T.V.Beryozkina, P.S.Silaichev, V.G.Ilkin, V.A.Bakulev
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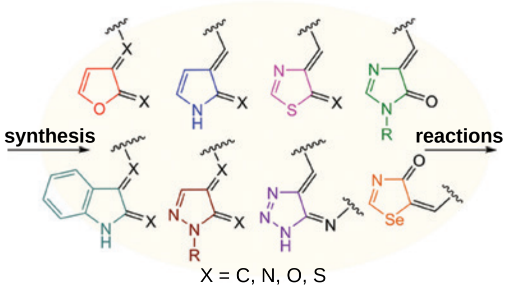
Synthesis and properties of five-membered heterocycles containing two exocyclic conjugated double bonds

Tetyana V. Beryozkina,[a]* **Pavel S. Silaichev,**[b] **Vladimir G. Ilkin,**[a] **Vasiliy A. Bakulev**[a]*

[a] *Ural Federal University named after the first President of Russia B.N.Yeltsin, 620002 Ekaterinburg, Russian Federation*
[b] *Perm State National Research University, 614990 Perm, Russian Federation*



Heterocyclic compounds containing two exocyclic double bonds are underrepresented in the literature compared with aromatic heterocycles. However, over the past decade, there has been a growing interest among organic chemists, both in Russia and globally, in developing effective methods for the synthesis (or generation) of heterocycles that incorporate two or more exocyclic double bonds. Exocyclic bonds are involved in chemical reactions that yield products of various structural forms, including spirocyclic compounds, condensed heterocycles and indolones featuring a C3 quaternary stereocentre. Among these compounds, compounds with diverse biological activities were identified. Currently available reviews focus on specific types of heterocycles or particular scaffolds, or address catalytic reactions only. This review summarizes and systematizes the literature concerning the synthesis, properties, and biological activities of five-membered heterocycles containing two exocyclic conjugated bonds such as C=C and C=C, C=C and C=N, C=C and C=O, C=O and C=N, and C=C and C=S, with a primary focus on materials published between 2016 and 2025.

The bibliography includes 218 references.

Keywords: heterocycles, furans, pyrroles, indoles, thiazoles, pyrazoles, selenazoles, imidazoles, 1,2,3-triazoles, synthesis, mechanism.

Contents

T.V.Beryozkina. PhD in Chemistry, Leading Researcher at the Department of Technology for Organic Synthesis, Institute of Chemical Engineering, Ural Federal University.
E-mail: tetber@mail.ru
Current research interests: chemistry of materials, synthesis of azoles and azines, rearrangements and transformations of 1,2,3-triazoles, synthesis of heterocycles.

P.S.Silaichev. PhD in Chemistry, Senior Researcher at the Department of Organic Chemistry, Perm State National Research University.
E-mail: silaichevp@yandex.ru
Current research interests: synthesis and properties of nitrogen-containing heterocycles, aliphatic and heterocyclic diazo compounds, enamines and natural compounds. Optimization of syntheses for industry, chemoinformatics.

V.G.Ilkin. PhD in Chemistry, Senior Researcher at the Department of Technology for Organic Synthesis, Institute of Chemical Engineering, Ural Federal University. E-mail: v.g.ilkin@urfu.ru
Current research interests: chemistry of diazo compounds and thioamides, catalysis by transition metals, asymmetric synthesis, chemistry of heterocycles.

V.A.Bakulev. Dr. Sci., Professor, The Head of Department of Technology for Organic Synthesis, Institute of Chemical Engineering, Ural Federal University.
E-mail: v.a.bakulev@urfu.ru
Current research interests: pericyclic reactions, chemistry of azides, diazo compounds, enamines, thioamides and 1,2,3-triazoles, synthesis, rearrangements, and transformations of heterocycles.

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1. Introduction

Heterocyclic compounds are undoubtedly among the most important objects of modern organic chemistry due to their wide application in medicine[1–4] and materials chemistry.[5–9] Heterocycles are widely present in nature, being key motifs in the structure of complex metabolites.[10–16] This certainly stimulates the continuation of research aimed at developing new synthetic approaches to nitrogen-containing heterocycles.

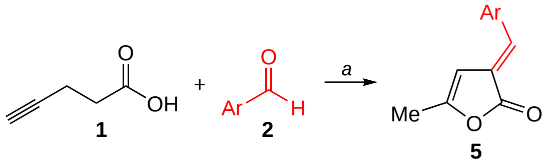
The research efforts led to the creation of novel types of heterocyclic compounds, *vis.*, fused compounds,[17–20] heterocycle assemblies,[21–24] hybrids of two heterocycles connected by a linker[25,26] and non-aromatic heterocycles.[27–29] In the last decade, the interest of organic chemists in the synthesis of heterocycles containing two conjugated exocyclic bonds has increased. Efficient methods have been developed for the synthesis of such compounds containing 1,2,3-triazole,[30] imidazole,[21,31–34] pyrrole,[35–37] pyrazole,[23,38] thiazole,[39–43] indole,[27,37,44–58] (benzo)thiophene,[59] (benzo)furan[28,35,60–67] and selenazole[68] rings. Such molecules react with compounds containing double[29,45,69–72] and triple bonds,[73–75] naphthols,[76] active methylene compounds,[19,25,38,77–82] azomethine ylides[83] and other zwitterionic compounds[21,84] and are the starting materials for the preparation of fused[19,29,38,46,73,74,85–87] and spiroheterocycles.[24,42,45,70,71,78–83,88–96] Heterocycles with three exocyclic bonds have been reported.[97–101] The reviews by Belikov and Milovidova,[37] as well as Yurovskaya and co-workers[102] describe the synthesis and some properties of heterocycles containing conjugated double bonds. The first of the mentioned reviews[37] focuses on compounds containing a dicyanoacrylamide moiety, and the second one[102] highlights reactions catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO), and therefore do not cover the entire variety of compounds containing two conjugated double bonds.

This review provides the first generalization and systematization of the methods of synthesis and features of thermal and catalytic reactions of five-membered heterocycles with two exocyclic double bonds, mainly over the period 2016–2025.

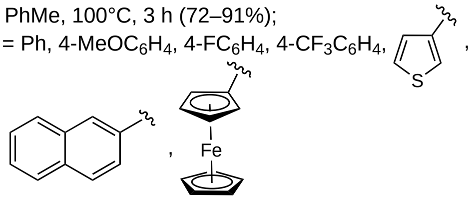
2. Furane derivatives

Among the known five-membered heterocycles with two conjugated exocyclic bonds, the greatest number of publications relate to furan-2-ones containing an aryl(alkyl)idene moiety at position 3 of the ring. Such compounds are of interest due to their diverse biological activities such as antituberculotic,[103] antimalarial,[104] analgesic[105] and anti-inflammatory.[106] In addition, furan-2-ones are useful substrates for the synthesis of various oxacycles[107] and azacycles.[108–110] This Section provides information on the synthesis and properties of furan-2-ones containing either C=C or C=N bonds at position 3 of the ring.

Scheme 1



(*a*) 40 mol.% 2-amino-3-picoline (**3**), 5 mol.% $(PPh_3)_3RhCl$ (**4**), PhMe, 100°C, 3 h (72–91%);
Ar = Ph, $4\text{-}MeOC_6H_4$, $4\text{-}FC_6H_4$, $4\text{-}CF_3C_6H_4$,



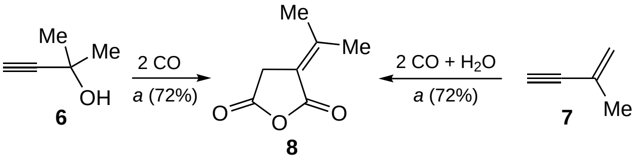
2.1. Metal-catalyzed reactions

Pent-4-ynoic acid **1** react with aldehydes **2** in the presence of 2-amino-3-picoline **3** as the base and Wilkinson's complex **4** to give (*E*)-3-arylidene-3*H*-furan-2-ones **5** (Scheme 1).[111] The reaction pathway includes Rh-catalyzed cyclization of acid **1** to the corresponding lactone, which condenses with aldehydes **2** in the presence of picoline **3**.

When the reaction is carried out under the same conditions, but in the absence of picoline **3**, it delivers only 5-methylenedihydrofuran-2-one.

Alkynes **6** and **7** undergo a catalytic formal carbonylation with carbon(II) monoxide at elevated pressures to yield teraconic anhydride **8** (Scheme 2).[112]

Scheme 2

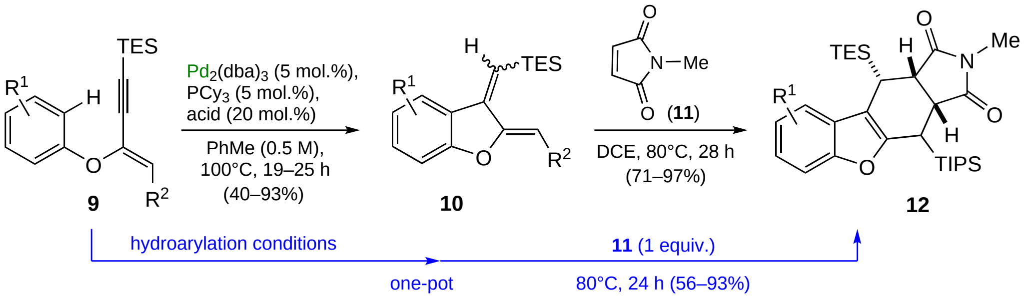


(*a*) PdI_2 (0.1 mmol), KI (1 mmol), H_2O/1,4-dioxane, 60°C, 40 h, 1.5 MPa

An intramolecular *exo*-hydroarylation of 2-aryloxy-1,4-disilylbutenynes **9** *via* the *ortho* C–H bond activation using Pd(0) and acid catalysis furnishes 2,3-bis(silylmethylidene)-2,3-dihydrobenzofurans **10** (Scheme 3).[29]

According to the authors, two silyl groups promote the reaction and play a key role in stabilizing the resulting product

Scheme 3

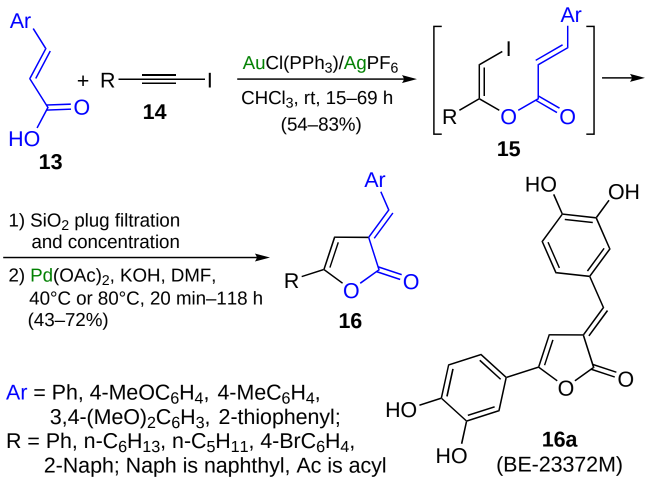


R^1 = H, MeO, F, Ph, CF_3, Me; R^2 = TBS, TIPS; acid = $1\text{-}AdCO_2H$ or Bu^tCO_2H; TBS is *tert*-butyldimethylsilyl; TIPS is triisopropylsilyl, TES is triethylsilyl; dba is dibenzylideneacetone, Cy is cyclohexyl, DCE is dichloroethane, Ad is adamantyl

10. As a result of cycloaddition to *N*-methylmaleimide **11**, *exo*-dienes **10** are easily converted into *endo*-cycloadducts **12** (see Scheme 3). In addition, the developed one-pot protocol allows the use of unstable dienes **10** *in situ* in the reaction with pyrroledione **11**.

The reaction between readily available cinnamic acids **13** and iodoacetylenes **14** gives rise to unstable iodo enol acrylates **15**, which undergo 5-*exo*-*trig*-cyclization *in situ* in the presence of palladium acetate to give the target 3-arylidene-5-aryl(alkyl)-2(3*H*)-furanones **16** (Scheme 4).[60] In some cases, the reaction is rather prolonged and the yields of the target compounds **16** are low. It should be noted that this approach was used in the synthesis of the natural kinase inhibitor BE-23372M (**16a**). Two examples demonstrate the possibility of a one-pot synthesis of 2(3*H*)-furanones **16**, which simplifies their isolation and reduces the reaction time.

Scheme 4

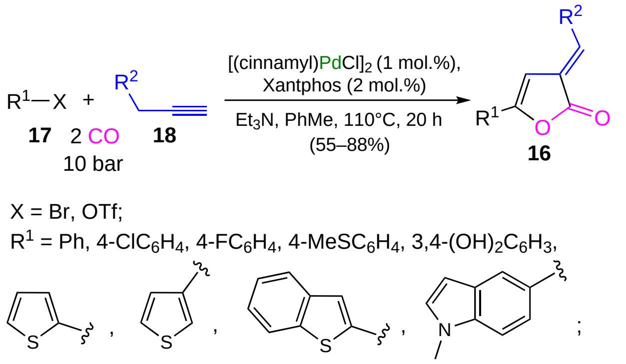


Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 2-thiophenyl;
R = Ph, n-C$_6$H$_{13}$, n-C$_5$H$_{11}$, 4-BrC$_6$H$_4$, 2-Naph; Naph is naphthyl, Ac is acyl

A three-component catalytic reaction of readily available alkyl, aryl, and hetaryl bromides or triflates **17**, acetylenes **18**, and carbon(II) monoxide is a general and efficient method for the synthesis of 5-aryl-3-alkyl(aryl)idenefuranones **16** (Scheme 5).[61] The versatility of this approach is supported by more than thirty examples of the synthesis of compounds **16** in good yields, including the kinase inhibitor BE-23372M (**16a**) (see Scheme 4).

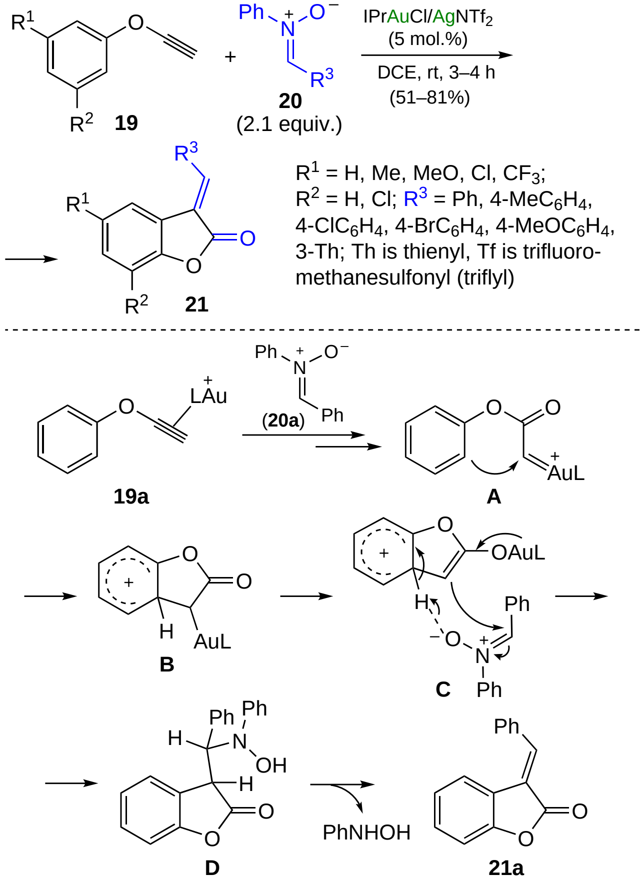
The catalytic reaction of arylpropargyl ethers **19** with nitrones **20** in the presence of gold and silver salts affords 3-alkylidenebenzofuran-2-ones **21** as a mixture of *E*/*Z*-isomers with the *E*-isomer predominating ($E/Z = 2.7–16:1$) (Scheme 6).[84]

Scheme 5



X = Br, OTf;
R^1 = Ph, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeSC$_6$H$_4$, 3,4-(OH)$_2$C$_6$H$_3$, , , , ;
R^2 = 3-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 3,4-(Me)$_2$C$_6$H$_3$, 4-MeSC$_6$H$_4$, 3,4-(OH)$_2$C$_6$H$_3$, 4-(Me)$_2$NC$_6$H$_4$, Pr^n, Bu^n, n-C$_5$H$_{11}$, n-C$_7$H$_{15}$, Cy

Scheme 6

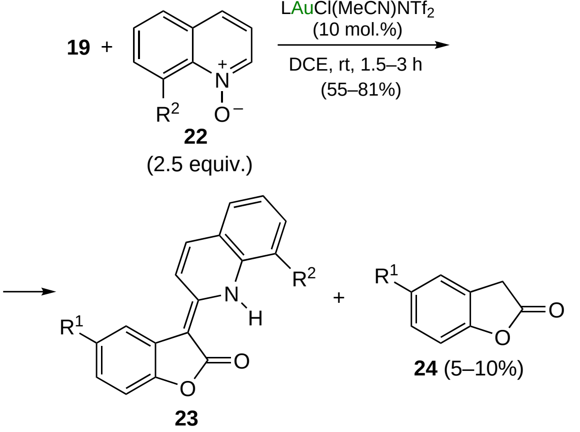


R^1 = H, Me, MeO, Cl, CF$_3$;
R^2 = H, Cl; R^3 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-Th; Th is thienyl, Tf is trifluoromethanesulfonyl (triflyl)

The oxidation reaction pathway involves the formation of a gold carbene **A** (see Scheme 6).[84] After arylation of carbene **A**, the resulting gold enolate **B** reacts with a second nitrone molecule, converting into a complex intermediate **C**. The formation of a new C–C bond induces the formation of intermediate **D**, which then eliminates *N*-hydroxyaniline to give benzofuran-2-one **21a**.

The gold-catalyzed oxidative cycloalkenylation of aryl propargyl ethers **19** with quinoline N-oxides **22** affords 3-alkylidenebenzofuran-2-ones **23** (Scheme 7).[22] Benzofuran-2-ones **24** were isolated as by-products of this reaction. The

Scheme 7



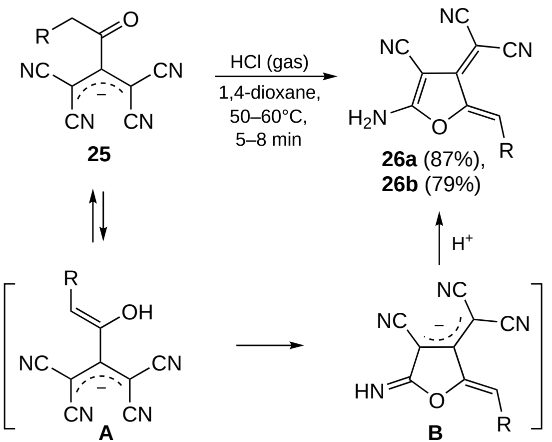
R^1 = H, Me, OMe, Cl, CF$_3$; R^2 = Me, Et, Pr^i, Bn (Bn = CH$_2$Ph);
L = P(Bu^t)$_2$(*o*-biphenyl)

mechanism for the formation of benzofuran-2-ones **23** involves the initial formation of a gold α-oxocarbene that is attacked by a tethered arene to form a gold enolate that reacts with quinoline N-oxide to complete the olefination process. This reaction pathway is similar to that represented in Scheme 6.

2.2. Metal-free methods of synthesis

In solvents with low dielectric constant that do not have nucleophilic properties, alkyl derivatives of propenides **25** react with hydrogen halides (HCl or HBr) to give furans **26**, which contain exocyclic C=C bonds in positions 2 and 3 (Scheme 8).[113]

Scheme 8

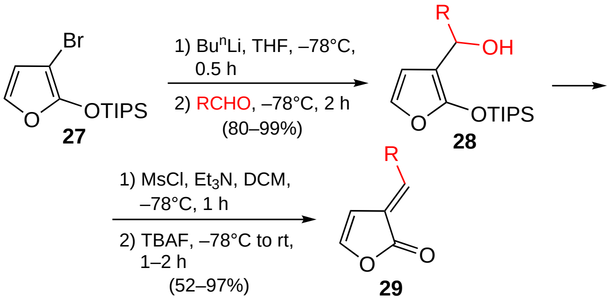


R = Me (**a**), Et (**b**)

Hydrogen halide catalyzes the keto-enol tautomerism and the formation of enol **A**, which undergoes heterocyclization to intermediate **B**. Neutralization of the reaction mixture affords *Z*-alkylidene tetrahydrofurans **26**. The authors assume that the stereoselectivity of the reaction is due to the steric factor, since unlike *E*-isomer of enol **A**, its *Z*-isomer is susceptible to further cyclization. In a follow-up study,[28] compounds **26** were obtained under mild basic catalysis conditions, though in lower yields.

Bromosilyloxyfuran **27** was used to obtain 3-(1-hydroxyalkyl)-2-silyloxyfurans **28** *via* halogen–metal exchange with *n*-butyllithium followed by exposure of the *in situ* generated 3-lithiated 2-triisopropyl silyloxyfuran to aldehydes (Scheme 9).[114]

Scheme 9

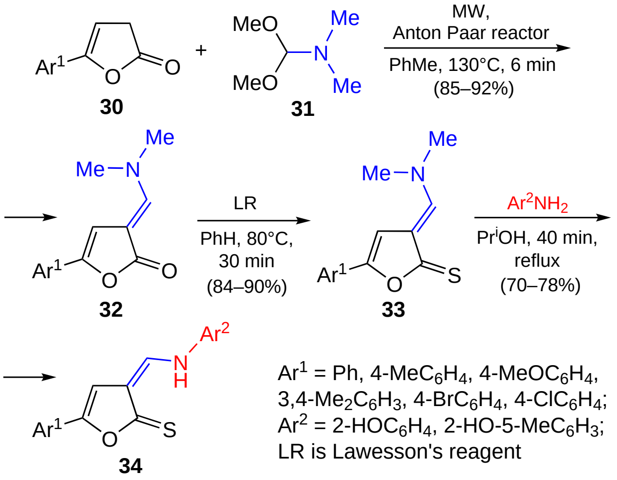


R = Pr^i, Bu^t, n-C_5H_{11}, Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 3-ClC_6H_4, 4-PhC_6H_4, 2-Fu; Fu is furyl, Ms is methanesulfonyl (mesyl), DCM is dichloromethane; TBAF is tetra-*n*-butylammonium fluoride

With the exception of *p*-nitrobenzaldehyde, all aliphatic and aromatic aldehydes used in the reaction gave high yields of carbinols **28**. (*E*)-3-Alkylmethylidene- and (*E*)-3-(arylmethylidene)-2(3*H*)-furanones **29** were synthesized with high stereoselectivity by mesylation of 2-silyloxyfurans **28**, followed by elimination of mesyltriisopropylsilyl moiety (see Scheme 9).

Yegorova and co-workers[115] showed the possibility of a microwave-assisted enamination of 5-arylfuran-2(3*H*)-ones **30** with dimethylformamide dimethyl acetal (DMF–DMA) (**31**) in toluene under elevated pressures. This reaction furnishes furanones **32** containing exocyclic C=O and C=C bonds (Scheme 10).

Scheme 10

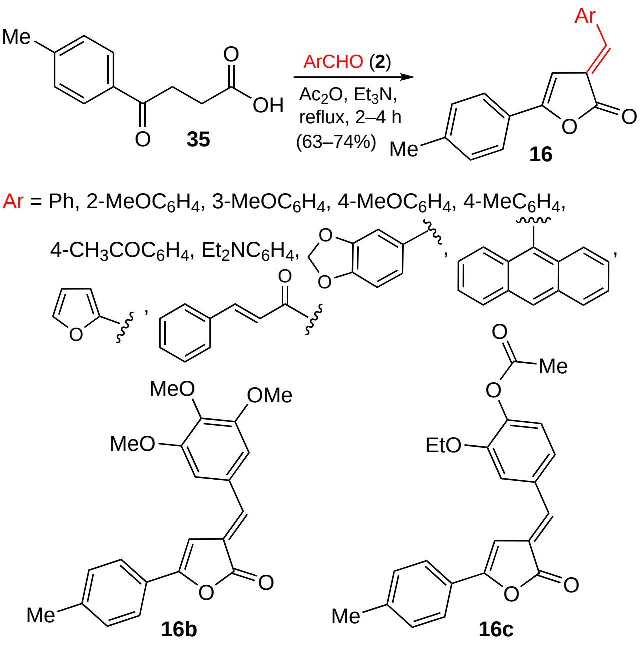


Ar^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,4-$Me_2C_6H_3$, 4-BrC_6H_4, 4-ClC_6H_4;
Ar^2 = 2-HOC_6H_4, 2-HO-5-MeC_6H_3;
LR is Lawesson's reagent

According to the data of 1D NOESY experiments, compounds **32** have the *E*-configuration and are absolutely inactive to *N*-nucleophilic reagents. Furanones **32** were treated with Lawesson's reagent in benzene, after which the resulting thioanalogues of furans **33** were reacted with arylamines containing electron-donating substituents (see Scheme 10).[64] As a result of transamination, furan-2(3*H*)-thiones **34** were obtained in high yields.

Husain *et al.*[116] showed that 3-arylidene-5-(4-methylphenyl)-2-(3*H*)-furanons **16** are accessible from 3-(4-methylbenzoyl) propanoic acid **35** by the reaction with aromatic aldehydes **2** in

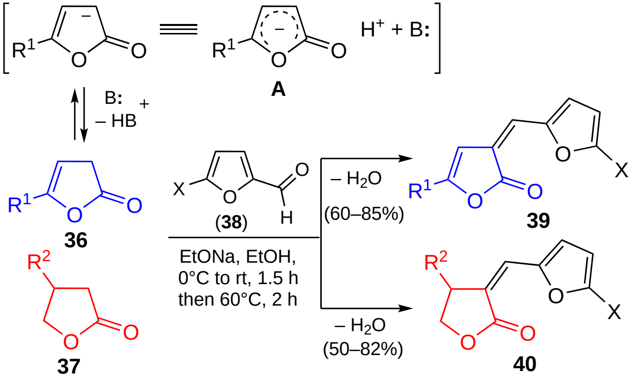
Scheme 11



Ar = Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$CH_3COC_6H_4$, $Et_2NC_6H_4$, the presence of triethylamine in acetic anhydride under modified Perkin reaction conditions (Scheme 11). Furanones **16b**,**c** showed significant anti-inflammatory and analgesic activities.

5-Alkylfuran-2(3*H*)-ones **36** and 4-alkyldihydrofuran-2(3*H*)-ones **37** can be condensed with 5-substituted furan-2-carbaldehydes **38** under base catalysis conditions to give butenolides **39** and butanolides **40**, respectively (Scheme 12).[26]

Scheme 12

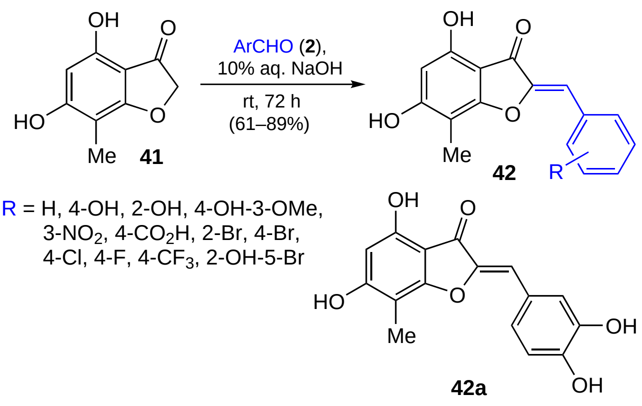


R^1 = Me, Bu; R^2 = Cy, Bn;
39: X = H, Me, Cl, Br, Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$;
40: X = Me, Br

The reactivity of furanones **36** is higher than that of dihydrofuranones **37** due to the formation of an intermediate conjugated anion **A**, so that the reaction runs under milder conditions.

Shubin *et al.*[66] used the reaction of active methylene compounds with aldehydes to introduce a C=C bond into furan-3-one molecules. In particular, it was shown that 4,6-dihydroxy-7-methylbenzofuran-3(2*H*)-one **41** undergoes base-catalyzed crotonic condensation with substituted benzaldehydes **2** to yield aurones **42**, including an analogue of natural 7-methylaureusidin isolated from *Cyperus capitatus* extract (compound **42a**) (Scheme 13).

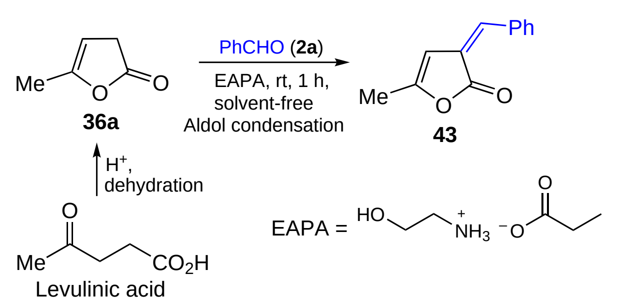
Scheme 13



R = H, 4-OH, 2-OH, 4-OH-3-OMe, 3-NO_2, 4-CO_2H, 2-Br, 4-Br, 4-Cl, 4-F, 4-CF_3, 2-OH-5-Br

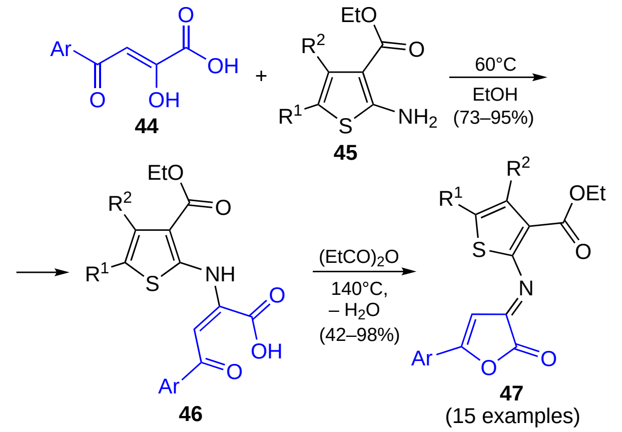
The aldol condensation of lactone **36a** with benzaldehyde **2a** catalyzed by the ionic liquid EAPA is an environmentally friendly protocol for the synthesis of 3-arylidenefuranone **43**, but the authors did not report the yield of the product (Scheme 14).[117] It should be noted that both reagents can be obtained from renewable raw materials. Lactone **36a** is a product of the dehydration of levulinic acid, which can be derived from both cellulose[118] and hemicellulose;[119] benzaldehyde is produced by photocatalyzed selective oxidation of a model compound, lignin β-1.[120,121]

Scheme 14



2-Hydroxy-4-oxobut-2-enoic acids **44** react with 2-aminothiophenes **45** in ethanol at 60°C to give 2-(thiophen-2-yl)amino-4-oxobut-2-enoic acids **46**, which undergo intramolecular cyclization in the presence of propionic anhydride (Scheme 15).[25] The 3-(thiophen-2-yl)amino-3*H*-furan-2-ones **47** obtained by cyclization were reacted with nitriles to afford compounds for testing for antitumour activity (see Section 3.2, Scheme 24).

Scheme 15



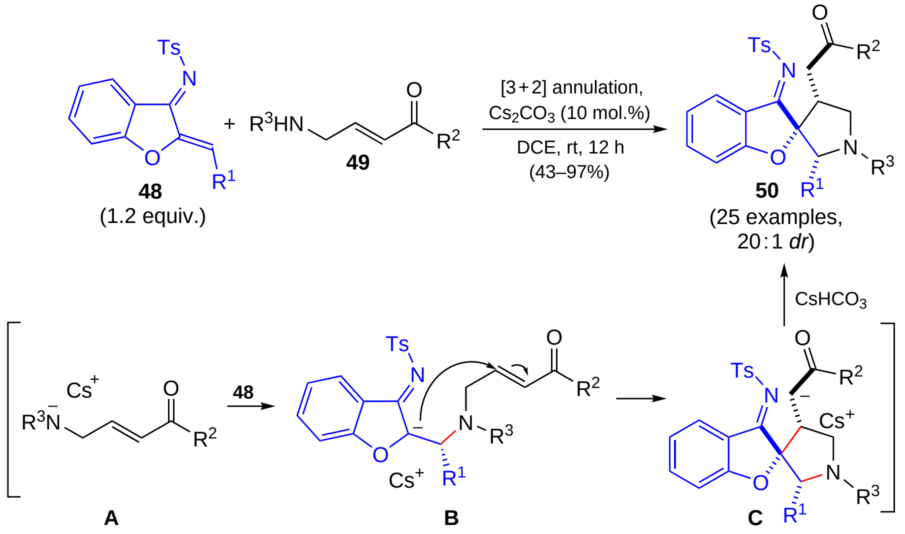
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-ClC_6H_4, 2-Th;
R^1, R^2 = Me, $-(CH_2)_n-$ (n = 4–6)

Annulation reactions have found wide application in the synthesis of various heterocyclic compounds due to their efficiency in constructing complex cyclic structures.[122–124] Chen *et al.*[125] suggested that allylamines **49** as C,N-synthons can undergo [3+2] or [3+4] cycloaddition with benzofuranazadienes **48** in a basic medium (Scheme 16).

In search for the optimal reaction conditions, the authors varied the reagent ratio, the type of solvent and used different bases (organic and inorganic). It was found that spiranes **50** are formed mainly in high yields and with diastereoselectivity >20 : 1 when carrying out the reaction of benzofuranazadienes **48** with allylamines **49** in the presence of cesium carbonate in DCE at room temperature.

According to the proposed mechanism (see Scheme 16), allylamine **49** is converted into intermediate product **A** when treated with cesium carbonate. Then, the nucleophilic attack of the latter on the molecule of azadiene **48** gives adduct **B**, which is further converted into intermediate **C** *via* the [3+2] cycloaddition pathway. In turn, intermediate **C**, in the presence of cesium hydrogen carbonate, forms spirocyclic product **50**. According to the authors, the developed approach to spiranes **50** is consistent with the principles of 'green' chemistry, since it is implemented without the use of transition metals that are toxic to living cells.

Scheme 16



R^1 = Ph, 4-NCC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, Bu^t, 2-Naph;
R^2 = Bu^{t}O, EtO, BnO, Ph$_2$CHO, Me, cyclo-C$_3$H$_5$, PhO; R^3 = Ts, PhSO$_2$, 4-O$_2$NC$_6$H$_4$SO$_2$; Ts is *p*-toluenesulfonyl (tosyl)

3. Pyrrole derivatives

2-Oxopyrroles are five-membered lactams. They exhibit a variety of biological activities,[126] including antimicrobial[127] and antimalarial,[128] and are found in a variety of natural compounds,[129] examples of which include the antitumour alkaloid Jatropha[130] and the platelet aggregation inhibitor PI-091 (Ref. 131) (Fig. 1).

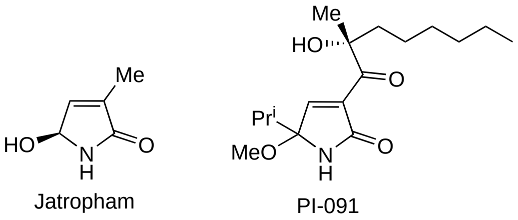


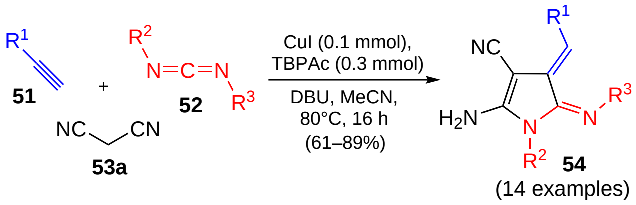
Figure 1. Examples of natural pyrrolones.

This Section provides data on the synthesis of properties of pyrroles containing conjugated exocyclic bonds.[35,69,126–128,132]

3.1. Synthesis of pyrroles with exocyclic C=C and C=N bonds

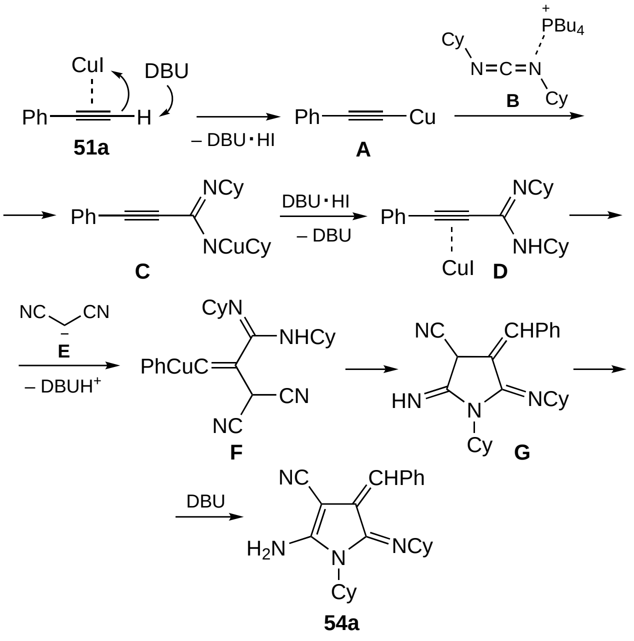
Three-component condensation of terminal alkynes **51** with carbodiimides **52** and malononitrile **53a** in the presence of CuI, DBU, and tetra-n-butylphosphonium acetate (TBPAc) in anhydrous acetonitrile under optimized conditions gives rise to pyrroles **54** in good yields (Scheme 17).[69] Various alkynes **51** (alkyl-, aryl-, and heteroarylalkynes) can be used in this reaction. Carbodiimides **52** can be symmetrical and unsymmetrical, with aryl or alkyl substituents.

Scheme 17



R^1 = Ph, 3-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$, PhCH$_2$CH$_2$, Bu^n, 2-Fu, 2-Th, TMS;
R^2 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, Pr^i, Cy;
R^3 = Ph, Pr^i, Bu^n, Cy;
TBPAc is tetrabutylphosphonium acetate, TMS is trimethylsilyl

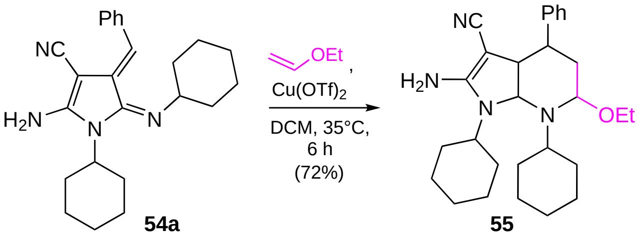
Scheme 18



The authors proposed a mechanism for the formation of pyrrole **54a** (Scheme 18). In the first step, copper(I) iodide reacts with phenylacetylene **51a**, thus activating the terminal C–H bond. The abstraction of the terminal proton with DBU generates copper acetylide **A**, which attacks the electrophilic carbon of carbodiimide **B** in the presence of TBPAc to afford phenylpropionimidamide **C**. Apparently, DBU promotes the removal of CuI from the amidine moiety of intermediate **C** to give complex **D**. After this, the conjugate base of malononitrile **E** reacts with its triple bond and then intermediate **F**, the amino group of which is involved in nucleophilic addition to the nitrile carbon by intramolecular exocyclization, is converted to intermediate **G**. Tautomerization of the latter yields the target product **54a**.

In order to determine the possibility of using the above method in the Diels–Alder reaction, the reaction of diene **54a** with alkynes and alkenes was explored.[69] It was shown that diene **54a** reacts smoothly with ethoxyethene in the presence of $Cu(OTf)_2$ in dichloromethane to give bicyclic heterocycle **55** in 72% yield (Scheme 19).

Scheme 19

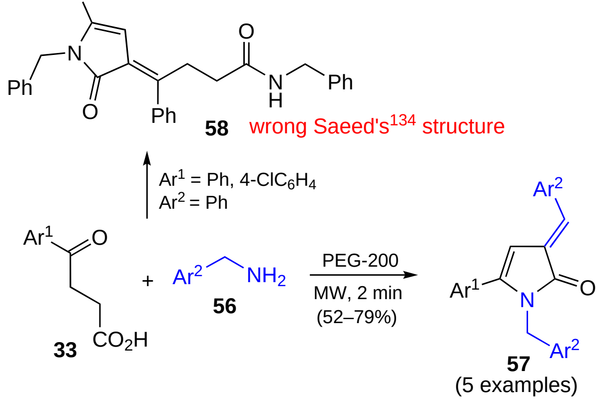


Unlike alkenes, diene **54a** reacts with dimethyl acetylenedicarboxylate (DMAD) to give a complex mixture that could not be separated. Thus, the studied cycloaddition of pyrroles **54** containing two exocyclic bonds to dienophiles has limited application in organic synthesis.

3.2. Synthesis of pyrroles with exocyclic C=C and C=O bonds

In order to obtain pyrrolidones, Rao *et al.*[133] carried out the microwave-assisted condensation of 4-oxo-4-phenylbutanoic acids **33** with benzylamines **56** and obtained the target compounds **57** in good yields (Scheme 20). Interestingly, in 1986, Saeed[134] assigned structure **58** to the products of this reaction.

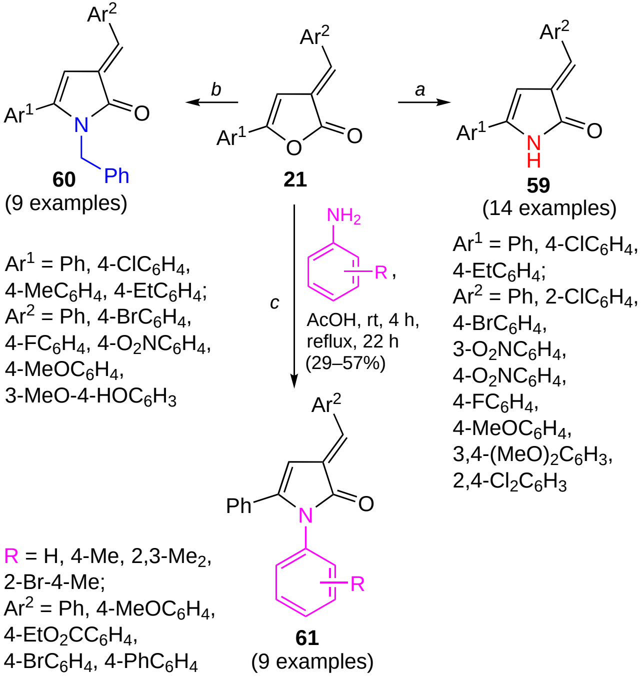
Scheme 20



Ar^1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4; Ar^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4

Rao *et al.*[133] carefully revised these data[134] and confirmed the structure of the resulting compounds **57** based on the data of IR, ^1H, ^{13}C NMR and mass spectra. It was shown that the reaction of acids **33** with amines **56** can afford the target products **57** also on heating at 140°C for 2 hours, but the reaction rate is higher under microwave irradiation.

Scheme 21



(*a*) $NH_3/AcONH_4$, MeOH, reflux, 5 h, or NH_3 gas, EtOH, rt, 1 h (46–51%);
(*b*) $PhCH_2NH_2$, PhH, reflux (68–100%);

The oxygen atom in butenolides **21** can be easily replaced by a nitrogen atom by reaction with a 30% ammonia solution in the presence of glacial acetic acid in boiling methanol[62] or by purging dry ammonia through solutions of butenolides **21** in anhydrous ethanol (Scheme 21, reaction *a*).[132] Both pyrrolones **59** (Ar^1 = Ph, 3,4-$(MeO)_2C_6H_3$, Ar^2 = Ph) and the starting butenolides **21** demonstrated efficient *cis-trans* photoisomerization, comparable to the behaviour of autofluorescent proteins (AFP).[62] Remarkably, the configuration was determines using structure-adapted NMR measurements and their interpretation in view of theoretical calculations. Thus, a strategy was developed to enable rapid identification of photoisomerization features in AFP chromophore analogues.

1-Benzyl-2(3*H*)-pyrrolones **60** were obtained from the appropriate butenolides **21** and benzylamine in yields from moderate[132] to quantitative (see Scheme 21, reaction *b*).[133] Among pyrrolones **59**, **60**, compounds exhibiting antibacterial or fungicidal activity were identified.[132]

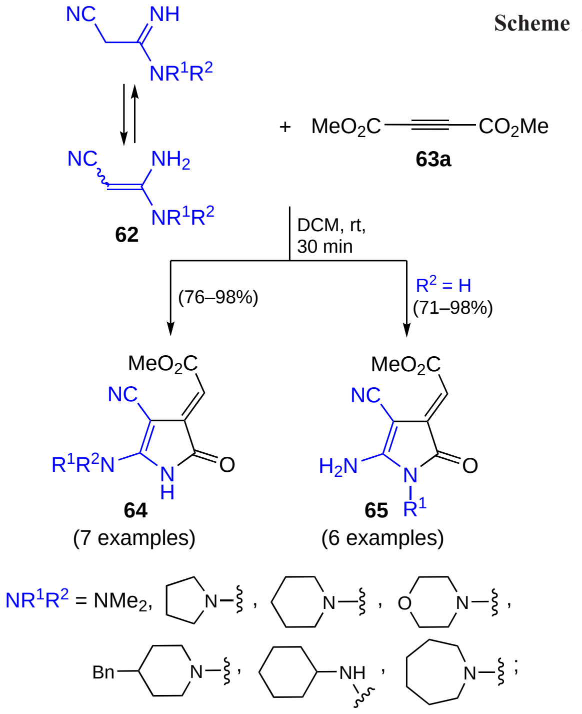
Butenolides **21** react with substituted anilines in glacial acetic acid in a similar manner to give 1-aryl-2(3*H*)-pyrrolones **61** in low yields (see Scheme 21, reaction *c*).[63] All 1-arylpyrrolones **61** were tested for their potential antiviral activity using hepatitis C virus (HCV) replication and cytostatic assays. Compounds **61** (Ar^2 = 4-$EtO_2CC_6H_4$, Ph and R = 2-Br, 4-Me) exhibited the highest antiviral activity.[63]

Silaichev *et al.*[135] studied the reaction of 3,3-diaminoacrylonitriles **62** with dimethyl acetylenedicarboxylate (DMAD) (**63a**) and showed that the reaction pathway depends on the structure of substrate **62** (Scheme 22).

Thus, DMAD **63a** reacts with acrylonitriles **62** containing an *N,N*-disubstituted amidine moiety to give 1-NH-5-aminopyrroles **64**. On the other hand, using acrylonitriles **62** containing a monosubstituted amidine group, 1-substituted 5-amino-2-oxopyrrol-3(2*H*)ylidenes **65** are formed. In both cases, pyrroles containing two conjugated exocyclic C=O and C=C bonds are produced in high yields. A significant drawback of this method is the low availability of the starting acetylenes.

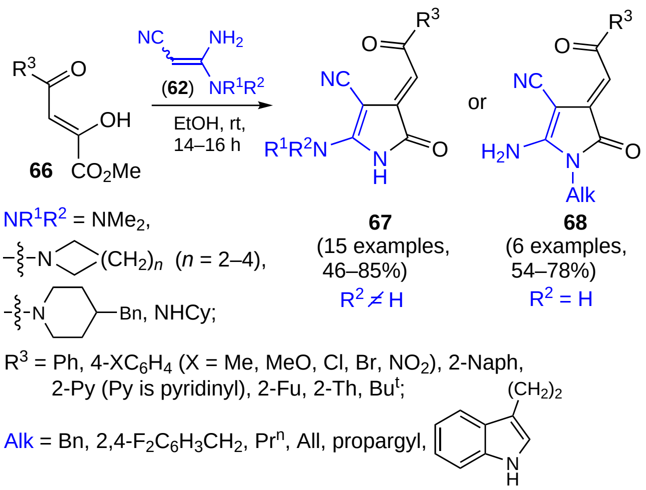
Aroyl(heteroaroyl)pyruvic acid esters **66** provide a more accessible alternative to disubstituted acetylenes and can be used to prepare pyrrolones **67** and **68** bearing variously substituted 2-oxoethylidene moiety (Scheme 23).[136]

Scheme 22



R^1 = Bn, 2,4-$F_2C_6H_3CH_2$, Pr, All, propargyl, $(MeO)_2CHCH_2$;
All is allyl

Scheme 23



R^3 = Ph, 4-XC_6H_4 (X = Me, MeO, Cl, Br, NO_2), 2-Naph, 2-Py (Py is pyridinyl), 2-Fu, 2-Th, Bu^t;

Alk = Bn, 2,4-$F_2C_6H_3CH_2$, Pr^n, All, propargyl,

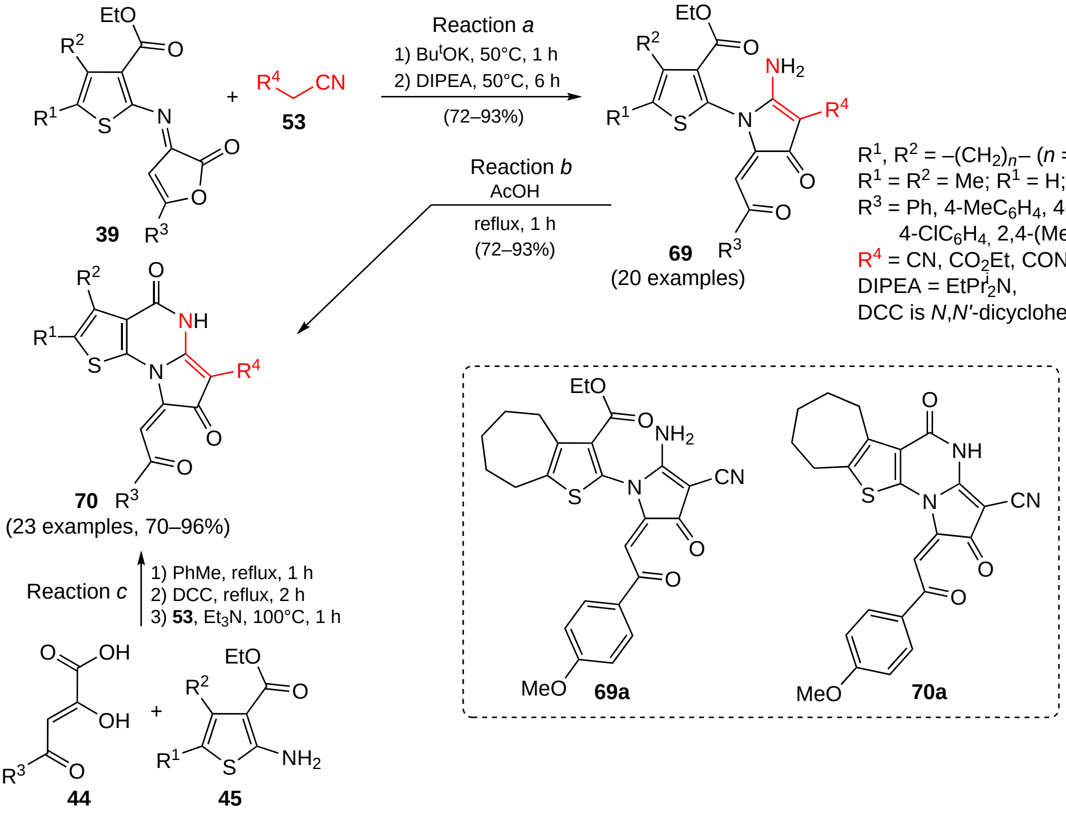
Rogova *et al.*[25] showed that (thiophen-2-yl)imino-3*H*-furan-3-ones **39** react with acetonitrile derivatives **53** to give thiophenylaminopyrroles **69** containing a system of two conjugated exocyclic C=O and C=C bonds (Scheme 24, reaction *a*).

Heating of compounds **69** in acetic acid at 120°C induces their intramolecular cyclization to give fused pyrrolones **70** in high yields (see Scheme 24, reaction *b*). The results of *in vitro* tests of compounds **69a** and **70a** showed their high antiproliferative activity and low cytotoxicity towards normal cells in a mouse lung metastatic melanoma model.[25]

A one-pot protocol for the synthesis of thieno[3,2-*e*]pyrrolo[1,2-*a*]pyrimidines **70** was developed, based on a cascade reaction of acids **44** with various Gewald's aminothiophenes **45** (see Scheme 24, reaction *c*).[80] This method represents a new synthetic approach to the preparation of fused pyrroles. The thieno[3,2-*e*]pyrrolo[1,2-*a*]pyrimidine core of compounds **70** is an important scaffold of new poly(ADP-ribose) polymerase (PARP) inhibitors, which play an important role in the development of new drug candidates.

The similar reaction of thiophene-3-carbonitriles **71** with acetonitriles **53** under milder conditions affords 2-amino-1-(thiophen-2-yl)dihydropyrroles **72**, which, without further purification, were cyclized to pyrrolo[1,2-*a*]thieno[3,2-*e*]-

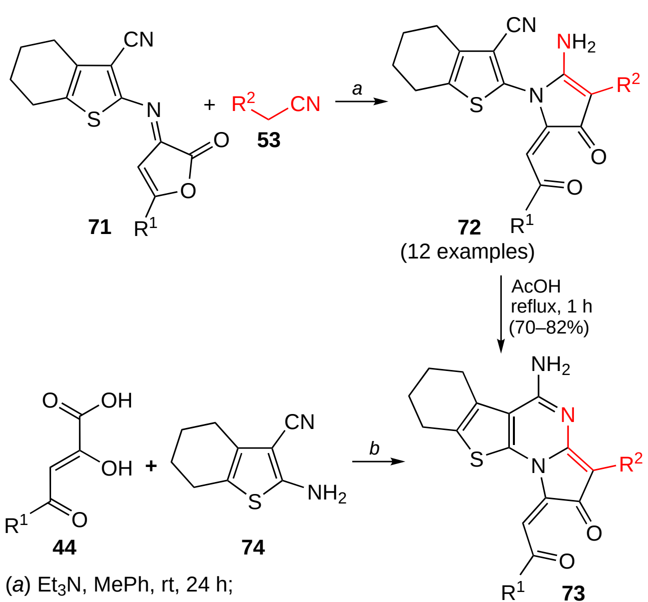
Scheme 24



R^1, R^2 = $-(CH_2)_n-$ (*n* = 4–6);
R^1 = R^2 = Me; R^1 = H; R^2 = Me;
R^3 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-EtC_6H_4, 4-ClC_6H_4, 2,4-$(MeO)_2C_6H_3$, 2-Th;
R^4 = CN, CO_2Et, $CONH_2$;
DIPEA = $EtPr^i_2N$,
DCC is *N*,*N*'-dicyclohexylcarbodiimide

pyrimidines **73** in boiling glacial acetic acid (Scheme 25).[19] Compounds **73** are accessible through a one-pot protocol from acids **44** and thiophene-3-carbonitrile **74**.

Scheme 25



71 **53** **72** (12 examples) **44** **74** **73** (17 examples)

(*a*) Et_3N, MePh, rt, 24 h;
(*b*) 1) DCC (2 equiv.), 1,4-dioxane, reflux, 2 h;
2) **40**, DIPEA (1 equiv.), 80°C, 1 h (73–98%);
R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-Th;
R^2 = CN, CO_2Et, $CONH_2$

In vivo experiments with melanoma-bearing mice demonstrated the high potential of compound **73a** (R^1 = Ph, R^2 = CN) in the treatment of melanoma and showed significant suppression of tumour growth on the 15th day after the start of therapy.[19]

4. Indolone derivatives

The oxindole ring is one of the key scaffolds in many alkaloids and highly active biologically active compounds. Among them, 3-alkylideneoxindoles can be distinguished, which are important targets for the synthesis of compounds of interest in medicinal chemistry and are present in many natural compounds.[136] This Section includes data on the synthesis and properties of indole derivatives containing conjugated exocyclic bonds.

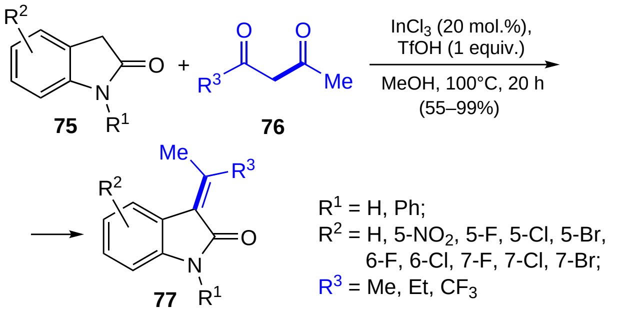
4.1. Synthesis of 3-alkylideneoxindoles

In 2010, Millemaggi and Taylor[137] published a review of classical methods for the synthesis of 3-alkylideneoxindoles developed before 2010. Many of them are still in use. The review includes data on the synthesis of 3-alkylidene-2-oxindoles from: (*a*) aryl alkynes using carbonylating annulation; (*b*) aryl propionamides, including arene-alkyne cyclization; (*c*) 1-benzylisatins with various active methylene compounds *via* the Knoevenagel reaction; (*d*) benzofurandiones and triphenylphosphine derivatives, as well as methods based on the Heck/Suzuki–Miyaura reactions and the use of an approach involving reactions of activated aryls, as well as arene–alkyl cyclizations.

4.1.1. Reactions of active methylene indolones with carbonyl compounds

Considering the high synthetic potential of 3-alkylidene-oxindoles, the search for methods for their synthesis is currently ongoing. In particular, Chen *et al.*[44] developed an effective approach to 3-alkylideneoxindoles using a tandem Knoevenagel/deacetylation reaction. Thus, the reaction of 2-oxindoles **75** with acetyl ketones **76** in the presence of $InCl_3$ catalyst and acids affords the target products **77**, mainly in high yields (Scheme 26).

Scheme 26

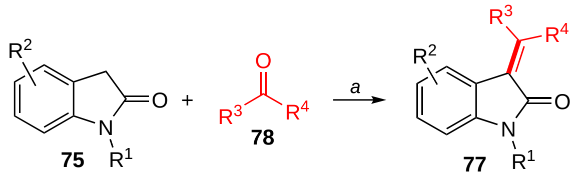


75 **76** **77** (18 examples)

R^1 = H, Ph;
R^2 = H, 5-NO_2, 5-F, 5-Cl, 5-Br, 6-F, 6-Cl, 7-F, 7-Cl, 7-Br;
R^3 = Me, Et, CF_3

As an alternative to 1,3-dicarbonyl compounds **76**, the authors propose using more accessible aldehydes and ketones **78** to obtain 3-alkylideneoxindoles **77** (Scheme 27).

Scheme 27



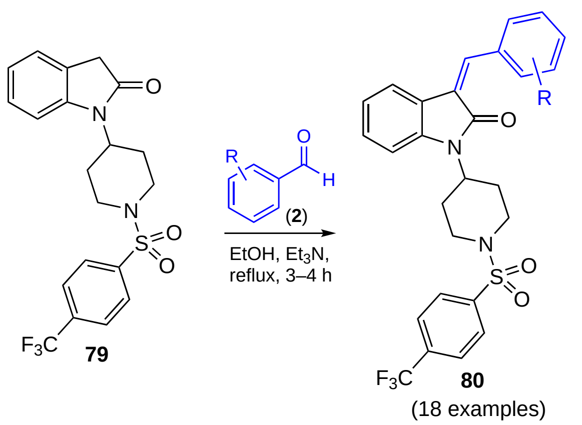
75 **78** **77** (33 examples)

(*a*) $InCl_3$ (20 mol.%), TfOH (1 equiv.), MeOH, 100°C, 20 h (55–99%);
R^1 = H, Me, Ph;
R^2 = H, 5-MeO, 5-NO_2, 5-F, 5-Cl, 5-Br, 6-F, 6-Cl, 6-CF_3, 7-F, 7-Cl, 7-Br;
R^3 = Me, Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-ClC_6H_4, 4-PhC_6H_4, Et, Naph;
R^4 = H, Me, Et, Ph;
R^3, R^4 = cyclopenthyl, Cy

With the aim of obtaining novel effective antidiabetic agents, Mukhliss *et al.*[138] carried out a reaction of sulfonylpiperidin-4-ylindol-2-one **79** with substituted benzaldehydes **2** in ethanol in the presence of triethylamine to obtain 3-arylidene oxindoles **80** (Scheme 28).

Unfortunately, the article does not provide data on the melting points and yields of the resulting compounds. 3-Arylideneoxindoles **80** were tested for their α-glucosidase and α-amylase inhibitory activities. Compared with the standard inhibitor acarbose, which has an IC_{50} value of 100.30±0.20 μM for α-amylase and 9.80±0.20 μM for α-glucosidase, all compounds **80** showed complete inhibition of α-amylase and α-glucosidase. 3-Arylideneoxindole **80a** (R = 2,4,6-$(OH)_3$) is the most potent compound in this series with an IC_{50} value of 0.30±0.05 μM for α-amylase and 0.40±0.05 μM for

Scheme 28

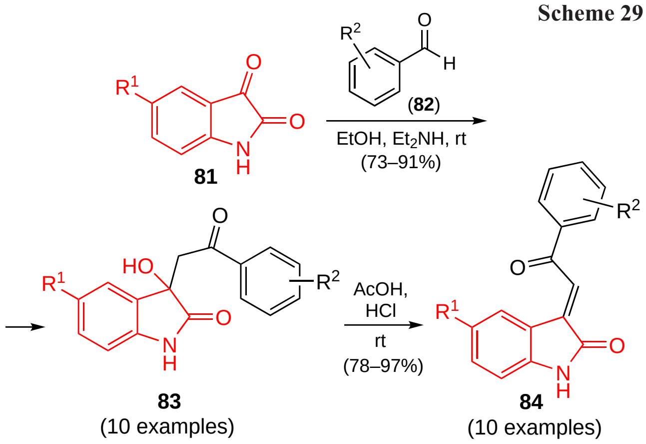


R = 2,5-$(OH)_2$, 3,4-$(OH)_2$, 2,3-$(OH)_2$, 2,4-$(OH)_2$, 3,5-$(OH)_2$,
2,4,6-$(OH)_3$, 3-OH, 4-OH, 2-F, 3-F, 4-F, 2-Cl, 3-Cl, 4-Cl,
2-MeO, 3-MeO, 4-MeO

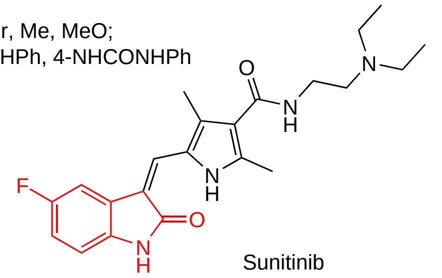
α-glucosidase, which is significantly superior to the standard values. The structure-activity relationship (SAR) was established based on the change in the position of the R substituents in the arylidene moiety. The most effective drug interactions were studied by molecular docking.

It is known that VEGF (vascular endothelial growth factor, a signalling protein produced by cells to stimulate the growth of new vessels in the vascular system) and its receptors are hyperactivated in many types of cancer tumours and are considered promising targets for the administration of antitumour agents.[139] In order to find new VEGFK-2 inhibitors, Aboshouk *et al.*[140] carried out a study aimed at the synthesis of modified 2-oxoindolin-3-ylidenes containing an urea moiety. The target compounds were obtained in two steps. Addition of the corresponding 1-(acetylphenyl)-3-phenylurea **82** to isatins **81** in ethanol containing Et_2NH, followed by acidic dehydration (AcOH/HCl) of the intermediates **83** gave the target 2-oxoindolin-3-ylidenes **84** in high yields (Scheme 29).

Scheme 29



R^1 = H, F, Cl, Br, Me, MeO;
R^2 = 3-NHCONHPh, 4-NHCONHPh



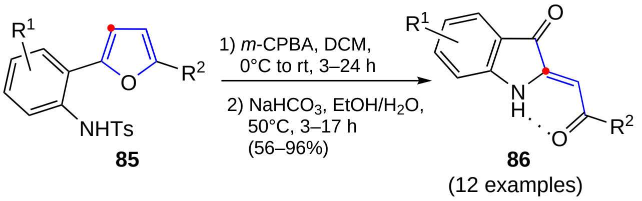
Sunitinib

The authors note the presence of promising antiproliferative properties (according to MTT assay data) in most of the synthesized compounds **84** against colon, breast and pancreatic cancer cell lines. Compound **84a** (R^1 = H, R^2 = 4-NHCONHPh, 87.2% inhibition) is the most promising anti-VEGFR-2 agent. Its activity is similar to that of Sunitinib (an antitumour agent that inhibits multiple kinases involved in tumour growth processes) (89.4% inhibition) at a concentration of 10 μM.

4.1.2. Furan ring transformation

The discovered oxidative transformation of furans **85** into indole derivatives **86** in the presence of bases served as the basis for the development by Uchuskin and co-workers[27] of a new and effective approach to 2-alkylideneoxindoles (Scheme 30). The driving force of the second step of the process is apparently the formation of a strong hydrogen bond, similar to that observed previously[30] for the synthesis of 1,2,3-triazoles containing two exocyclic double bonds.

Scheme 30

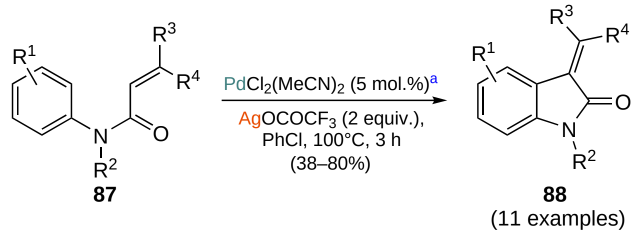


R^1 = H, 5-Cl, 5,6-$(Me)_2$, 6-Me, 6-MeO, 6-Cl, 6-Br;
R^2 = Me, Et, 4-ClC_6H_4; *m*-CPBA is *meta*-chloroperoxybenzoic acid

4.1.3. Intramolecular alkenylation

Ueda *et al.*[141] developed a method for the synthesis of 3-benzylidenindol-5-ones based on the construction of a pyrrolone ring to the benzene ring in *N*-cinnamoyl anilines **87** by palladium-catalyzed intramolecular alkenylation in the presence of silver trifluoroacetate as an oxidant (Scheme 31). This reaction can be used to synthesize NH-, *N*-aryl-, and *N*-alkyloxindoles **88**, which opens an access to structurally diverse oxindoles with two exocyclic C=O and C=C bonds from readily available starting materials.

Scheme 31

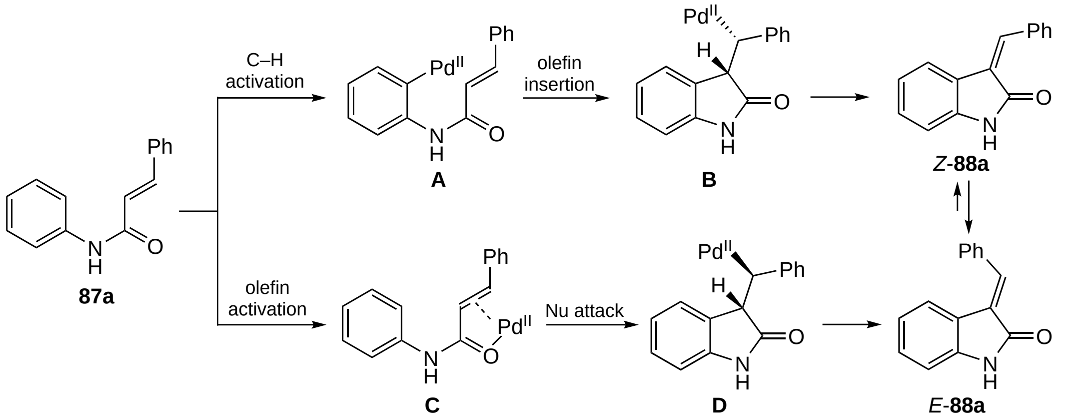


[a] for $R^1 \neq$ H: $PdCl_2(MeCN)_2$ (5 mol.%), PhCl, 110°C, 12 h;
R^1 = H, 5-Me, 5-EtO, 5-F, 5-Cl, 6-Me; R^2 = H, Me, Ph;
R^3 = H, R^4 = Ph, 4-MeC_6H_4, 4-$Pr^iC_6H_4$; $R^3 = R^4$ = Me

In the case where $R^3 \neq R^4$, compounds **88** are formed as a mixture of isomers with the *E*-isomer predominating (Scheme 32). The authors proposed a mechanism for the formation of each isomer.

C–H-Activation of aniline **87a** with palladium to form intermediate **A**, followed by *syn*-insertion of the olefin and β-hydride elimination affords *Z*-oxindole **88a**. The *E*-isomer is formed from the palladium π-complex **C** with subsequent nucleophilic attack of the arene and elimination of β-H.

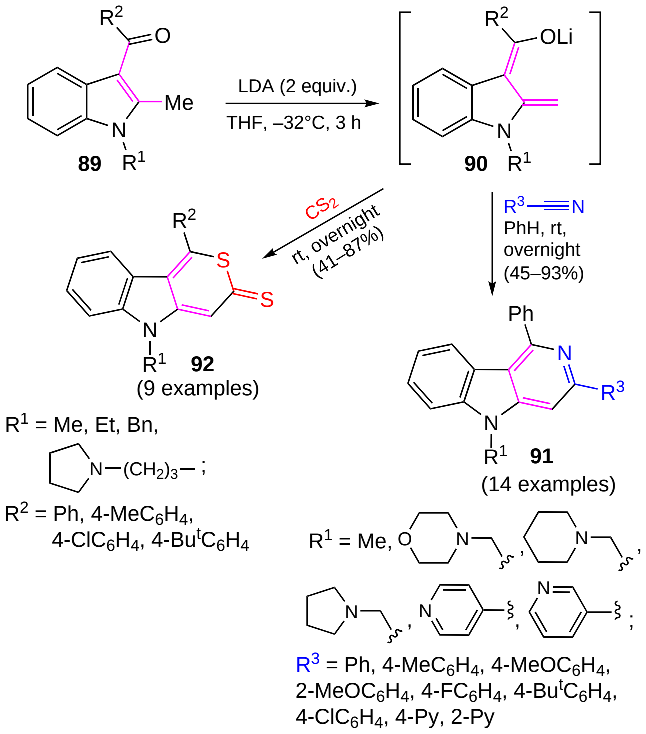
Scheme 32



4.1.4. Generation of unstable 3-alkylydeneindoles

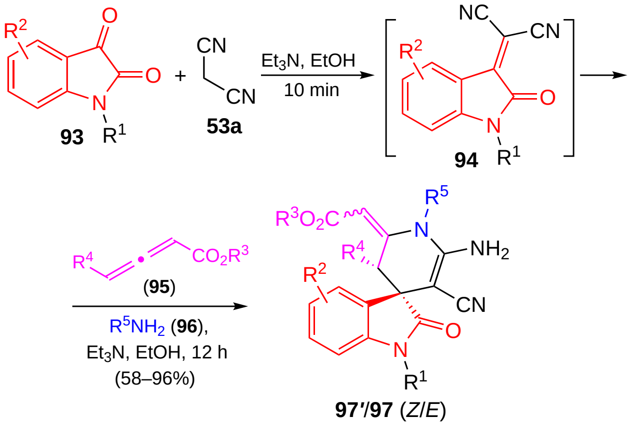
In order to synthesize tricyclic fused heterocycles, Vyalyh *et al.*[142] used the reaction between 2-methylindoles **89** with lithium diisopropylamide (LDA) to generate indole-2,3-dienolates **90** (Scheme 33). Since the resulting compounds **90** were not stable enough to be isolated, they were used *in situ* to obtain carbolines **91** and thiopyranindoles **92** *via* reactions with nitriles[142] and carbon disulfide,[46] respectively.

Scheme 33



Knoevenagel condensation of isatins **93** and malononitrile **53a** in the presence of triethylamine gives rise to another type of 3-alkylidene-2-oxoindoles **94** (Scheme 34).[45] The authors did not identify these compounds, but used them *in situ* in reactions with allenes **95** and amines **96** to obtain spirocyclic indolones **97**. The mixture of *Z*/*E*-isomers can be separated into individual isomers by column chromatography on silica gel.

Scheme 34



R^1 = Me, Et, Pr, Bu^t, Bn, 4-FC$_6$H$_4$CH$_2$;
R^2 = H, 5-Me, 5-OMe, 5-Cl, 5-Br, 5,7-Me$_2$;
R^3 = Me, Et, Bu^t; R^4 = Me, Bu, Ph, Bn;
R^5 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-CF$_3$OC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-IC$_6$H$_4$, 1-Naph, propargyl

4.2. Properties of 3-alkylydeneoxindoles

4.2.1. Reactions of the C=N bond

The development of a strategy for the synthesis of spirooxindoles is well advanced due to their wide application in medicine.[143,144] Traditional synthetic approaches to these compounds include transition metal (Mn, Fe, Ni, Cu, Zn, Ag, Au and Pd) catalysis[145] and the use of a 'green' synthesis strategy.[146,147]

Spirooxindoles contain, in addition to the indole unit, a spirocyclic moiety. They are part of some natural compounds[148,149] and exhibit a wide range of biological activities (Fig. 2).[149–152]

The absolute configuration and the nature of the substituents in the spirocycle have been shown to significantly affect the biological activity of spirooxindoles. Advances in stereoselective and asymmetric synthesis of spirooxindoles have led to the discovery of new biologically active natural compounds such as horsfilin, kerulescin, and spirotryprostatins A and B (see Fig. 2).[148,149] Synthetic analogues, chiral spiropyrrolidinyl- and spiropiperidinyl oxindoles containing a nitrogen atom located near the spiro-quaternary stereocenter, have antitumour, anticancer, and antimalarial activities.[150–152] These promising

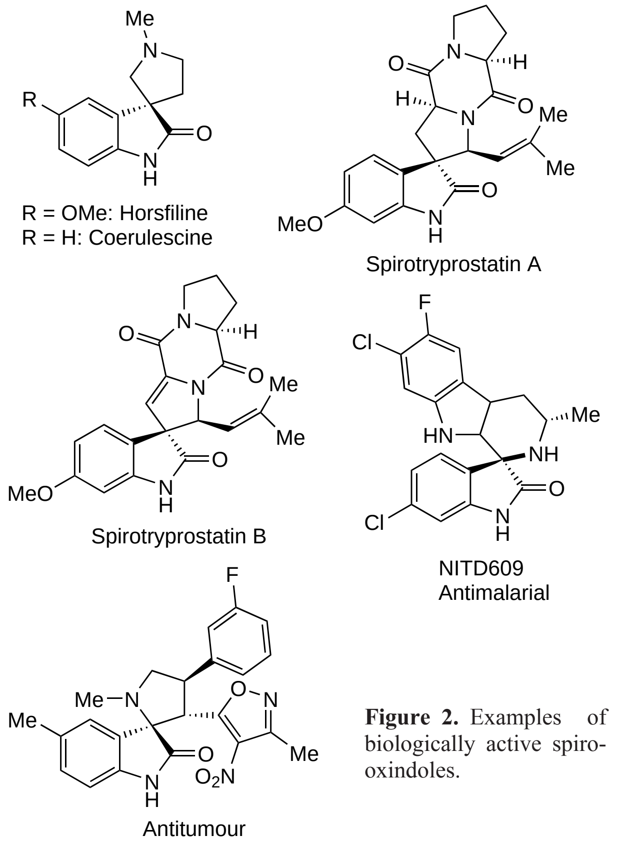
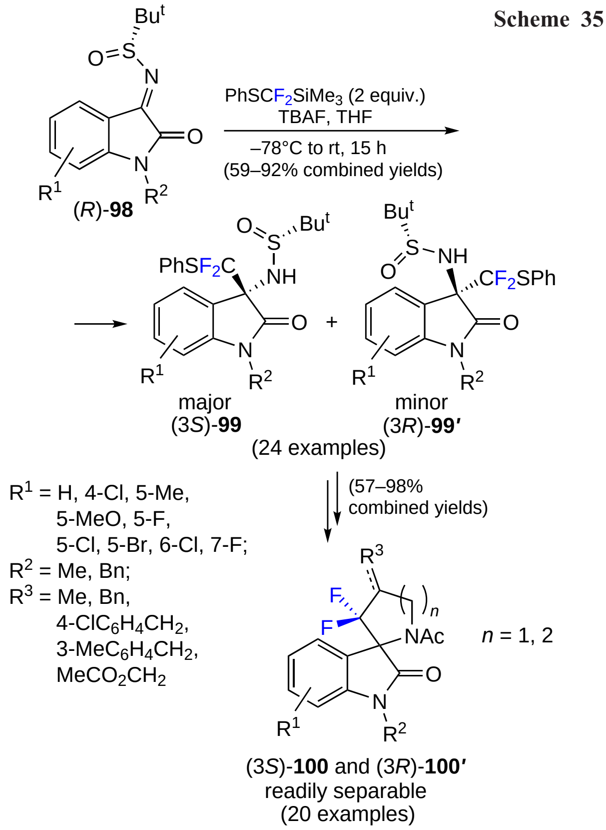


Figure 2. Examples of biologically active spiro-oxindoles.

biological data have stimulated the development of new stereoselective methods for the synthesis of spiropyrrolidinyl oxindoles.

One such study concerns the synthesis of enantio-enriched *gem*-difluoromethylated spiro-pyrrolidinyl- and spiro-piperidinyl oxindoles.[153] Diastereoselective nucleophilic addition of $PhSCF_2SiMe_3$ to chiral *N-tert*-butylsulfinyl-ketimines **98** obtained from isatins was a key step in the study and opened the way to diastereomeric adducts **99** (Scheme 35).

Scheme 35

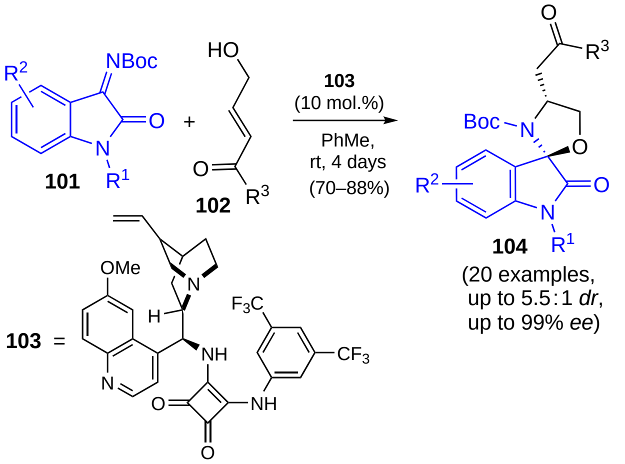


R^1 = H, 4-Cl, 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 6-Cl, 7-F;
R^2 = Me, Bn;
R^3 = Me, Bn, 4-$ClC_6H_4CH_2$, 3-$MeC_6H_4CH_2$, $MeCO_2CH_2$

Removal of the chiral sulfinyl group followed by structural modification delivered chiral *gem*-difluoromethylenated spiro-pyrrolidinyl- and spiro-piperidinyloxindoles **100**.

Parida *et al.*[70] studied the aza-Michael reaction of *N*-Boc-aza-derivatives of isatin **101** with γ-hydroxyenones **102** in the presence of various catalysts and found that the quinine-derived bifunctional squaramide catalyst **103** performed best in the organocatalytic asymmetric synthesis of spirooxindoles **104** (Scheme 36). Compounds **104** were obtained using the optimized protocol with good diastereoselectivity and high enantioselectivity.

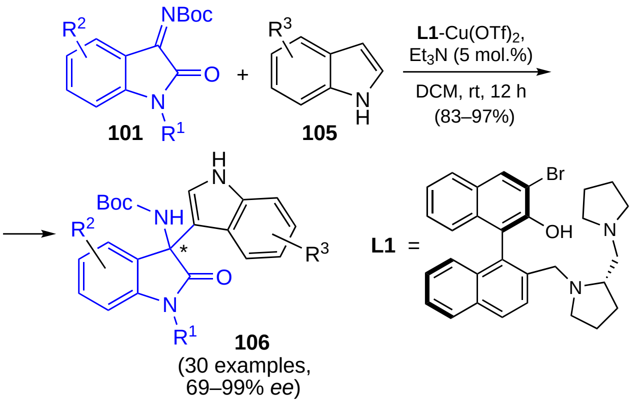
Scheme 36



R^1 = Me, Et, Pr, Bn; R^2 = H, Me, MeO, Br, Cl;
R^3 = Ph, 4-MeC_6H_4, 4-$Pr^iC_6H_4$, 4-$Bu^tC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 2-Th, $PhCH_2CH_2$;
Boc is *tert*-butoxycarbonyl

In order to develop an enantioselective approach to indolone derivatives, Xue *et al.*[154] carried out a Cu(II)-catalyzed aza-Friedel–Crafts reaction of *N*-Boc derivatives of azaisatin **101** with indoles **105** using chiral O–N–N tridentate ligands derived from BINOL (1,1′-bi-2-naphthol) and proline. As a result, chiral 3-indolyl-3-aminooxindoles **106** were obtained in high yields

Scheme 37

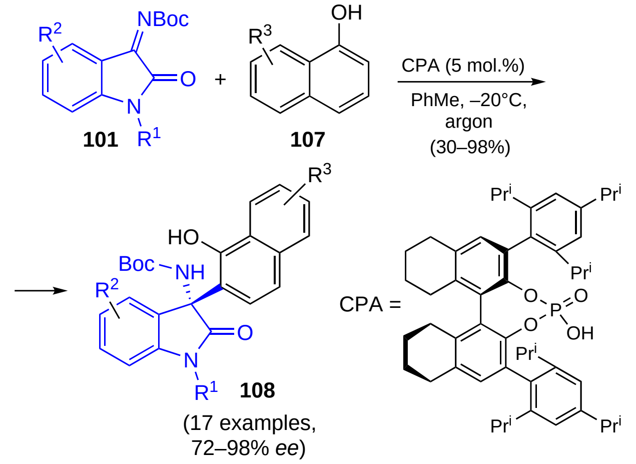


R^1 = Me, Et, Bn; R^2 = H, 5-Me, 5-MeO, 5-F, 6-Cl, 5-Br, 5-NO_2, 6-F, 6-Cl, 6-Br, 7-F, 7-Cl, 7-Br, 7-MeO;
R^3 = 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 5-MeO_2C, 6-Me, 6-MeO, 6-F, 7-Cl, 6-Br, 7-Me

and with high enantiomeric excess (*ee*) under mild conditions in the presence of ligand **L1** (Scheme 37).

Duan *et al.*[76] showed that it is possible to use naphthalene derivatives **107** instead of indole derivatives[154] in the aza-Friedel–Crafts reaction (Scheme 38). Here, H_8-BINOL-derived chiral biarylphosphoric acid (CPA) was employed as a catalyst. The possibility of using a wide range of isatin-derived ketenimines **101** in this reaction for the synthesis of a series of chiral 3-amino-2-oxindoles **108** in good yields and with high optical purity was also demonstrated.

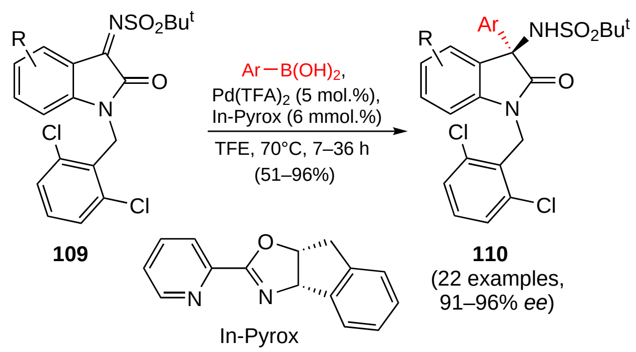
Scheme 38

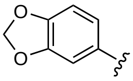


R^1 = H, Me; R^2 = 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 5,7-Me_2, 7-CF_3;
R^3 = 4-MeO, 4-Cl, 6,7-Me_2, 6,7-$(MeO)_2$, 6,7-Br_2

Asymmetric addition of organometallic reagents to imines is an effective strategy for the design of chiral polysubstituted amines.[155,156] In line with such studies, Zhang and co-workers[157] developed the Pd(II)/Pyrox-catalyzed enantioselective addition of arylboronic acids to 3-ketimino oxindoles **109**, delivering chiral 3-amino-2-oxindoles **110** with a quaternary stereocenter in high yields and with good enantioselectivity (Scheme 39).

Scheme 39



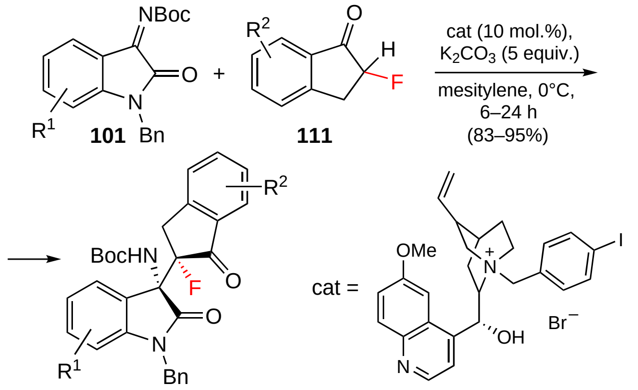
R = H, 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 6-Cl, 6-Br, 7-F, 7-Br;
Ar = Ph, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-Cl-C_6H_4, 4-BrC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 3-BrC_6H_4, 3,5-$Me_2C_6H_3$,
2-Th,  ; TFA is trifluoroacetate,
TFE is trifluoroethanol

This reaction tolerates 3-ketimino oxindoles **109** with various substituents in the benzene ring and substituted arylboronic acids. The proposed asymmetric arylation of 3-ketimino oxindoles **109** represents an effective catalytic method for the preparation of chiral 3-aryl-3-amino-2-oxindoles and is the first example of Pd(II)-catalyzed addition of arylboronic acids to exocyclic ketimines.

β-Fluoramine is an interesting scaffold that plays an important role in pharmaceutical chemistry and is found in many biologically active substances, including drug candidates. β-Fluoro substitution can lower the pK_a value of amines, which improves many pharmacological properties.[158] In this context, effective methods of catalytic asymmetric synthesis of chiral β-fluoroamines are very attractive. One of the direct approaches to β-fluoroamines is the asymmetric Mannich reaction of α-fluoroketones. Therefore, the development of new methods for obtaining chiral fluoroamines is an important challenge in organic synthesis.

To advance this area, Zhao *et al.*[159] developed a method for the catalyzed enantioselective Mannich reaction of isatin-derived *N*-Boc-ketimines **101** with α-fluoroindanones **111** in the presence of a quinine-containing phase transfer catalyst (Scheme 40). As a result, various 3-substituted 3-amino-2-oxindoles **112** containing a fluorine atom and vicinal tetrasubstituted stereocentres were synthesized in good yields and with high diastereoselectivity. The above studies are the first example of an organocatalytic, dia- and stereoselective Mannich reaction of ketenimines with fluoroindanones.

Scheme 40



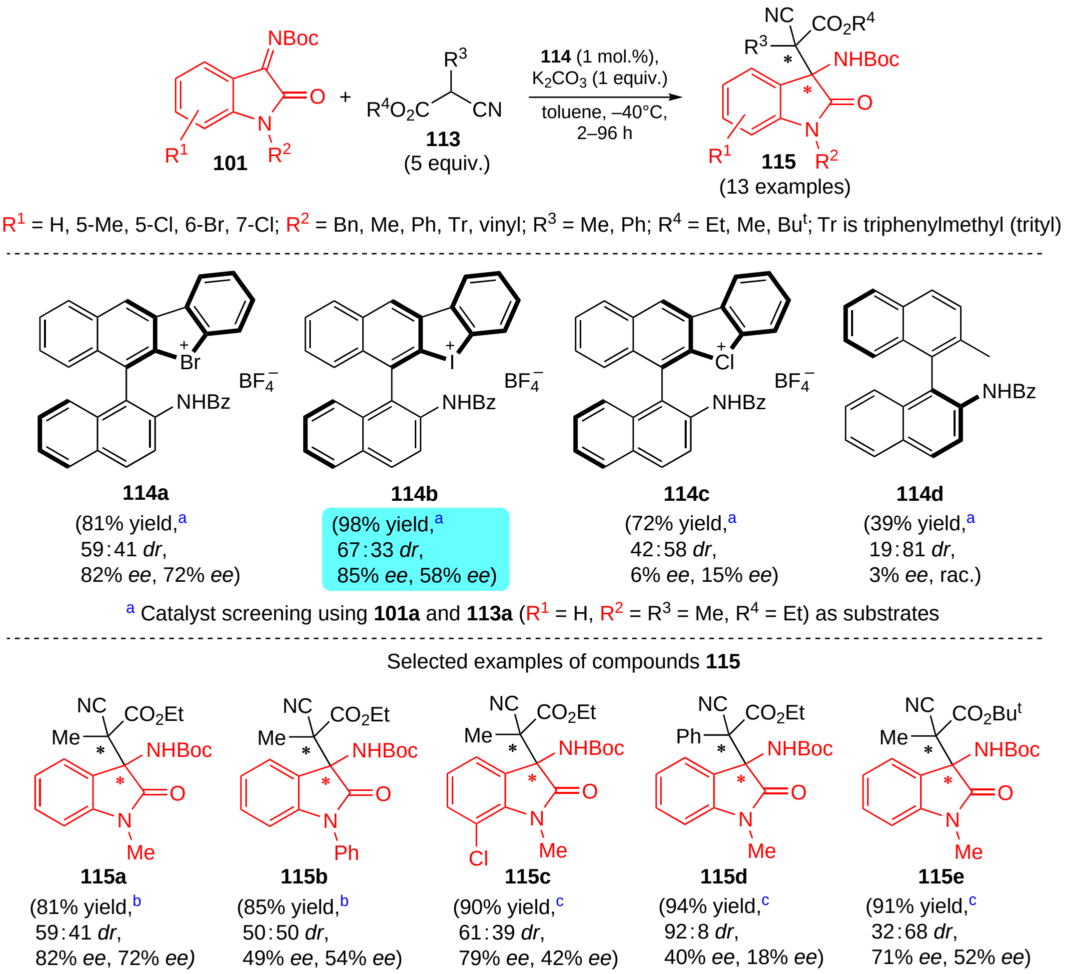
112
(20 examples,
up to 99:1 *dr*,
up to 91% *ee*)

R^1 = H, 5-Cl, 5-Me, 5-MeO, 6-F, 6-MeO, 5,7-Me_2, 7-Cl, 7-Me;
R^2 = H, 4-F, 4-Me, 5-F, 5-Cl, 5-Br, 5-Me, 6-Br, 6-Cl, 6-Me

Yoshida *et al.*[160] reported the first example of asymmetric synthesis of 2-aminocyanoacetic esters with vicinal tetrasubstituted carbon centres using chiral halonium salts **14a–c** as catalysts. The Mannich reaction involved isatin-based *N*-Boc-ketimines **101** and cyanoacetic esters **113** (Scheme 41).

Optimization of the reaction conditions included varying catalysts **114a–d**, solvent, and temperature. It was shown that the use of bromonium salt **114a** is optimal for achieving high enantioselectivity, while iodonium salt **114b** provides higher diastereoselectivity of the process. Carrying out the reaction in non-polar solvents improved the yields of the reaction products, and the optimal temperature is –40°C. The use of a fivefold excess of cyanoacetic esters **113** is necessary to achieve high yields of compounds **115** and higher enantioselectivity of the reaction. A study of the effect of substituents at position 1 of the indolone ring showed that products **115** with higher enantioselectivity are formed from sterically less hindered *N*-substituted substrates **101** (R = Me, Bn). The authors report that studies of the reaction pathway and the possible application of compounds **115** are ongoing.

Scheme 41



R^1 = H, 5-Me, 5-Cl, 6-Br, 7-Cl; R^2 = Bn, Me, Ph, Tr, vinyl; R^3 = Me, Ph; R^4 = Et, Me, Bu^t; Tr is triphenylmethyl (trityl)

114a (81% yield,[a] 59 : 41 *dr*, 82% *ee*, 72% *ee*)

114b (98% yield,[a] 67 : 33 *dr*, 85% *ee*, 58% *ee*)

114c (72% yield,[a] 42 : 58 *dr*, 6% *ee*, 15% *ee*)

114d (39% yield,[a] 19 : 81 *dr*, 3% *ee*, rac.)

[a] Catalyst screening using **101a** and **113a** (R^1 = H, R^2 = R^3 = Me, R^4 = Et) as substrates

Selected examples of compounds **115**

115a (81% yield,[b] 59 : 41 *dr*, 82% *ee*, 72% *ee)*

115b (85% yield,[b] 50 : 50 *dr*, 49% *ee*, 54% *ee*)

115c (90% yield,[c] 61 : 39 *dr*, 79% *ee*, 42% *ee)*

115d (94% yield,[c] 92 : 8 *dr*, 40% *ee*, 18% *ee*)

115e (91% yield,[c] 32 : 68 *dr*, 71% *ee*, 52% *ee*)

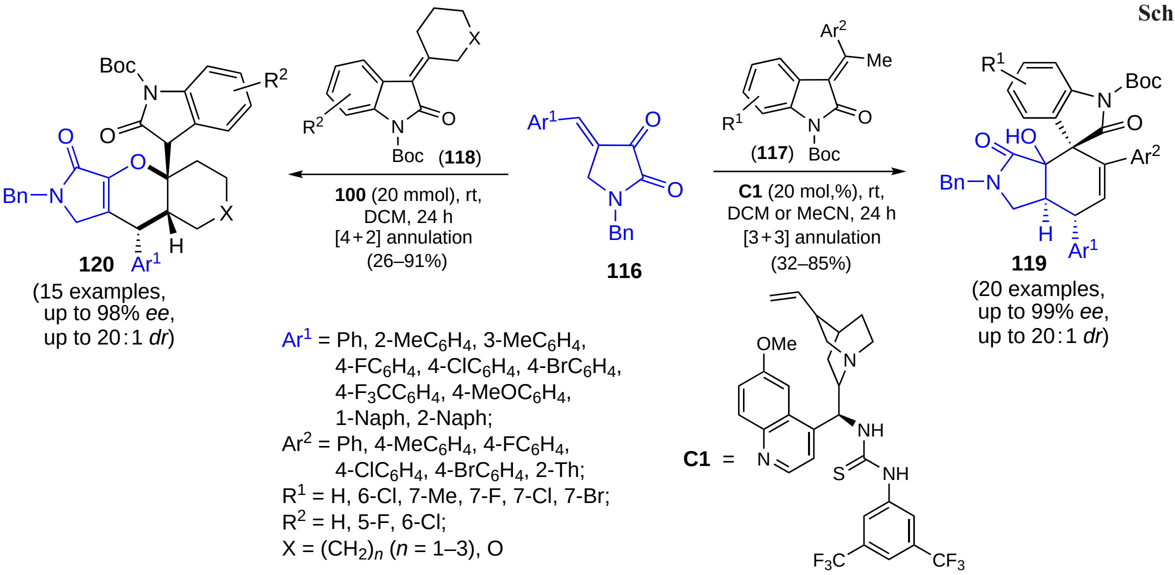
[b] using **114a** as a catalyst, [c] using **114b** as a catalyst

4.2.2. Reaction of the C=C bond

Another type of spirocyclic compounds bearing an indolone ring was synthesized by Huang *et al.*,[85] who developed two methods for the substrate-controlled regiodivergent annulation of 2,3-dioxopyrrolidines **116** with 3-alkylideneoxindoles **117** and **118** (Scheme 42).

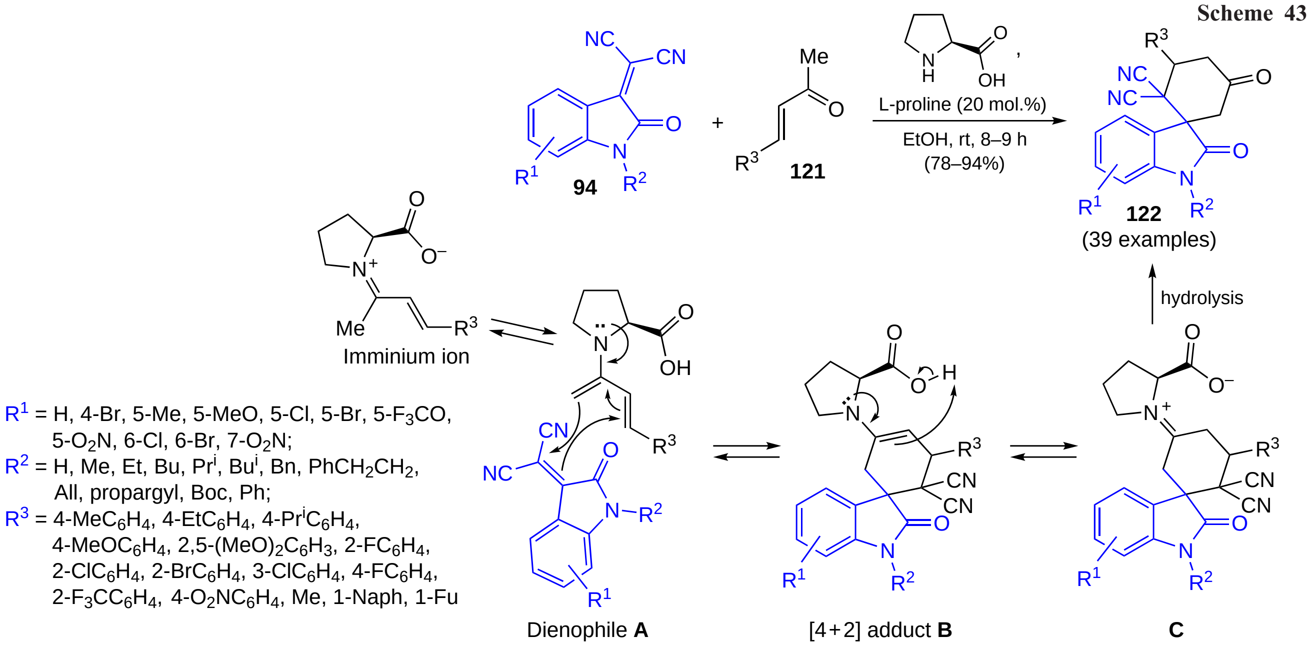
Spirofused indoline-3,4′-isoindoles **119** and indolylchromenopyrrolones **120** were obtained in high yields and with high stereoselectivities. The authors proposed mechanisms for both annulation reactions. It is assumed that [3+3] annulation involves conjugate Michael addition followed by intramolecular aldol cyclization, whereas [4+2] annulation proceeds *via*

Scheme 42



Ar^1 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$, 1-Naph, 2-Naph;
Ar^2 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-Th;
R^1 = H, 6-Cl, 7-Me, 7-F, 7-Cl, 7-Br;
R^2 = H, 5-F, 6-Cl;
X = $(CH_2)_n$ (*n* = 1–3), O

Scheme 43



R^1 = H, 4-Br, 5-Me, 5-MeO, 5-Cl, 5-Br, 5-F_3CO, 5-O_2N, 6-Cl, 6-Br, 7-O_2N;
R^2 = H, Me, Et, Bu, Pr^i, Bu^i, Bn, $PhCH_2CH_2$, All, propargyl, Boc, Ph;
R^3 = 4-MeC_6H_4, 4-EtC_6H_4, 4-$Pr^iC_6H_4$, 4-$MeOC_6H_4$, 2,5-$(MeO)_2C_6H_3$, 2-FC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 3-ClC_6H_4, 4-FC_6H_4, 2-$F_3CC_6H_4$, 4-$O_2NC_6H_4$, Me, 1-Naph, 1-Fu

conjugate Michael addition followed by oxa-Michael cyclization.

Patil *et al.*[161] synthesized a number of spirooxindoles **122** *via* [4+2] cycloaddition of isatylidene malononitrile **94** and α,β-unsaturated ketones **121** using L-proline as an organocatalyst (Scheme 43).

In order to optimize the synthesis procedure, the authors tested various amines (pyrrolidine, piperidine, morpholine, 2-amino-*N*-(4-chlorophenyl)propanamide and an ionic liquid based thereon) as a catalyst, and also varied the catalyst loading. The use of 20 mol.% L-proline is optimal for achieving high yields of spiranes **122** and a short reaction time. When comparing the reaction rates of substrates with electron-withdrawing and electron-donating substituents, it was noted that the reaction rate is higher for compounds with electron-withdrawing groups.

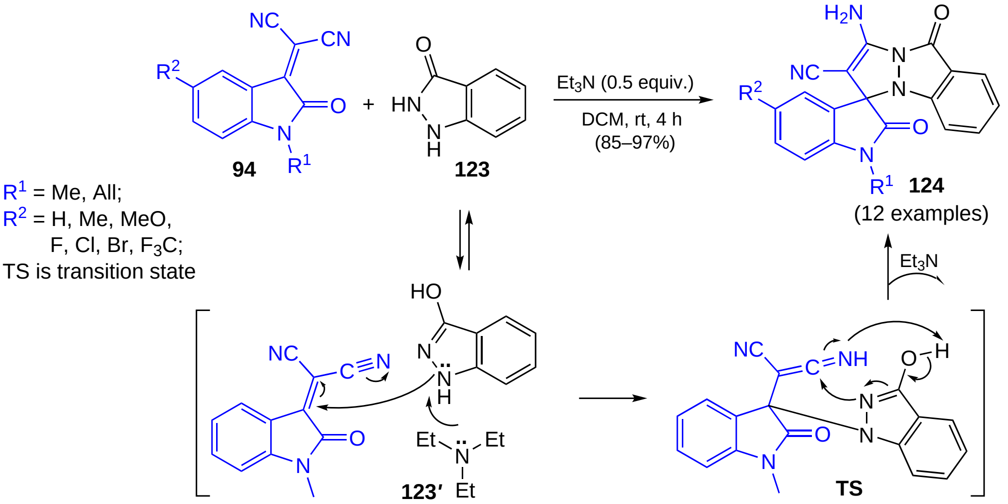
The authors propose that initially, L-proline reacts with ketone **121** to form an imminium ion, which is converted to an enamine that acts as a 1,3-diene (see Scheme 43). Isatilydene malononitrile **94** acts as a dienophile in the [4+2] cycloaddition, forming the [4+2] adduct **B**. Subsequent hydrolysis of adduct **C** delivers spirocyclohexanone oxindoles **122** and regenerates L-proline for the next catalytic cycle.

An efficient synthetic approach to spiro(indoline-3,3′-pyrazolo[1,2-*a*]indazoles) **124** using the [3+2] *N*,*N*-cycloaddition strategy for isatilydene malononitriles **94** and 1,2-dihydro-3*H*-indazol-3-one **123** under mild conditions has been developed (Scheme 44).[162] A number of organic bases (DMAP, pyridine, DBU, DABCO, triethylamine) were tested as reaction catalysts in various solvents at ambient and elevated temperatures and it was found that the optimal conditions for the synthesis of spiranes **124** includes the use of triethylamine as a base, dichloromethane as a solvent, and carrying out the reaction at room temperature.

Kumar *et al.*[162] proposed that 1,2-dihydro-3*H*-indazol-3-one **123** can readily tautomerize to isomer **123′**, which reacts with indolone **94** according to the Michael reaction pathway. Subsequent cyclization and isomerization lead to rearrangement of the π-bonds and formation of three new C–N bonds of spirocyclic indolone **124** (Scheme 44).

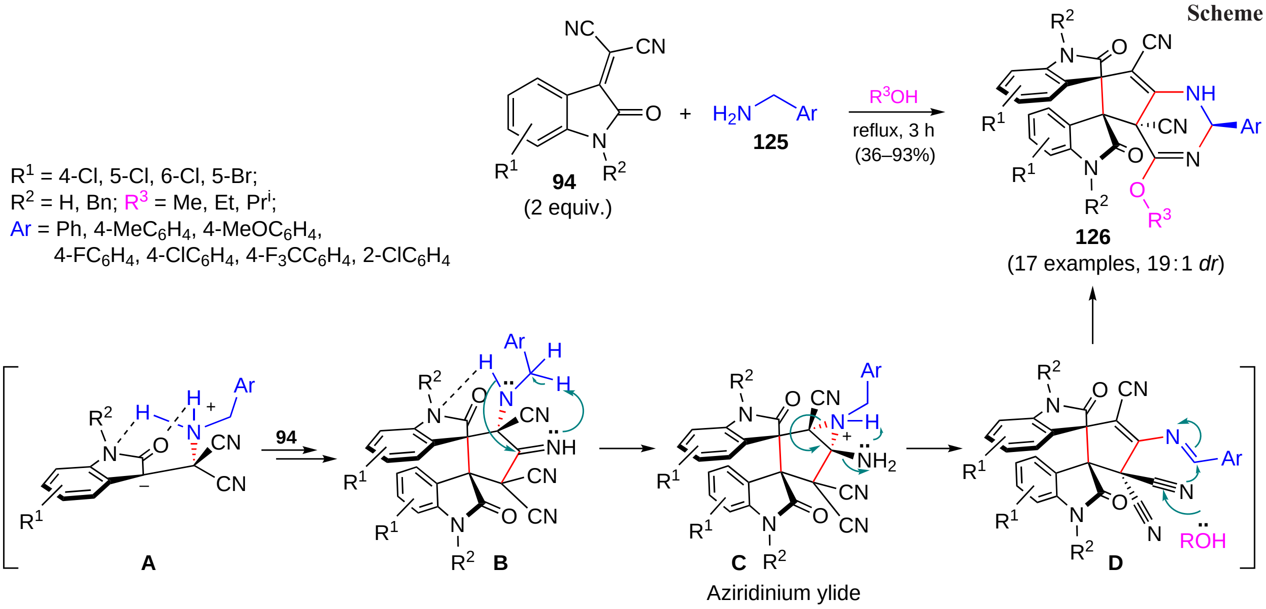
Compounds **124** were evaluated for cytotoxicity against various cancer cell lines, including MCF-7 (breast cancer), A549 (lung cancer), Colo-205 (colon cancer) and A2780 (ovarian cancer).[162] It should be noted that compound **124a** (R^1 = All, R^2 = Me) showed the highest apoptotic activity,

Scheme 44



R^1 = Me, All;
R^2 = H, Me, MeO, F, Cl, Br, F_3C;
TS is transition state

Scheme 45



R^1 = 4-Cl, 5-Cl, 6-Cl, 5-Br;
R^2 = H, Bn; R^3 = Me, Et, Pr^i;
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$,
4-FC_6H_4, 4-ClC_6H_4, 4-$F_3CC_6H_4$, 2-ClC_6H_4

exhibiting the lowest IC_{50} values among all four cancer cell lines. In addition, the observed biological activity was confirmed by molecular docking studies, suggesting that these compounds may interact with relevant cellular targets, potentially accounting for their cytotoxic effects.

Yavari *et al.*[163] described a cascade reaction between two equivalents of isatylidene malononitriles **94** and benzylamines **125** to afford dispirocyclopentene oxindoles **126** with high diastereoselectivity (*dr* ⩾ 19:1) (Scheme 45).

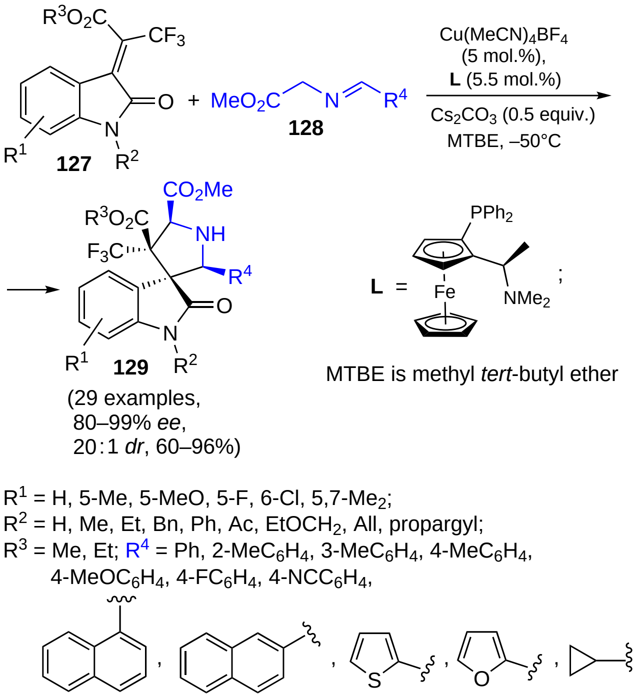
Molecules of **126** comprise four chiral centres, including two vicinal spiro-quaternary chiral centres. The structures of compounds **126** were confirmed by X-ray diffraction analysis.

The authors proposed a reaction pathway for the formation of spiranes **126**, which probably begins with the reaction of isatylidene malononitrile **94** with benzylamine **125** to give an intermediate product **A**, which reacts with a second molecule of **94** and then undergoes intramolecular cyclization to form aziridinium ylide **C**. Aziridinium ylide **C** subsequently undergoes ring opening and elimination reaction to afford dispirocyclopentene **D**. Attack of the alcohol molecule on the cyano group of intermediate **D** initiates a second cyclization reaction, which delivers the target dispiroindoline-cyclopentapyrimidinindolines **126**.

It should be noted that the unique structural features of bispirooxindoles impart significant conformational rigidity, which often leads to increased biological activity of various biomolecules. According to recent findings, they can be uses as acetylcholinesterase inhibitors, which represents a promising therapeutic strategy for the treatment of Alzheimer's disease.[164, 165]

Isatin-derived trifluoromethyl-substituted alkyl acrylates **127** undergo an intermolecular [3+2] cycloaddition to azomethine ylides **128**.[166] Unusual highly substituted pyrroledines **129** bearing adjacent quaternary all-carbon stereocentres, one of which being spirocyclic and another containing a trifluoromethyl group, were obtained in good yields and with high stereoselectivity (*ee* 80–99%, *dr* > 20:1) (Scheme 46).

Scheme 46



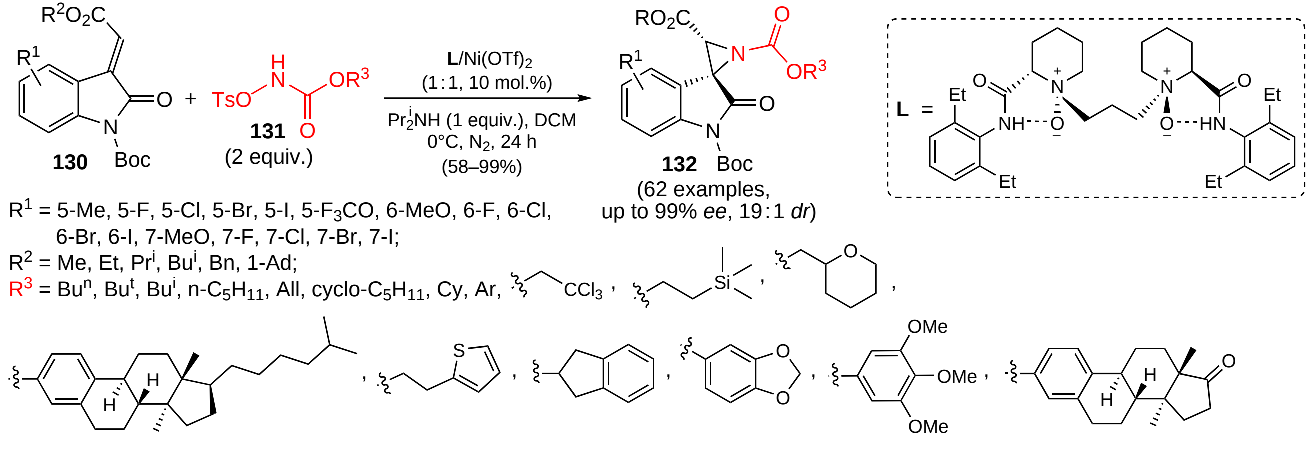
R^1 = H, 5-Me, 5-MeO, 5-F, 6-Cl, 5,7-Me_2;
R^2 = H, Me, Et, Bn, Ph, Ac, $EtOCH_2$, All, propargyl;
R^3 = Me, Et; R^4 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4,
4-$MeOC_6H_4$, 4-FC_6H_4, 4-NCC_6H_4,

The authors used copper salts ($Cu(OTf)_2$, $Cu(CH_3CN)_4PF_6$, CuI and $Cu(OAc)_2$) as catalysts, six different ligands, various bases and also varied a solvent to optimize reaction conditions. Maximum yields, the highest diastereoselectivities and enantioselectivities were achieved when using $Cu(CH_3CN)_4PF_6$, a chiral ligand 2-(1-(dimethylamino)ethyl)-1-(diphenylphosphino)ferrocene (**L**), Cs_2CO_3 as a base and MTBE as a solvent. The authors scaled up the reaction and reacted the resulting spiranes **129** with phenylboronic acid and Boc_2O under Suzuki–Miyaura conditions thereby demonstrating the synthetic potential of these compounds.[166]

Liu and co-workers[167] reported the asymmetric catalytic aza-Michael-initiated ring-closure of methylene indolinones **130** with *N*-tosyloxycarbamates **131** (Scheme 47).

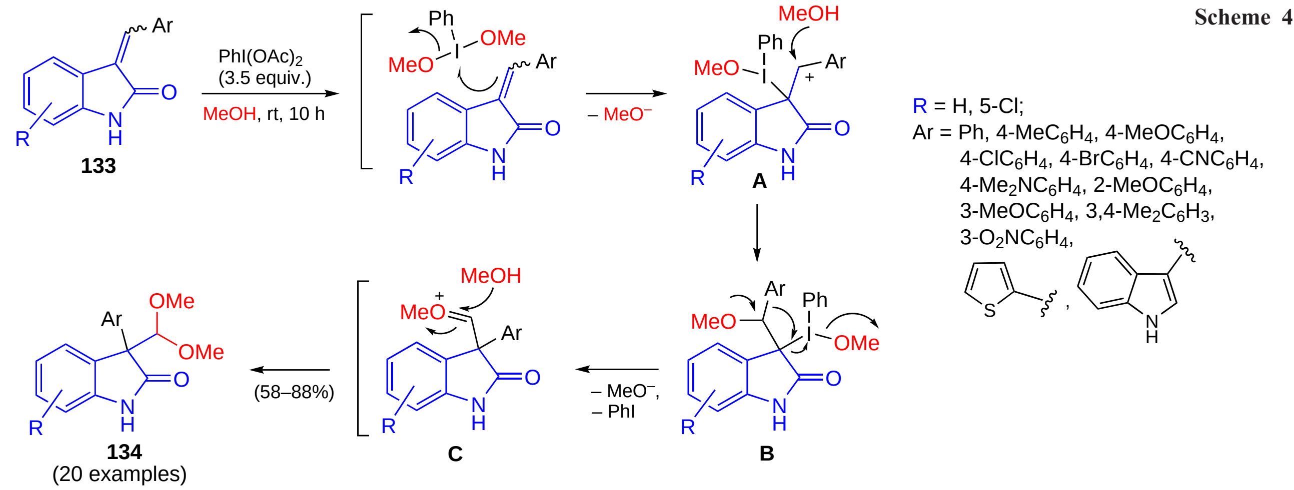
The use of chiral nickel complex catalyst **L**/$Ni(OTf)_2$ with good functional tolerability and wide versatility in this reaction under ambient conditions enabled the synthesis of spiro-aziridine oxindoles **132** in good yields (up to 99%) and with high stereoselectivity (up to 97% *ee*, >19:1 *dr*) under mild conditions. The effect of substituents in the benzene ring of the ligand was studied, and the optimal reaction conditions were

Scheme 47



R^1 = 5-Me, 5-F, 5-Cl, 5-Br, 5-I, 5-F_3CO, 6-MeO, 6-F, 6-Cl, 6-Br, 6-I, 7-MeO, 7-F, 7-Cl, 7-Br, 7-I;
R^2 = Me, Et, Pr^i, Bu^i, Bn, 1-Ad;
R^3 = Bu^n, Bu^t, Bu^i, n-C_5H_{11}, All, cyclo-C_5H_{11}, Cy, Ar, CCl_3, Si, ...

Scheme 48



R = H, 5-Cl;
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 4-$Me_2NC_6H_4$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3,4-$Me_2C_6H_3$, 3-$O_2NC_6H_4$,

searched for by varying various metal triflates, various bases and solvents. All experiments were carried out in a nitrogen atmosphere at 0°C. The optimal conditions include the use of the **L**/Ni(OTf)$_2$/diisopropylamine catalytic system and dichloromethane as a solvent.

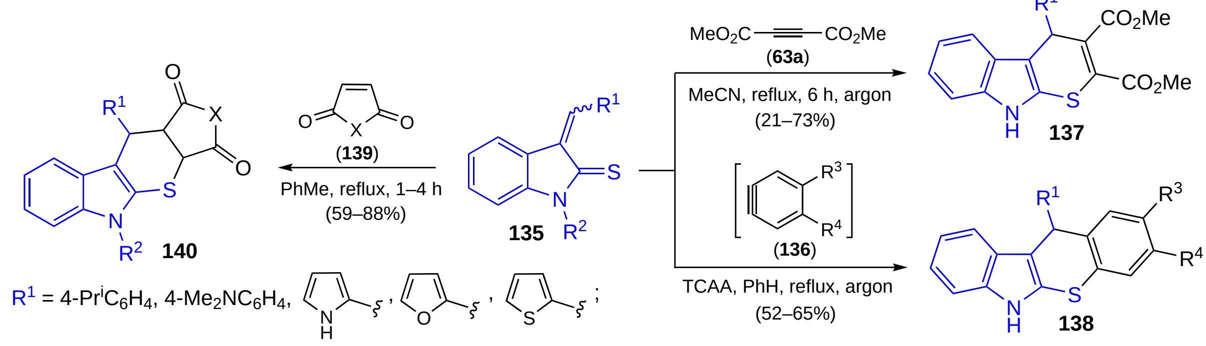
Karade and co-workers[168] presented a new efficient method for the synthesis of 3-aryloxindoles from 3-arylideneindolin-2-ones. (Diacetoxyiodo)benzene initiates a skeletal rearrangement involving 1,2-aryl migration to position 3 of the ring. Ligand exchange between (diacetoxyiodo)benzene and methanol affords the trivalent iodine compound PhI(OMe)$_2$ (Scheme 48).

The reaction begins with electrophilic activation of 3-arylideneindolin-2-one **133** by PhI(OMe)$_2$ leading to a stabilized benzyl carbocation **A**, which is trapped with methanol and converted to adduct **B**. Migration of the aryl substituent then occurs, facilitated by elimination of iodobenzene. This generates an intermediate oxonium ion **C**, which undergoes nucleophilic attack by the second molecule of methanol to give 3-(dimethoxymethyl)-3-arylindolin-2-ones **134**.

This effective method provides an access to oxindoles with a quaternized C3 atom of the oxindole ring under mild conditions and demonstrates broad substrate tolerability, allowing the preparation of various 3-aryloxindoles in good yields.

Benzylidene indoline-2-thiones **135** react with DMAD **63a** and benzynes **136** generated *in situ* from the appropriate

Scheme 49



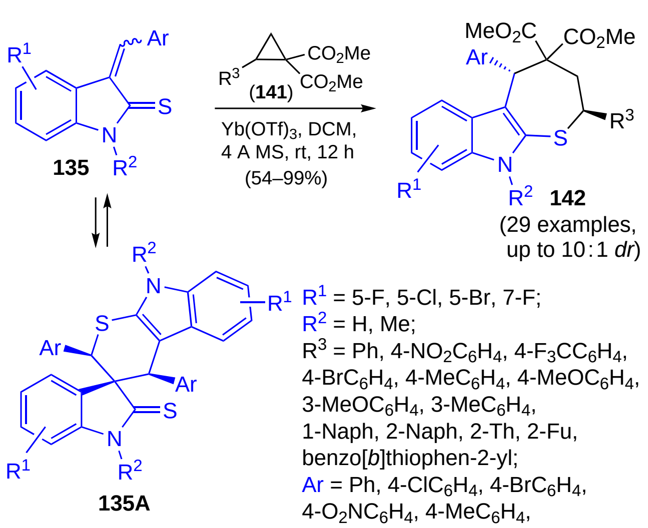
R^1 = 4-$Pr^iC_6H_4$, 4-$Me_2NC_6H_4$, ...;
R^2 = H, Et, Ph; R^3 = R^4 = OMe, R^3 = H, R^4 = OMe; X = N, O;
TCAA is trichloroacetic acid

2-diazonio benzenecarboxylate hydrochlorides to form tetracyclic compounds **137** and **138** (Scheme 49).[169]

Subsequently, the number of dienophiles was expanded by using 2,5-diones **139**, which made it possible to obtain tetracyclic compounds **140** (Ref. 74) (see Scheme 49). The use of only highly electrophilic dienophiles narrows the applicability of this reaction. That could be the reason why there are no data on the use of indole thiones in other types of pericyclic reactions, *e.g.*, in [4+3] cycloaddition.

It should be noted that benzylideneindoline-2-thiones **135** are unstable and exist as dimers **135A** (Scheme 50).

Scheme 50



R^1 = 5-F, 5-Cl, 5-Br, 7-F;
R^2 = H, Me;
R^3 = Ph, 4-$NO_2C_6H_4$, 4-$F_3CC_6H_4$, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3-MeC_6H_4, 1-Naph, 2-Naph, 2-Th, 2-Fu, benzo[*b*]thiophen-2-yl;
Ar = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-MeC_6H_4, 3-$MeOC_6H_4$, 2-MeC_6H_4, 2-Naph, benzo[*b*]thiophen-2-yl;
MS is molecular sieve

Jiang *et al.*[86] drew attention to donor-acceptor cyclopropanes **141**, which are widely used for the preparation of complex cyclic and acyclic compounds. It was shown that cyclopropanes **141** can be suitable partners for $Yb(OTf)_3$-catalyzed formal [4+3] cycloaddition to benzylideneindolin-2-thiones **135**, yielding thiepino[2,3-*b*]indoles **142** (see Scheme 50).

5. Thiazole derivatives

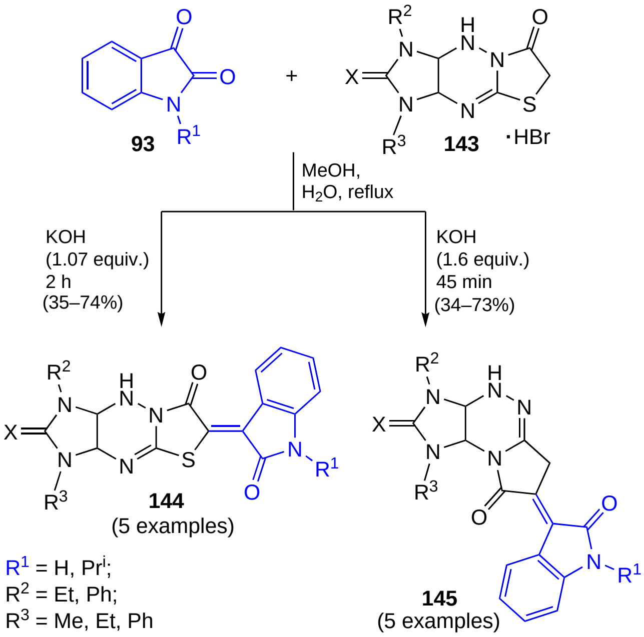
Thiazolidinones functionalized at position 5 of the ring exhibit a variety of biological activities, *vis*., antifungal,[170] neuroleptic,[171] antidiabetic,[172] anti-inflammatory[173] and antitumour activities.[174] The search for new biologically active substances among compounds of this class is ongoing.

In the search for novel inhibitors of cancer cell division, Izmest'ev *et al.*[175] reacted isatins **93** with imidazothiazolotriazines **143** under aldol-croton condensation basic conditions and obtained two series of regioisomeric compounds, imidazo-[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazines **144** and imidazo[4,5-*e*]-thiazolo[2,3-*c*][1,2,4]triazines **145** (Scheme 51). Compound **145a** ($R^1 = Pr^i$, R^2 = Ph, R^3 = Et) showed significant cytostatic activity against most of the cell lines tested.[175]

In order to synthesize new urease inhibitors,[176] Elbastawesy *et al.*[177] designed and obtained hybrids of well-known biologically active objects, quinoline-2-one and thiazolidinone, connected by a hydrazone linker. Refluxing a mixture of equimolar amounts of thiosemicarbazides **146** and DEAD **63b** in DMF in the presence of triethylamine affords thiazolidin-4-ones **147** in high yields (Scheme 52).

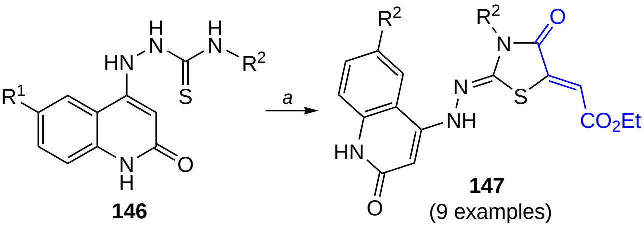
It is noted that all the synthesized target compounds **147** showed different degrees of urease inhibitory activity in the IC_{50} range of 0.46–27.1 μM, which is higher than similar values for thiourea, which was chosen as a standard ($IC_{50} = 21.9 \pm 0.89$ μM). Compounds **147a–c** (R^1 = Me, R^2 = Ph (**147a**), R^1 = Cl, R^2 = Ph (**147b**), R^1 = Br, R^2 = Ph (**147c**)) demonstrated outstanding urease inhibitory potential (IC_{50} 0.92±0.17, 0.74±0.14 and 0.46±0.04 μM, respectively). The binding interactions of compounds **147** were confirmed by molecular docking studies. The most active compounds showed complete overlap and a binding mode close to the standard.

Scheme 51



$R^1 = H, Pr^i$;
R^2 = Et, Ph;
R^3 = Me, Et, Ph

Scheme 52



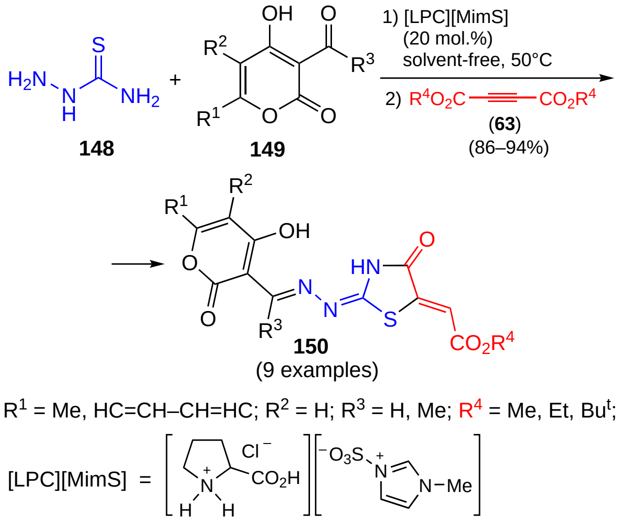
(*a*) $EtO_2C-C\equiv C-CO_2Et$ (**63b**), DMF, Et_3N, reflux 8–12 h (71–88%); R^1 = H, Me, MeO, Cl, Br; R^2 = Ph, Bn, All

Hydrazone 4-thiazolidinones **150** were obtained by the sequential reaction of thiosemicarbazide **148**, 3-acyl-4-hydroxypyran-2-ones **149** and dialkyl acetylenedicarboxylates **63** using a new binary ionic liquid [LPC][MimS], [L-prolinium chloride][1-methylimidazolium-3-sulfonate], as a catalyst (Scheme 53).[178]

The reaction occurs under mild and solvent-free conditions. The binary ionic liquid melts at near room temperature and can be considered as a solution of HCl in a 1:1 mixture of two zwitterionic compounds. It appears to activate carbonyl compounds **149** either by conversion to a proline-based imine or as an acid catalyst. It should be noted that [LPC][MimS] is stable in air and in the presence of moisture and can be reused repeatedly without any noticeable loss in its catalytic activity. Some of the resulting compounds **150** exhibited pronounced antibacterial activity.

Condensation of thioureas **151**, including their cyclic analogues, with acetylenedicarboxylic acid esters (**63a,b**) gives

Scheme 53

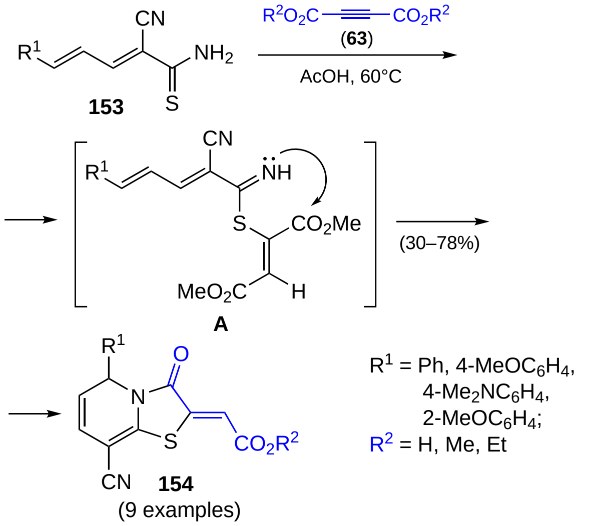


rise to a variety of functionalized thiazolidin-4-ones and their analogues with heterocyclic rings **152** (Scheme 54).[179]

The reaction is highly selective and leads to the formation of a five-membered thiazole ring rather than a six-membered triazine ring, which is demonstrated by comparison with the literature data[180] regarding the spin–spin coupling constants between the carbonyl carbon atom (C4=O) and the vinyl hydrogen atom (=CH). The authors[179] note that the bulky cyclohexyl substituent in the starting thiosemicarbazide **151C** reduces the nucleophilicity of the corresponding nitrogen atom, resulting in intramolecular N-acylation at the N2 atom to give thiazolidin-4-one **152C** (R^3 = Cy). The reaction of 1,4-diphenylthiosemicarbazide with DMAD **63a** is non-selective and affords two regioisomeric products **152C** (R^3 = Ph) and **152C′** in equal amounts (according to ^{1}H NMR). The isomers were separated by fractional crystallization from methanol.

Gagarin *et al.*[39] synthesized penta-2,4-dienecarbothioamides **153** and reacted them with acetylenes **63** (Scheme 55). The key step of the process is 1,6-electrocyclization of 1-azahexatriene **A** to give pyridothiazoles **154** containing C=C and C=O bonds.

Scheme 55



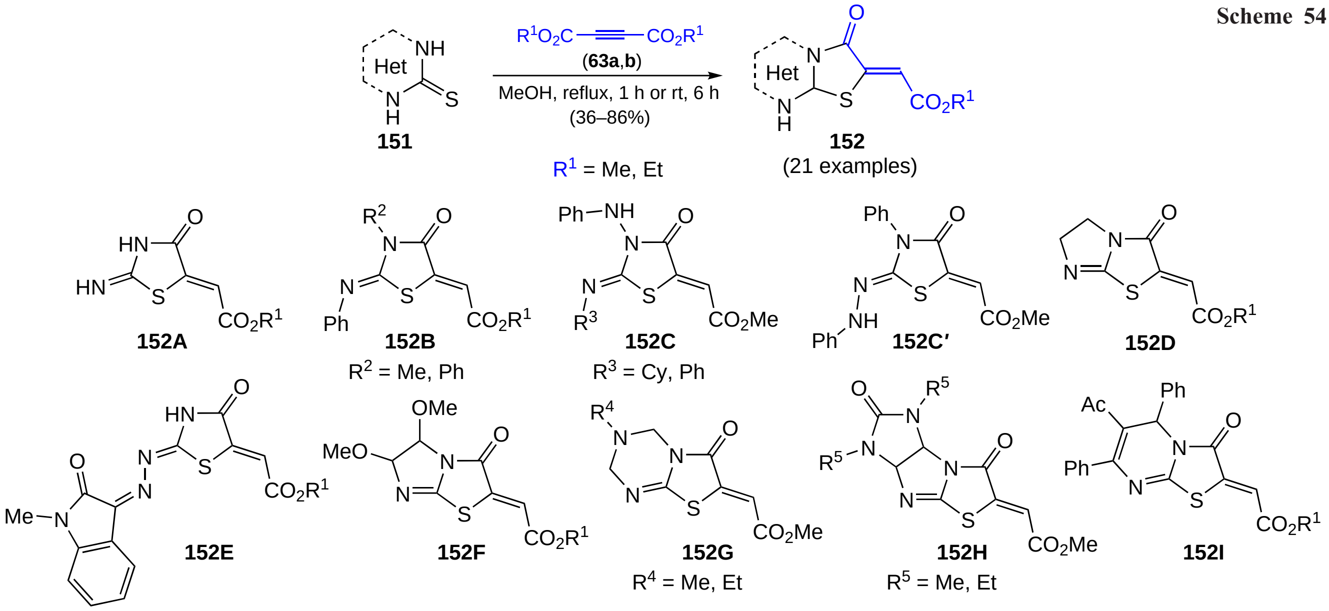
Berseneva *et al.*[181] found that active methylene 2-carbamoylthioamides **155** react with DMAD **63a** in ethanol to furnish 2-methylidene-1,3-thiazolidin-4-ones **156** (Scheme 56, reaction *a*).

Obydennov *et al.*[182] demonstrated the possibility of using compounds **156** in the synthesis of double bond-linked bicyclic heterocycles **157** (see Scheme 56, reaction *b*). A screening for fungicidal activity revealed compounds with high antifungal potency. The authors subsequently published a review devoted to the synthesis of bicyclic compounds linked by an exocyclic double bond.[183]

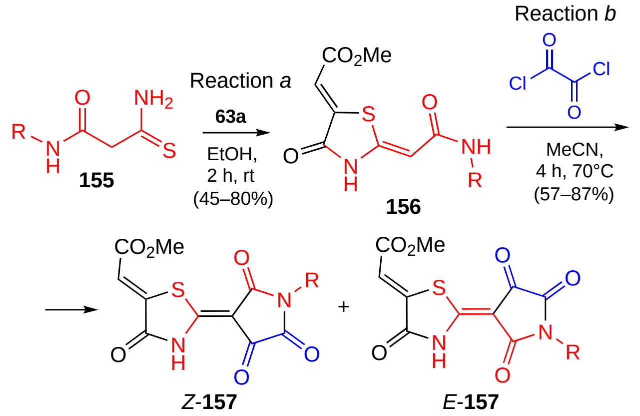
2-Phenylthiazolin-5-one **159**, generated *in situ* from thiohippuric acid **158**, was condensed with various aldehydes (Scheme 57).[184]

The reaction is catalyzed by basic lead acetate and runs equally successfully with both aliphatic and aromatic aldehydes. This version of the classical Erlenmeyer synthesis of azlactones under mild conditions is apparently possible due to the more pronounced aromaticity of the intermediate anionic thioazlactones **160**, which are converted to alcohols **161** when treated with aldehydes. Dehydration of compounds **161** gives 4-alkyl(aryl)ydenetiazolin-5-ones **162** in good yields.

Scheme 54

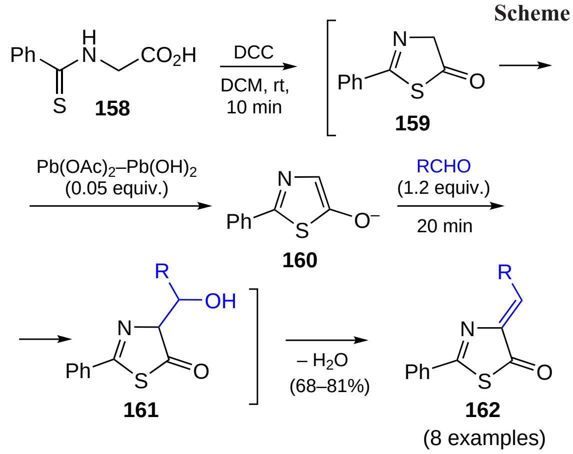


Scheme 56



R = Me, Ph, Bn, 4-MeOC$_6$H$_4$, 1-Naph, 2-Naph

Scheme 57



R = Et, Pr, Pr^i, Bu^i, n-C$_6$H$_{13}$, Ph, 4-MeOC$_6$H$_4$, PhCH=CH–

6. Selenazol derivatives

In contrast to sulfur-containing heterocyclic compounds, the chemistry of selenazoles is poorly represented in the literature.[68, 185–187] However, these compounds exhibit antibacterial, antitumour[187] and pesticidal activities,[68] which attracts interest in studying their properties.

Attanasi *et al.*[185] reported the synthesis of 2-selenazolin-4-ones **166** by the reaction of 1,3-butadienes **163** with selenoureas **164** in methanol at 0°C. It was noted that the resulting compounds **166** are predominantly in the form of hydrazones (Scheme 58).

According to the authors, the reaction involves nucleophilic addition of the selenium atom of selenoureas **164** to the terminal carbon atom of the heterodiene moiety. Subsequent intramolecular nucleophilic attack of the imide NH nitrogen on the carboxylate carbon of Michael adduct **165** and elimination of the alcohol molecule leads to the formation of the selenazoline ring. Tautomeric selenazolinones **166′** were isolated in low yields by fractional crystallization of mixtures of compounds **166**/**166′** from a MeOH/Et$_2$O mixture.

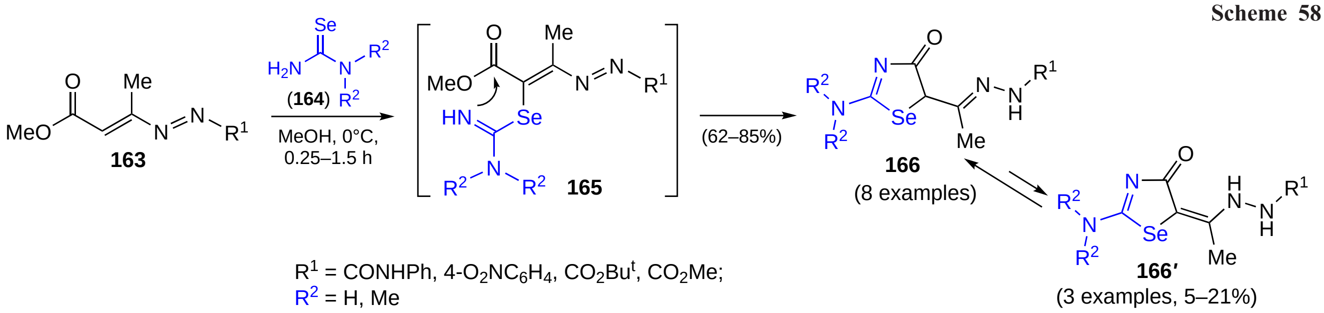
Taking into account the successful use of acetylenes in a variety of chemical reactions, Ramazani *et al.*[186] studied the reaction of acetylenedicarboxylates **63** with selenourea **167** (Scheme 59).

The authors believe that compounds **168** are formed *via* an initial Michael addition of selenourea **167** to the triple bond of acetylenes **63** to form adducts **A**, followed by intramolecular proton transfer from the amidine group to the C=C bond to give adducts **B**. Subsequent reaction of the imine nitrogen atom with the carbonyl group yields intermediates **C**. Intramolecular proton transfer in intermediate **C** affords 2-amino-4-oxo-1,3-selenazoles **168** in moderate yields.

In order to search for new fungicides, Galochkin *et al.*[68] designed and proposed a synthetic approach to fused compounds containing hexahydroimidazo[4,5-*d*]imidazole and -selenazole moieties. Four representatives of a new heterocyclic system, 3,3a-dihydro-1*H*-imidazo[4′,5′:4,5]imidazo[2,1-*b*][1,3]-selenazoles (imidazo-imidazoselenazoles) **170** were obtained for the first time, based on the reaction of bicyclic selenoureas **169** with DEAD **63b** (Scheme 60).

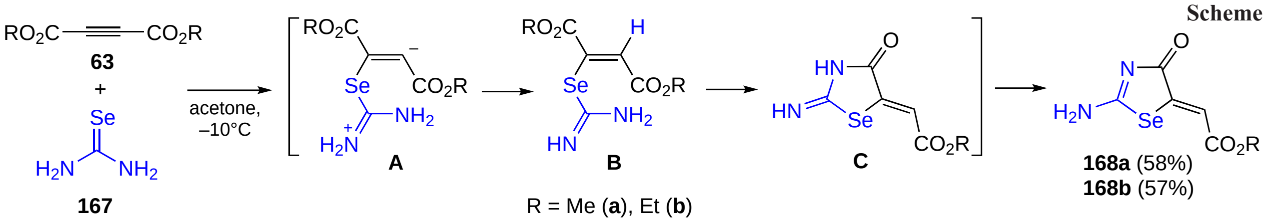
Selenazoles **170** were obtained under mild conditions (rt, 1–2 h), but at R = H, the reaction mixture requires heating under reflux. The structure of compounds **170** was established using two-dimensional NMR spectroscopy, ^{13}C GATED NMR spectra and high-resolution mass spectra.

Scheme 58



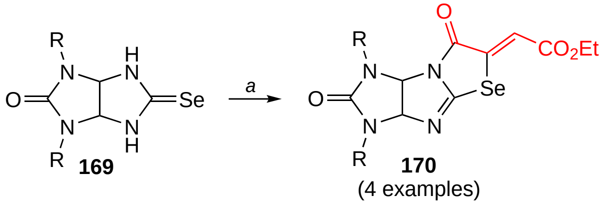
R^1 = CONHPh, 4-O$_2$NC$_6$H$_4$, CO$_2$Bu^t, CO$_2$Me;
R^2 = H, Me

Scheme 59



R = Me (**a**), Et (**b**)

Scheme 60



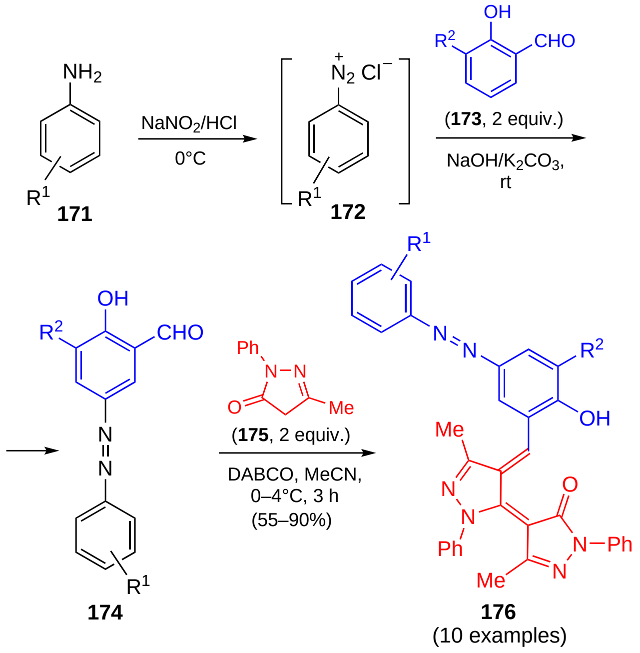
(*a*) $EtO_2C—\equiv—CO_2Et$ (**63b**), EtOH, rt, 1–2 h or reflux, 2 h (56–76%); R = H, Me, Et, Pr

7. Pyrazole derivatives

Pyrazole and its derivatives are used in pharmacy due to their broad spectrum of their biological activity.[188] For example, edaravone (5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one) is a drug with the trade name Radicut and is used to treat amyotrophic lateral sclerosis.[189]

In order to expand the range of practical applications of pyrazoles, Rabbani *et al.*[23] carried out a three-step synthesis of pyrazoles **176**, including diazotization of aromatic amines **171**, azo coupling of diazonium salts **172** with 2-hydroxybenzaldehydes **173** to afford aza compounds **174**, and their subsequent condensation with edaravone **175** in the presence of DABCO (Scheme 61).

Scheme 61

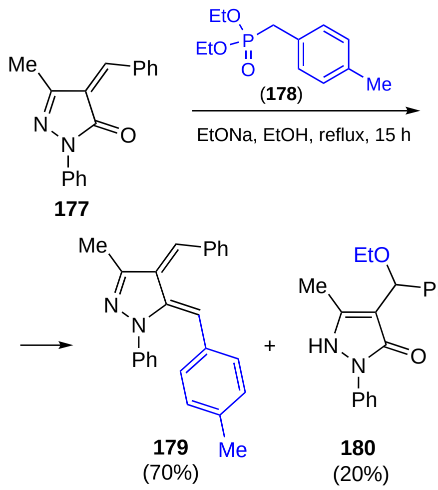


R^1 = H, 2-Me, 4-Me, 4-Et, 4-MeO, 4-Cl, 4-NO_2; R^2 = H, MeO

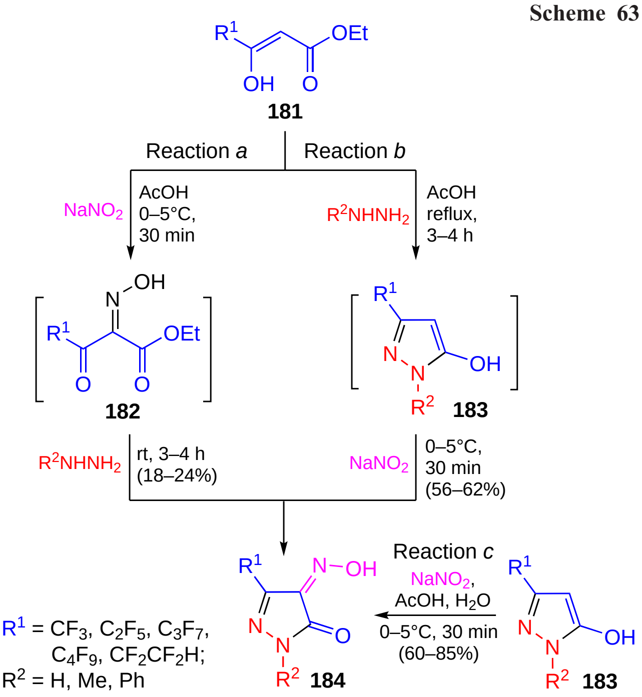
Condensation involves the aldehyde group of aza compounds **174** and the active methylene group of edaravone **175**. Among the resulting compounds **176**, those with antibacterial activity against Gram-positive and Gram-negative bacteria were identified (**176a** (R^1 = 4-Me, R^2 = MeO), **176b** (R^1 = 4-Et, R^2 = MeO), **176c** (R^1 = R^2 = H)).

Boulos *et al.*[38] reacted pyrazolone **177** with phosphonate **178** in the presence of sodium ethoxide to give pyrazole **179** (Scheme 62). Pyrazolone **180** was isolated as a by-product of this reaction.

Scheme 62



Scheme 63



R^1 = CF_3, C_2F_5, C_3F_7, C_4F_9, CF_2CF_2H;
R^2 = H, Me, Ph

Burgart *et al.*[190] proposed several ways for obtaining pyrazoles containing conjugated C=N–OH and C=O bonds. It was found that sequential treatment of esters **181** with sodium nitrite in acetic acid and subsequent heterocyclization of the intermediate hydroxyimines **182** with hydrazines delivers the target 4-hydroxyiminopyrazol-3-ones **184** in low yields (18–24%) (Scheme 63, reaction *a*).

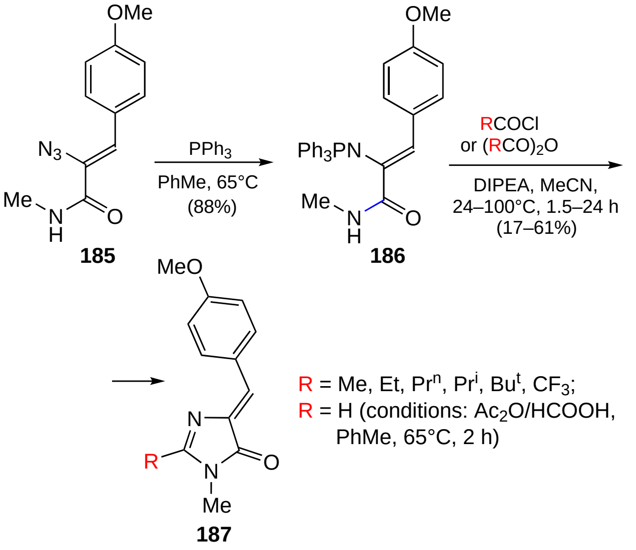
The use of another approach, including nitrosation of preliminary obtained pyrazol-5-oles **183** with sodium nitrite in acetic acid, allowed the yield of target compounds **184** to be increased to 85% (see Scheme 63, reaction *b*). In addition, the authors developed a one-pot procedure for obtaining pyrazolones **184** from esters **181** and hydrazines in acetic acid, followed by treatment of the reaction mixture with sodium nitrite (see Scheme 63, reaction *c*). Under these conditions, pyrazolones **184** are formed in 56–62% yields, which makes this method the most attractive for their synthesis, since it allows to exclude the step of isolation of pyrazolones **183**.

8. Imidazole derivatives

Imidazoles occupy a special place in heterocyclic chemistry due to their diverse chemical and pharmacological properties.[191–197] Compounds containing the imidazole ring exhibit a wide range of pharmacological activity, including antitumour,[193] antiepileptic,[194] antituberculotic,[195] antibacterial[196] and antifungal.[197] A number of well-known antitumour drugs, such as dacarbazine, nilotinib, ponatinib, bendamustine hydrochloride, contain an imidazole ring in their structure.[192] Imidazole derivatives are promising fluorophores for organic light-emitting diodes, chemo- and biosensors.[198] Therefore, the synthesis of new imidazole-based molecules is relevant.

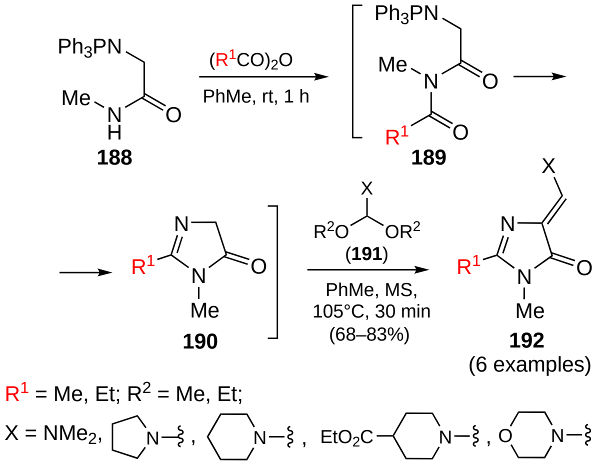
Baranov *et al.*[199] studied the reaction of azidomethylacrylamide **185** with triphenylphosphine, carboxylic acid anhydrides and acyl chlorides (Scheme 64). In the reaction with acyl chlorides, acrylamide **186** was preliminarily isolated, whereas in the case of using acid anhydrides, the reaction was carried out in a one-pot fashion. The yields of products **187** are low (17–45%), except for compound **187a** (R = Me, 61%). In the final step, to obtain the desired analogues of the GFP (Green Fluorescent Protein) chromophore, the authors[199] used standard conditions for phenol demethylation (BBr_3 in DCM). The experimental data obtained make it possible to introduce various substituents into the imidazole ring, as well as to obtain imidazolones unsubstituted at position 3 of the ring.

Scheme 64



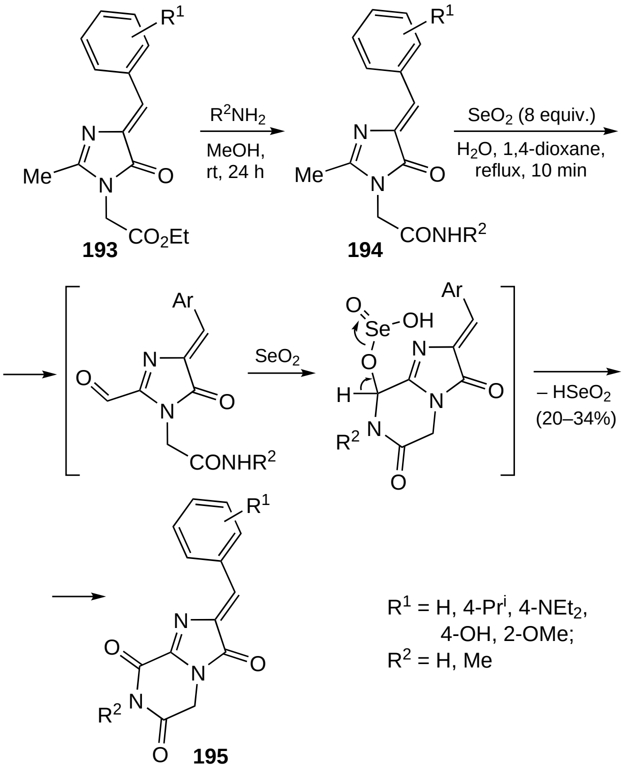
Imidophosphazene **188** and unstable imides **189** derived *in situ* therefrom, which cyclize to imidazol-4-ones **190**, were used to synthesize imidazoles containing two conjugated exocyclic C=C and C=O bonds (Scheme 65).[34] Formamidoacetals **191** were used for subsequent condensation. It was noted that the use of molecular sieves improved the yields of target compounds **192** by 15–20%.

Scheme 65



The number of imidazoles containing exocyclic C=C and C=O bonds can be increased by modifying the substituents at the ring and at the C=C bond. In particular, the reaction of benzylidene imidazolone esters **193** with ammonia and methylamine gives amides **194**, which were subjected to oxidation with SeO_2 (Scheme 66).[200] The authors found that, along with the oxidation of the methyl group, further oxidation and intramolecular condensation occur constructing the pyrazinone ring on the imidazole ring to form bicycles **195**; however, the yields of the products are low.

Scheme 66



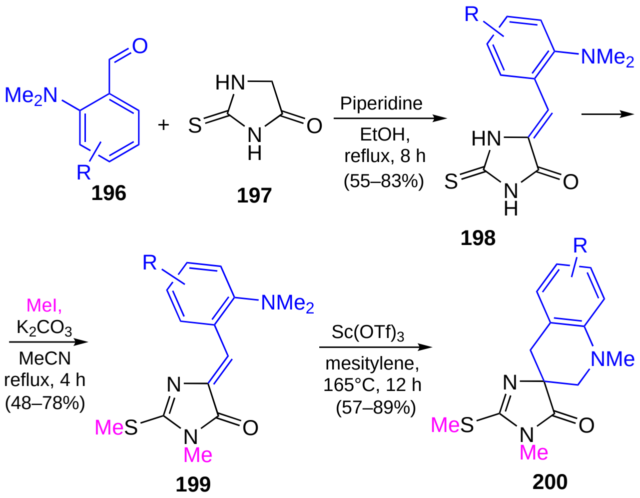
Baranov and co-workers[201] utilized the synthetic potential of 4-arylidenethioimidazolones to obtain imidazole-containing spirocycles. Research in this direction is particularly relevant, since it is part of a broader area — the creation of heterocyclic non-planar compounds.[202]

Taking into account their previous findings,[203] the authors[201] reacted aldehydes **196** with thioxoimidazolinone **197** to obtain imidazolones **198**, which were methylated and converted the resulting compounds **199** into spiro[imidazole-4,3′-quinolin]-ones **200** (Scheme 67). This transformation occurs due to a [1,5]-hydride shift and subsequent cyclization catalyzed by scandium triflate.

Kuleshov *et al.*[89] studied the cycloaddition of 4-arylidene-1*H*-imidazol-5(4*H*)-ones **201** to *N*-benzylazomethine methylide, using *N*-benzyl-1-methoxy-(trimethylsilyl)methylamine **202** as a precursor, in the presence of a catalytic amount of trifluoroacetic acid with the aim of synthesizing spirocyclic compounds **203** (Scheme 68).

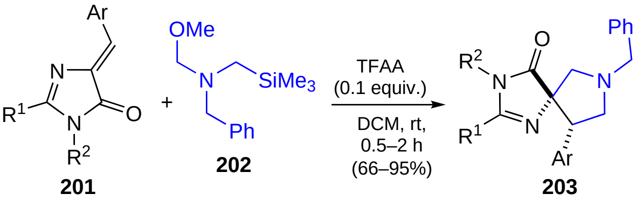
It was found that the reaction proceeds diastereoselectively yielding 1,3,7-triazaspiro[4.4]non-1-en-4-ones **203** as an individual diastereomer. A study of the effect of substituents on the course of the reaction showed that the aryl substituent has the greatest effect. In the presence of electron-donating substituents, the reaction proceeds more slowly and requires the

Scheme 67



R = H, 4-OMe, 4-CF$_3$, 2-CF$_3$, 2-Br, 3-NO$_2$

Scheme 68



R^1 = Me, CF$_3$; R^2 = Me, Bu;
Ar = 4-BrC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 4-(NC)C$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-Th;
TFAA is trifluoroacetic acid

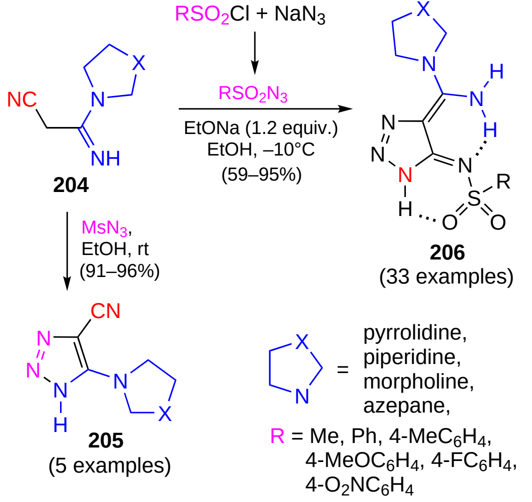
use of an excess of the precursor of azomethine methylide **202**. The developed synthesis method can be successfully used to create small libraries of spiro-imidazolinepyrrolidines for screening their biological activity.

9. 1,2,3-Triazole derivatives

Interest in 1,2,3-triazoles has increased rapidly since the discovery in 2002 by Meldal[204] and Sharpless[205] of the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, which is an extremely simple and effective synthetic approach to this class of compounds. In a series of synthesized 1,2,3-triazoles, compounds exhibiting diverse pharmacological activity[205–213] have been identified (antitumour,[205,206] antiviral,[207,209] antifungal,[210,211] antimicrobial,[212] antidiabetic[213]). 1,2,3-Triazoles have also found application in materials chemistry.[214,215] Despite the enormous interest in 1,2,3-triazoles, the synthesis of their derivatives containing exocyclic bonds is represented by only one report.

Bakulev and co-workers[30] showed that the reactions of 2-cyanoacetamidines **204** with sulfonyl azides proceed in two different routes to give 1-substituted 5-amino-1,2,3-triazoles **205** or 4-methylene-1*H*-1,2,3-triazole-5(4*H*)-imines **206** (Scheme 69).

Scheme 69



In the absence of base, the only products are 5-amino-1,2,3-triazoles **205**. The presence of 1.2 equiv. sodium ethoxide or DBU changes the direction of the reaction towards the formation of triazoles **206**. The authors developed methods for the selective and efficient synthesis of triazoles **205** and **206**, including a one-pot synthesis from sodium azide and sulfonyl chlorides without isolation of sulfonyl azides. The formation of compounds **206** with two exocyclic bonds was explained by the presence of two strong hydrogen bonds in these molecules, N···H and O···H, which stabilize this unusual structure.

The plausible mechanism for the formation of compounds **206** is shown in Scheme 70.

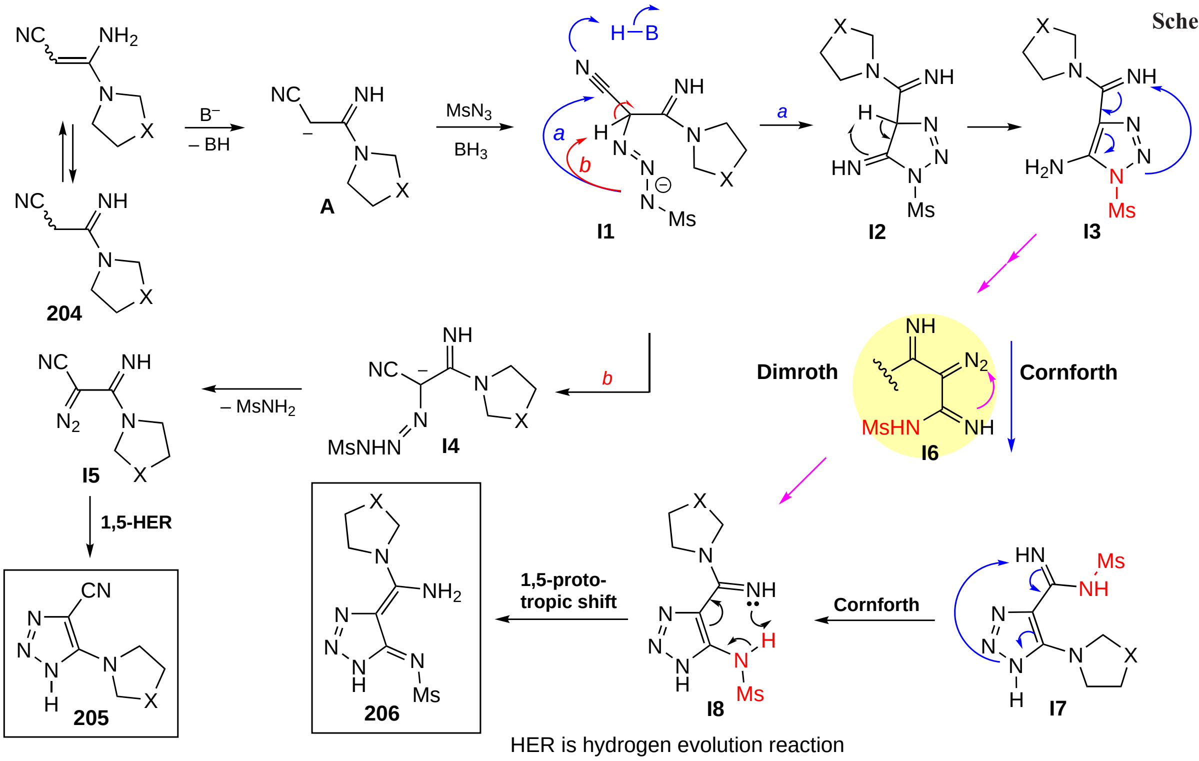
Apparently, the triazenide anion **I1**, resulting from the addition of mesyl azide to carbanion **A**, is a common intermediate for routes *a* and *b* leading to products **205** and **206**. The proton addition to the negatively charged mesylamino group with subsequent conversion of triazene **I1** to triazene **I4** (route *b*) and the formation of triazoline **I2** from triazene **I1** (route *a*) are competitive reactions.[216,217] Elimination of mesylamine from triazene **I4** furnishes diazoimine **I5**, which cyclizes to triazole **205**. The authors suggest that triazoline **I2** is easily converted to aromatic triazole **I3** in a basic medium, which is consistent with the formation of stable 5-amino-1-aryl-1,2,3-triazole-4-carbonitriles in reactions of malonodinitrile with aryl azides.[218] In turn, triazole **I3**, bearing an electron-withdrawing mesyl substituent at position 1, undergoes either a Dimroth-type or a double Cornforth rearrangement to give triazole **I8**. The final step of the rearrangement involves a 1,5-sigmatropic shift, leading to the target product **206**.

10. Conclusion

The data presented in this review indicate a rapidly growing interest of organic chemists in methods for synthesizing five-membered heterocycles containing conjugated exocyclic double bonds. Over the past 10 years, effective approaches have been developed to such compounds based on furan, pyrrole, pyrazole, indole, 1,2,3-triazole, thiazole, aurone, imidazole, and selenazole scaffolds. The trend of recent years, especially 2025, is the study of the chemical and biological properties of heterocycles with conjugated exocyclic C=C and C=N bonds, and the development of new synthetic methods for obtaining these compounds.

The possibility of modifying the C=C bond of such compounds by annulation with non-aromatic five-membered heterocycles, using iodonium salts, and also with more complex objects to afford various spirocyclic compounds was demonstrated. Also, as a result of research in this area, enantioselective asymmetric methods for the synthesis of indolones with a quaternary stereocenter were developed. It is among such substances that compounds with antitumour, pesticide and other types of biological activity have been

Scheme 70



HER is hydrogen evolution reaction

identified. It should be especially noted that in the first five months of 2025, 26 articles were published on the chemistry of heterocycles with two exocyclic bonds, exceeding the number of publications for any previous year. This is additional evidence of the prospects for further research in the field of synthesis, chemical and biological properties of heterocycles containing conjugated exocyclic bonds. We believe that the publication of this review will lead to a further increase in the interest of researchers in compounds containing conjugated exocyclic double bonds and, as a consequence, to the emergence of new scientific data and discovering practically useful properties of heterocyclic compounds.

This review was financially supported by the Russian Science Foundation (Project No. 24-23-00395).

10. List of abbreviations

Ac — acyl,
AFP — auto-fluorescent proteins,
All — allyl,
BINOL — 1,1′-bi-2-naphthol,
Boc — *tert*-butoxycarbonyl,
Bn — benzyl,
CPA — chiral biarylphosphoric acid,
Cy — cyclohexyl,
CuAAC — Cu(I)-catalyzed azide–alkyne cycloaddition,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCC — 1,3-dicyclohexylcarbodiimide,
DCE — 1,2-dichloroethane,
DCM — dichloromethane,
DEAD — diethyl acetylenedicarboxylate,
DIPEA — *N*,*N*-diisopropylethylamine,
DMF–DMA — dimethylformamide dimethyl acetal,
DMAD — dimethyl acetylenedicarboxylate,
DMAP — 4-dimethylaminopyridine,
EAPA — 2-hydroxyethane-1-ammonium propionate,
Fu — furyl,
GFP — green fluorescent protein,
HCV — hepatitis C virus,
LDA — lithium diisopropylamide,
m-CPBA — *meta*-chloroperbenzoic acid,
MTBE — methyl *tert*-butyl ether,
MTT assay — a colorimetric test for assessing cell metabolic activity,
MW — microwave radiation,
Naph — naphthyl,
NOESY — Nuclear Overhauser Effect Spectroscopy,
$Pd(TFA)_2$ — palladium(II) trifluoroacetate,
$Pd_2(dba)_3$ — dipalladium(0) tris(dibenzylideneacetone),
Py — pyridinyl,
TBAF — tetra-*n*-butylammonium fluoride,
TBPAc — tetra-*n*-butylphosphonium acetate,
TBS — *tert*-butyldimethylsilyl,
TCAA — trichloroacetic acid,
TES — triethylsilyl,
Tf — trifluoromethanesulfonyl (triflyl),
TFA — trifluoroacetate,
TFAA — trifluoroacetic acid,
Th — thienyl,
TIPS — triisopropylsilyl,
Ts — *p*-toluenesulfonyl,
VEGF — vascular endothelial growth factor,
VEGFR-2 — vascular endothelial growth factor receptor 2.

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