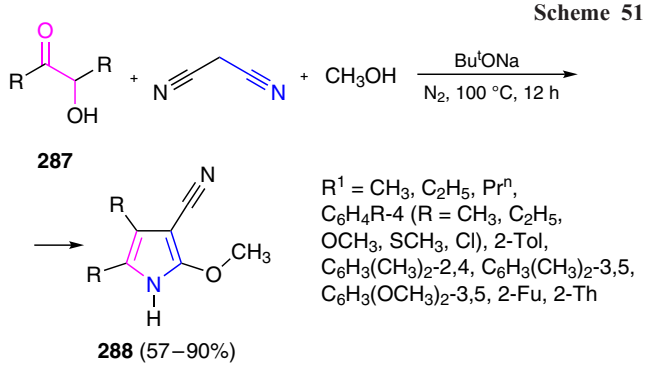
The Ni(dppe)Cl_2-catalyzed C–C, N–C cascade coupling of aromatic ketonitriles **284** with arylboronic acids **285** gives either 2,5-diaryl-3-pyrrolecarboxylates (R^1 = CO_2Et) or 2,5-diarylpyrroles (R^1 = H) **286**, depending on the structure of the starting ketonitrile (Scheme 50).[183] The reaction proceeds *via* intermediate **A** according to the Paal–Knorr reaction pathway.

Схема 50



The cascade reaction of α-hydroxy ketones **287**, malonodinitrile and methanol furnishes a series of structurally diverse and synthetically useful 2-alkyloxy-1*H*-pyrrole-3-carbonitrile derivatives **288** (Scheme 51).[184]

Scheme 51



6. Pyrrole synthesis from dicarbonyl compounds

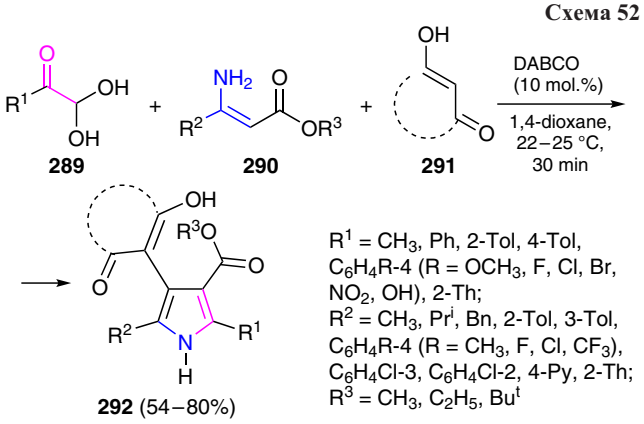
Due to limited size of the review, we cannot include all results attained in this actively developing field of knowledge. Therefore, while speaking about the synthesis of pyrroles from diketones, we have deliberately chosen only those studies in which the diketone forms only one pyrrole core, leaving aside the cases where each keto group of the diketone forms its own pyrrole ring, for example, *via* ketoxime, as it was shown in a large series of works by Academician B.A.Trofimov and co-workers collected in a monograph.[185]

6.1. Synthesis from 1,2-dicarbonyl compounds

1,2-Dicarbonyl compounds, in particular arylglyoxals, aromatic α-keto aldehydes, are widely used (in the form of monohydrates) as precursors in the pyrrole synthesis.[186,187]

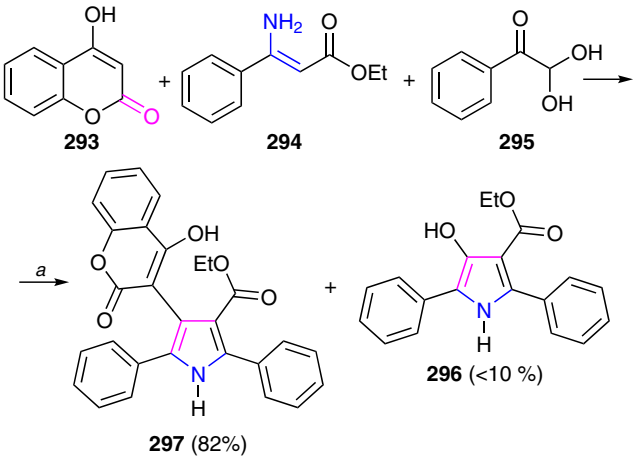
For example, the three-component domino reaction between arylglyoxal monohydrates **289**, enamino ethers **290** and cyclic 1,3-dicarbonyl compounds **291** catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) and proceeding under mild conditions results mainly in the formation of *NH*-pyrroles **292** (Scheme 52).[188]

Схема 52



In relation to hydroxycoumarin **293**, it was shown that the reaction with enamino ester **294** and phenylglyoxal monohydrate **295** is accompanied by the formation of minor amounts of *NH*-pyrrole **296** (Scheme 53).[188] Pyrrole **296** is the major product of the non-catalytic reaction between the above reactants in ethanol.

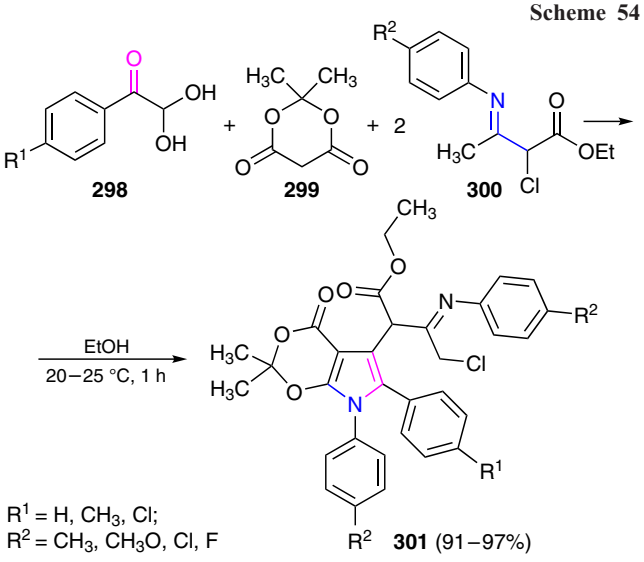
Scheme 53



(*a*) DABCO (10 mol.%), 1,4-dioxane, 22–25 °C, 30 min

The three-component reaction of arylglyoxal monohydrates **298** with Meldrum's acid **299** and two equivalents of ethyl

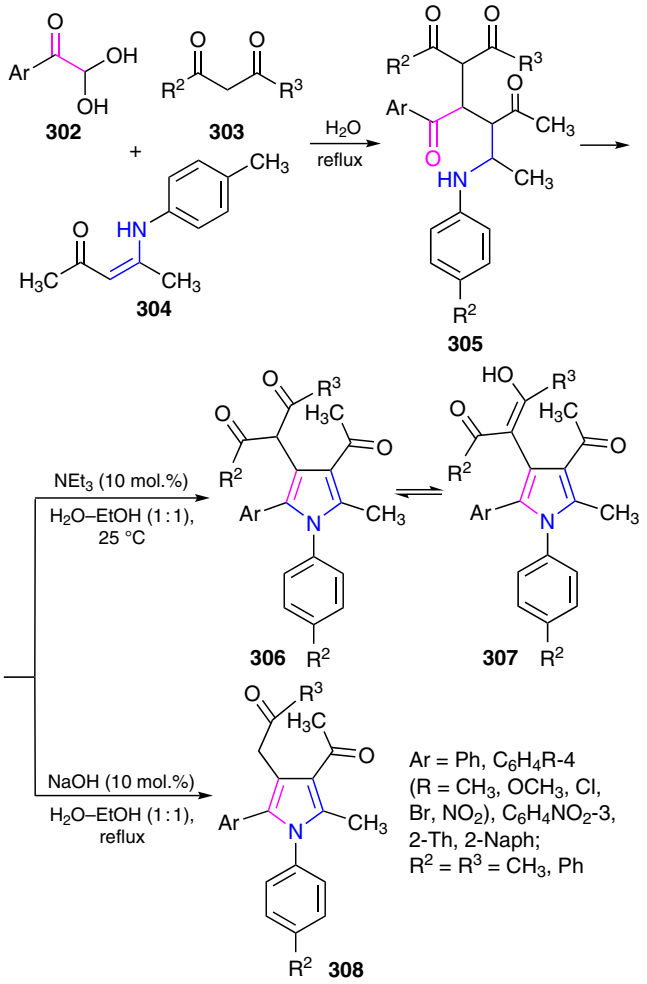
Scheme 54



2-chloro-3-(arylimino)but-2-enoates **300** furnishes functionalized pyrroles **301** in high yields (Scheme 54).[189]

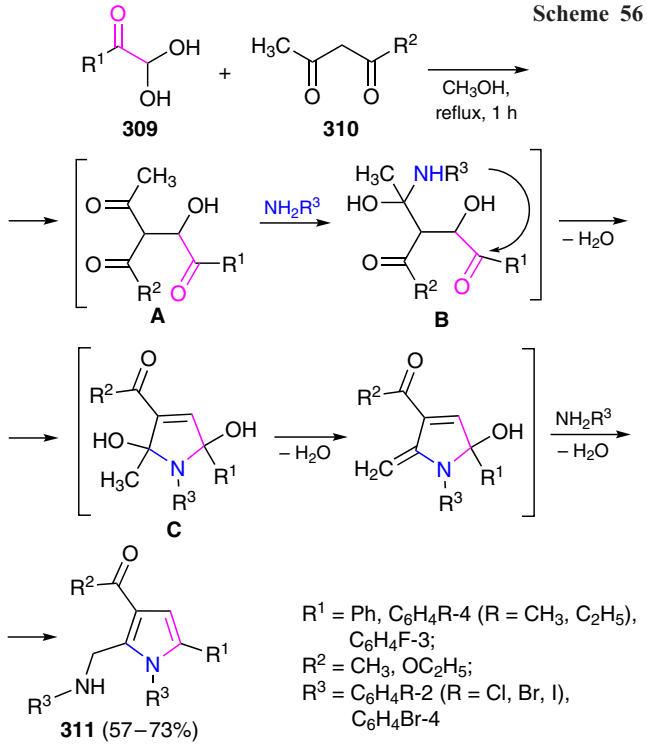
The three-component reaction of arylglyoxal monohydrates **302** with 1,3-diketones **303** and aminoenones **304** affords tetraones **305**, which are readily converted to polyfunctionalized pyrroles **306**–**308**. The reaction is carried out in water or in aqueous ethanol (Scheme 55).[190]

Scheme 55



The three-component condensation of arylglycolium hydrates **309**, acetylacetone or ethyl acetoacetate **310** and halo-substituted anilines carried out by refluxing in methanol yields tetrasubstituted pyrroles **311** (Scheme 56).[191] The reaction mechanism includes the initial formation of hydroxy ketone **A**, which reacts with aromatic amine to afford hemiaminal **B**. The subsequent Paal–Knorr cyclization to hydroxypyrroline **C**, its dehydration and 1,4-addition of a second aniline molecule complete the assembly of pyrrole **311**.

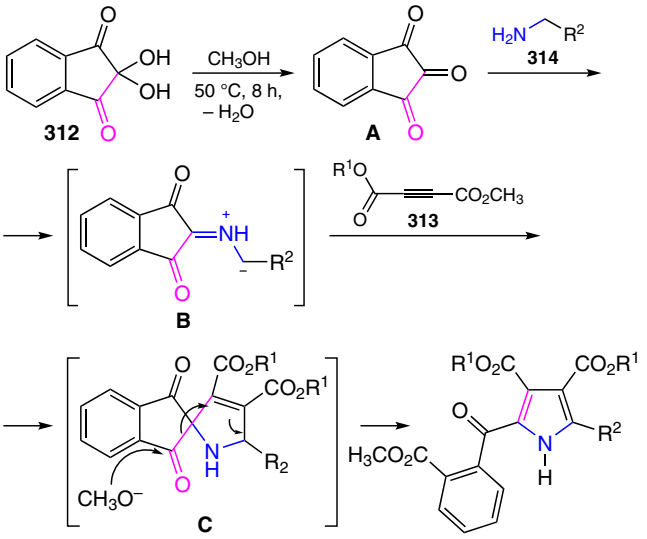
Scheme 56



The three-component reaction of ninhydrin **312**, dialkyl acetylenedicarboxylates **313** and amines **314** in methanol gives rise to pyrrole derivatives **315** (Scheme 57).[192,193]

Presumably, the reaction proceeds as a [3+2]-cycloaddition of azomethine ylide **B** to dipolarophile **313**. First, ninhydrin **312** is converted to 1,2,3-indanetrione **A** under the action of methanol; then compound **A** reacts with amine to give dipole **B**, which adds to dipolarophile **313**. The resulting spiro adduct **C** is converted to product **315**.

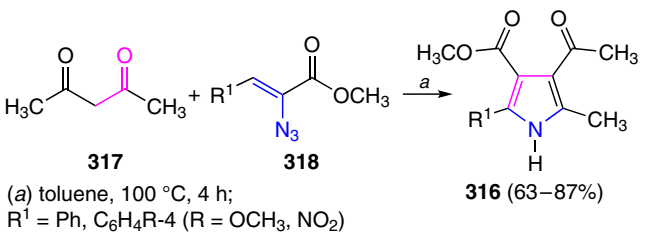
Scheme 57



6.2. Synthesis from 1,3-dicarbonyl compounds

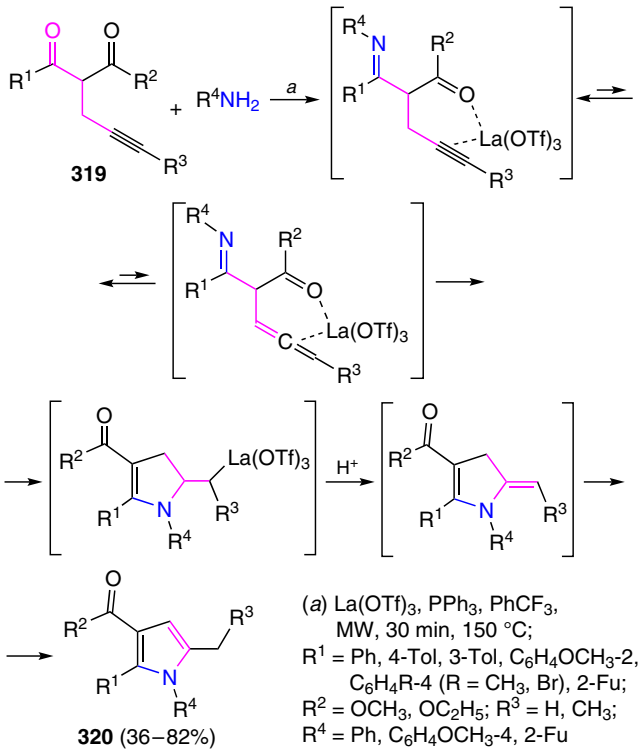
Tetrasubstituted pyrroles **316** were obtained by refluxing pentanedione **317** with vinyl azide **318** in toluene (Scheme 58).[194]

Scheme 58



The $La(OTf)_3$-catalyzed reaction of propargyl-β-ketoethers **319** with amines proceeds as successive condensation, cyclization and isomerization and thus results

Scheme 59



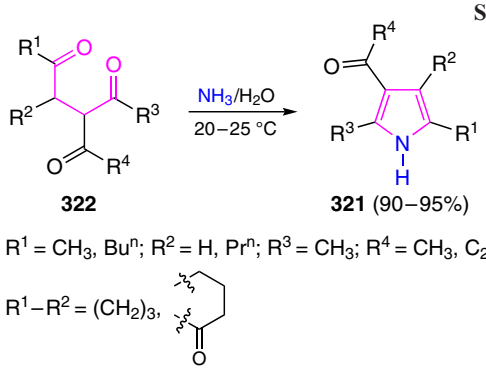
in the formation of tetrasubstituted 2-arylpyrroles **320** (Scheme 59).[195]

6.3. Synthesis from 1,4-dicarbonyl compounds

The condensation of amines with 1,4-dicarbonyl compounds, one of the most well-known methods for the synthesis of pyrroles (Paal–Knorr synthesis),[196] still attracts the attention of synthetic chemists owing to the ready availability of reactants.

For example, *NH*-pyrroles **321** with acyl substituents in position 3 of the pyrrole ring were obtained by intramolecular condensation of tricarbonyl compounds **322** with a 25% ammonium hydroxide solution under mild conditions (Scheme 60).[197]

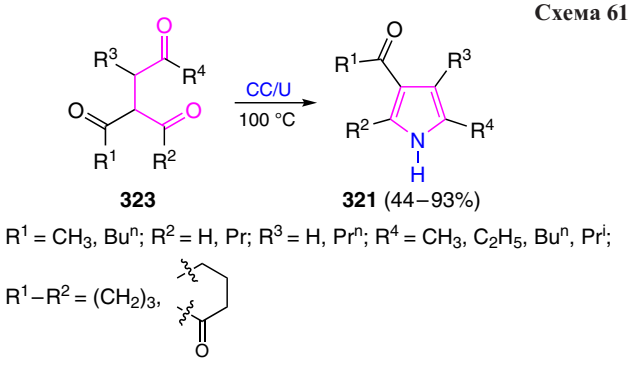
Scheme 60



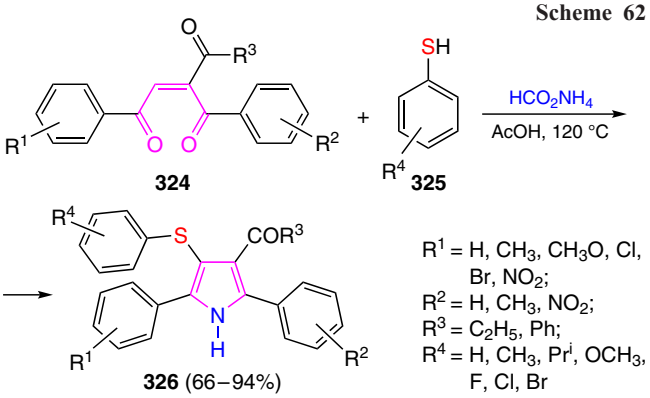
Analogous pyrroles **321** were obtained by intramolecular condensation of tricarbonyl compounds **323** with ammonia that is generated upon the decomposition of urea present as a part of a deep eutectic solvent such as choline chloride/urea (CC/U) (Scheme 61).[198]

The three-component reaction of 1,4-enediones **324**, thiols **325** and ammonium formate (Scheme 62), which includes the Michael addition of thiol **325** and the Paal–Knorr reaction to give one new C–S bond and two C–N bonds, affords 4-thioarylpyrroles **326** in high yields.[199]

Схема 61



Scheme 62



7. Conclusion

Thus, the material summarized in the review attests to significant advances in the field of synthesis of pyrroles with definite specified properties from ketones and diketones and can be recommended to a wide range of synthetic chemists. Along with the improvement of known synthetic routes, the search for new preparative reactions is in progress; this makes it possible to obtain pyrroles from more readily available starting compounds.

To summarize consideration of the methods for the pyrrole ring assembly from ketones and diketones, it may be noted that these methods are characterized by high selectivity, simple equipment design and ready availability of reactants and catalysts. Carbonyl and dicarbonyl compounds can be recommended as starting compounds for preparing a wide range of pyrroles with specified properties.

For the understanding of the current trends in the pyrrole chemistry, we will give a brief list of its most significant achievements. The heterocyclization of ketones (as oximes) with acetylene in an alkali metal hydroxide–dimethyl sulfoxide superbasic system is still one of the most convenient and popular methods for pyrrole synthesis. This reaction is known in the literature as the Trofimov reaction. It can be used to obtain various substituted pyrroles by varying the nature of the ketoximes. In addition, the use of cheap and readily available chemicals reduces the cost of pyrrole synthesis. However, gaseous acetylene is not always applicable for a selective synthesis and is unsafe, whereas the use of synthetic equivalents of acetylene (dihaloethanes, calcium carbide) is more promising, since these reagents are less hazardous and are easily applied in laboratory without any special equipment and skills for handling explosive gases.

Also noteworthy are the advances in the development of other classic reactions for the synthesis of various pyrroles: condensation of aminoketones (Knorr synthesis), reactions of ketones with amines or azirines and intramolecular cyclization reactions. Certainly, in some cases, these reactions require the use of expensive and poorly accessible catalysts, harsh reaction conditions (long-term refluxing, labourious isolation of target pyrroles), which markedly decreases their applicability for the synthesis of substituted pyrroles; however, microwave activation eliminates many restrictions and, hence, attracts the attention of synthetic chemists.

The preparation of pyrroles from 1,2-, 1,3- and 1,4-dicarbonyl compounds (Paal–Knorr synthesis) is still important. Owing to the simplicity and availability of 1,4-dicarbonyl compounds, the Paal–Knorr synthesis of pyrroles attracts attention of synthetic chemists, and the scope of this reaction is constantly expanding.

Along with the classic approaches, there is a large inventory of completely original methods, which not only provide a new look at classic processes, but also create novel synthetic strategies. Although most of these methods are more likely to fill the gaps of classic methods in the range of substrates and use less available starting compounds, the potential of development of these approaches will undoubtedly add completely new aspects to the already vivid pyrrole chemistry.

The authors hope that this review will expand the readers' views and will be useful for specialists in the pyrrole chemistry and or chemists engaged in the related fields of organic and medicinal chemistry

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8. Abbreviations

Ac — acetyl,
BM 212 — 1-[(1,5-bis(4-chlorophenyl)pyrrol-3-yl)methyl]-4-methylpiperazine,
Bn — benzyl,
BODIPY — difluoroboradiazaindacene type fluorescent dyes,
COVID-19 — coronaviral infection,
Cy — cyclohexyl,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
DCE — 1,2-dichloroethane,
DTMSM — dimethyl(methylthio)sulfonium trifluoromethanesulfonate,
EWG — electron-withdrawing group,
Fu — furyl,
HOMO — highest occupied molecular orbital,
IC_{50} — half-maximal inhibitory concentration;
IBM — International Business Machines
LUMO — lower unoccupied molecular orbital,
MIC — minimum inhibitory concentration,
MTB — *Mycobacterium tuberculosis*,
MW — microwave radiation,
Naph — naphthyl,
Py — pyridyl,
Pyr — pyrrolyl,
SARS-Cov-2 — virus causing the coronaviral infection,
TBAB — tetrabutylammonium bromide,
Tf — triflyl (trifluoromethanesulfonyl),
Th — thienyl,
TMPI — 3,4,5-trimethoxyphenyl isocyanide,
Tol — tolyl (methylphenyl),
p-TSA — *p*-toluenesulfonic acid.

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