Acyclic Unsaturated 2π-Electron Components

Subjects: Chemistry, Organic

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Azomethine ylides are nitrogen-based three-atom components commonly used in [3+2]-cycloaddition reactions with various unsaturated 2π-electron components. These reactions are highly regio- and stereoselective and have attracted the attention of organic chemists with respect to the construction of diverse heterocycles potentially bearing four new contiguous stereogenic centers.

Keywords: cycloaddition ; azomethine ylide ; pyrrolidine

1. Introduction

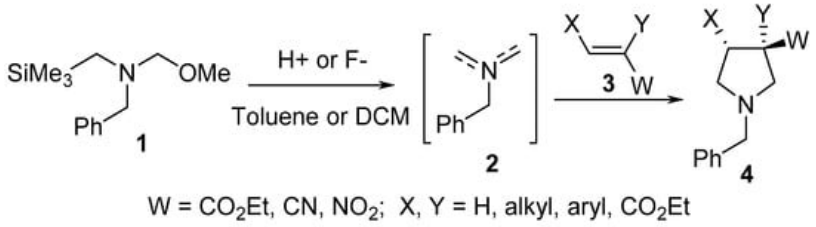
The three-atom component (TAC) is an organic species that is represented by zwitterionic octet structures and undergoes [3+2]-cycloadditions with an unsaturated 2π-electron component in a one-step reaction, often in an asynchronous and symmetry-conducive fashion, via a thermal six-electron Hückel aromatic transition state. The formal charges are lost in the [3+2→5] cycloaddition [1]. Recently, studies based on molecular electron density theory (MEDT) have suggested that the compounds involved in these reactions do not have a polar nature but a diradical, pseudoradical, or carbenoid nature. Therefore, the use of the term “1,3-dipole” is unjustified and should be replaced with “three-atom component”. It was also recommend that the designation of “dipolarophile” should be replaced with “unsaturated 2π-electron component”, and “1,3-dipolar cycloaddition” with “[3+2]-cycloaddition” [2].

While there is a mechanistic spectrum of this reaction from a synchronous one-step process to a stepwise overall transformation (including radical pathways), to avoid mechanistic digressions that may not have chemical or stereochemical consequences, the azomethine ylide reaction will be refered to as a pericyclic cycloaddition. [3+2]-Cycloadditions of azomethine ylide with homomultiple and heteromultiple unsaturated 2π-electron components have been extensively used to produce a wide range of heterocycles [3]. There are several methods for the formation of azomethine ylides, including the thermolysis or photolysis of readily prepared aziridines, the dehydrohalogenation of immonium salts, and proton abstraction from imine derivatives of *α*-amino acids [3]. They are often generated in situ because of their high reactivity and/or transient existence; however, in some cases, stabilized ylides have been isolated and used further [4][5][6].

The synthesis of five-membered heterocyclic systems through azomethine ylides is one of the most adopted, efficient, and powerful approaches. Since the first report of successful the enantioselective [3+2]-cycloaddition of an azomethine ylide in 1991 [7], there has been tremendous progress in the chemistry regarding azomethine ylides. Azomethine ylides are extensively used in the synthesis of various heterocyclic systems such as pyrrolidines, pyrrolizidines, indolizidines, piperidines, oxazolidines, spiroindoles, spiropyrrolidines, and spiropiperidines, but they are also used for the total synthesis of complex natural products as well as bioactive compounds [8][9][10][11][12][13][14][15]. In recent years, the [3+2]-cycloaddition reaction has been extensively studied for the synthesis of heterocycles using different synthetic strategies [16][17]. In addition, the reaction is also investigated to understand the related reactivity, reaction conditions, intermediates, etc. [18][19].

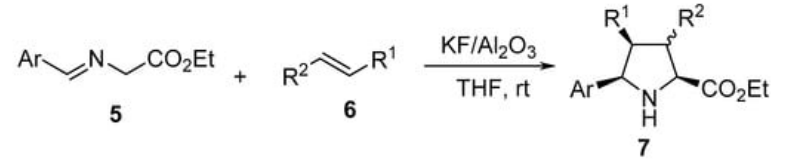
2. Intermolecular Cycloaddition Reaction of Azomethine Ylides to Acyclic Unsaturated 2π-Electron Components (Alkenes)

Unstabilized azomethine ylide **2** derived from benzyl(methoxymethyl)(trimethylsilylmethyl)amine **1** undergoes a [3+2]-cycloaddition reaction with electron-deficient alkenes **3** under continuous flow conditions in the presence of catalytic trifluoroacetic acid, thereby affording the corresponding pyrrolidines **4** (Scheme 1) [20].



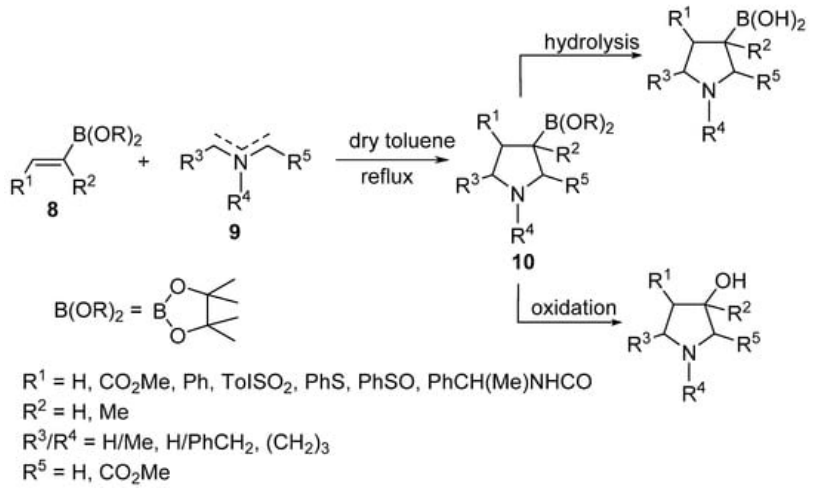
Scheme 1. Synthesis of pyrrolidines **4**.

Azomethine ylides generated via the deprotonation of *α*-imino-esters **5** undergo a [3+2]-cycloaddition reaction with unsaturated 2π-electron components **6** in the presence of the eco-friendly supported solid-base catalyst KF/Al_2O_3 to yield the corresponding pyrrolidines **7** with high regio- and diastereoselectivity (Scheme 2) [21].



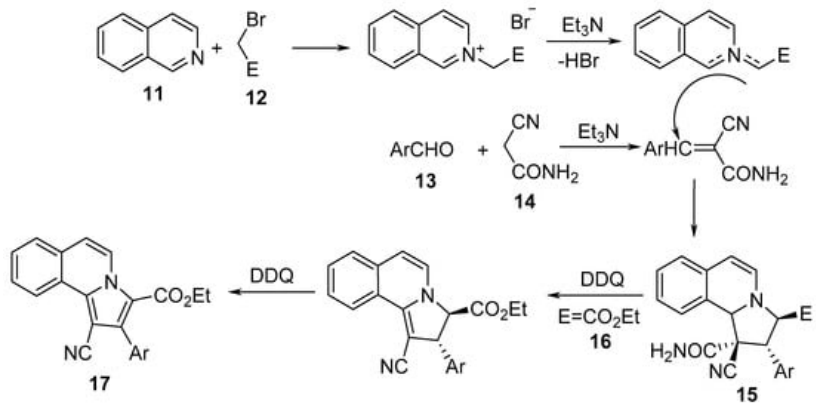
Scheme 2. Synthesis of pyrrolidines **7**.

Belfaitah et al. reported the cycloaddition reaction of azomethine ylides **9** with alkenyl boronates **8** to obtain the 3-boronic-ester-substituted pyrrolidines **10** (Scheme 3) [22].



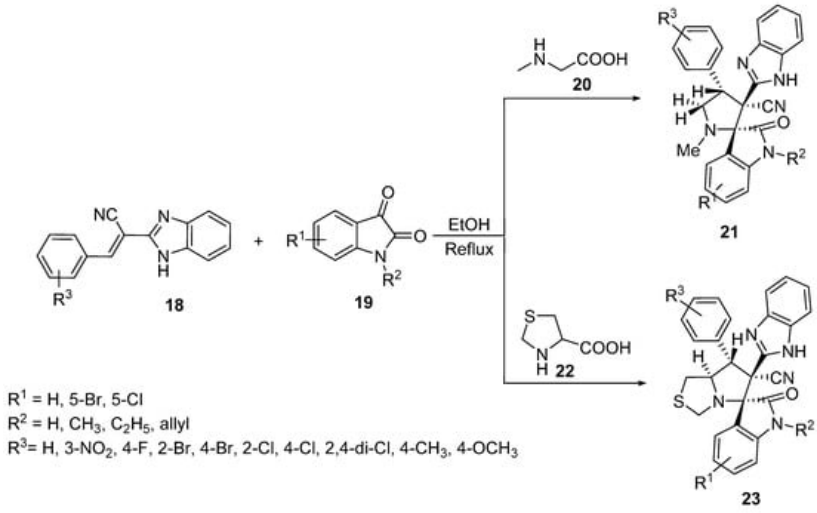
Scheme 3. Synthesis of 3-boronate pyrrolidines **10**.

Pyrrolo[2,1-*a*]isoquinolines **15** were obtained through a sequential one-pot, two-step tandem reaction of isoquinoline **11**, *α*-halogenated methylenes **12**, aromatic aldehydes **13**, and cyanoacetoamide **14** in the presence of triethylamine as a basic catalyst and 2,4-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidizing agent. The transformation was assumed to take place through [3+2]-cycloaddition of *N*-substituted carbonylmethyleneisoquinolinium bromide (formed via the reaction of isoquinoline **11** and **12**) with arylidene cyanoacetamide (formed via the condensation of cyanoacetamide **14** with aromatic aldehyde **13**) [23]. In the case of the ethyl bromoacetate **16** derivative, the formation of pyrrolo[2,1-*a*]isoquinolines **17** was observed probably due to DDQ oxidation (Scheme 4) [23].



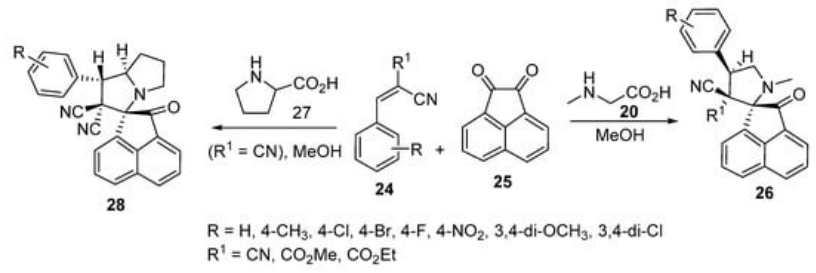
Scheme 4. Synthesis of pyrrolo[2,1-*a*]isoquinolines **15/17**.

Spiro[indoline-3,2′-pyrrolidines] **21** were prepared by the [3+2]-cycloaddition reaction of benzoimidazol-2-yl-3-phenylacrylonitriles **18** with azomethine ylides, which was generated in situ from the condensation of isatin **19** and sarcosine **20** in refluxing ethanol. Similarly, spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazoles] **23** were formed by using thioproline **22** as a secondary amino acid (Scheme 5) [24].



Scheme 5. Synthesis of spiro[indoline-3,2′-pyrrolidines] **21** and spiro[indoline-3,5′-pyrrolo[1,2-c]thiazoles] **23**.

The chemistry was extended further to obtain spiro[acenaphthylene-1,2′-pyrrolidines] **26** and spiro[acenaphthylene-1,2′-pyrrolizidines] **28** possessing a cyano group from the azomethine ylides (generated from acenaphthenequinone **25**) with *α*-amino acids (sarcosine **20** and proline **27**) and Knoevenagel adducts **24** (Scheme 6) [25].

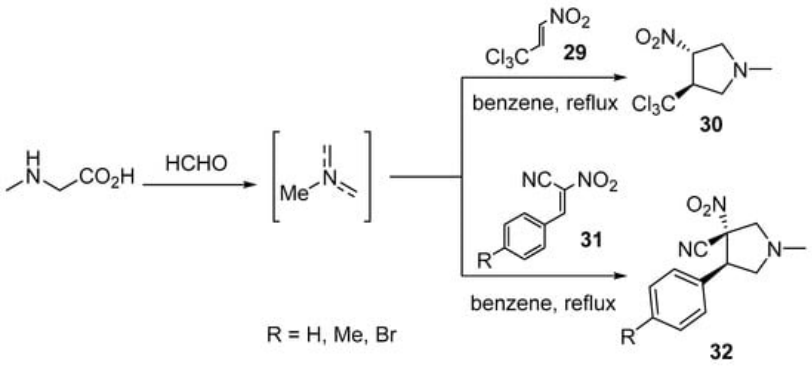


Scheme 6. Synthesis of spiro[acenaphthylene-1,2′-pyrrolidines] **26** and spiro[acenaphthylene-1,2′-pyrrolizidines] **28**.

3. Nitroalkenes

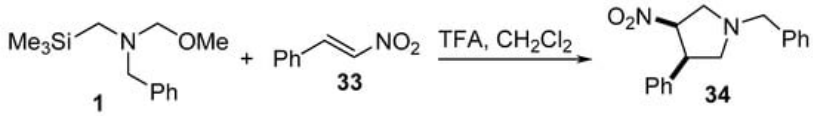
Nitroalkenes are reactive, unsaturated 2π-electron components that are intensively used in cycloaddition reactions by various researchers [26]. 3-Nitro-4-(trichloromethyl)pyrrolidine **30** was obtained through the cycloaddition of trans-3,3,3-trichloro-1-nitroprop-1-ene **29** with azomethine ylide (obtained from the condensation of paraformaldehyde and sarcosine in refluxing benzene). Quantum chemical calculations (DFT, M062X/6-311G(d)) explained the reaction pathway [27].

Analogously, 3-nitro-4-arylpyrrolidine-3-carbonitriles **32** were obtained through the cycloaddition of the azomethine ylide with (2*E*)-3-phenyl-2-nitroprop-2-enenitriles **31** [28] (Scheme 7).



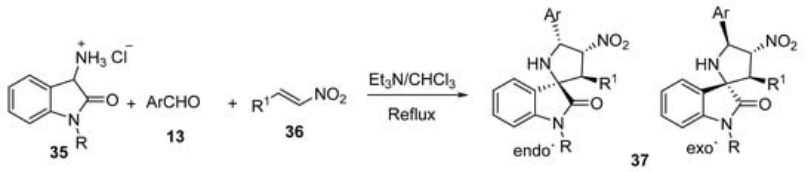
Scheme 7. Synthesis of 3-nitro-4-(trichloromethyl)pyrrolidine **30** and 3-nitro-4-arylpyrrolidine-3-carbonitriles **32**.

Trans-3-nitropyrrolidine **34** was prepared by reacting *trans*-1-nitro-2-phenylethylene **33** with *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]benzylamine **1**, which is an azomethine ylide equivalent, in the presence of trifluoroacetic acid in dichloromethane. Some of the synthesized **34** revealed promising inhibitory properties as Na^+ channel blockers, which are useful in the treatment of ischemic stroke (Scheme 8) [29].



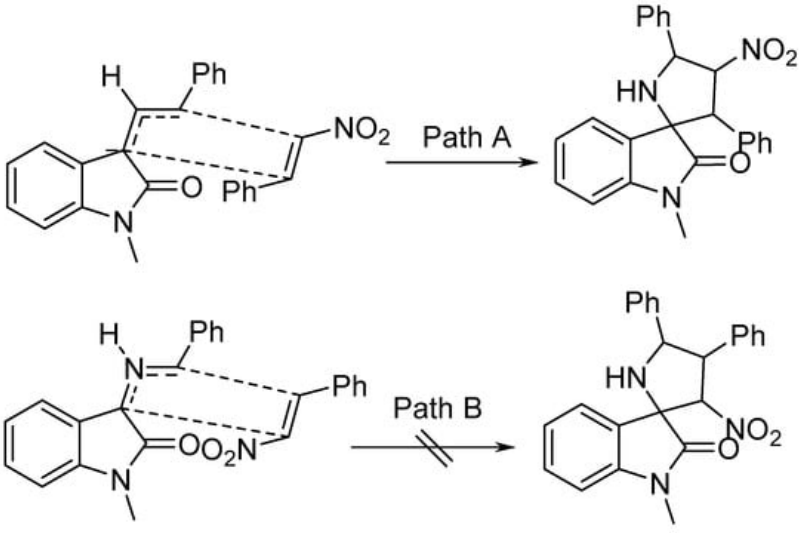
Scheme 8. Synthesis of trans-3-nitropyrrolidine **34**.

Another set of spiro compounds, spiro[pyrrolidine-2,3′-oxindoles] **37,** were regioselectively synthesized by a multicomponent reaction of azomethine ylides, generated in situ from 3-aminoindoline-2-ones hydrochloride **35**, with aldehydes **13** and (*E*)-nitroalkenes **36** (Scheme 9) [30].



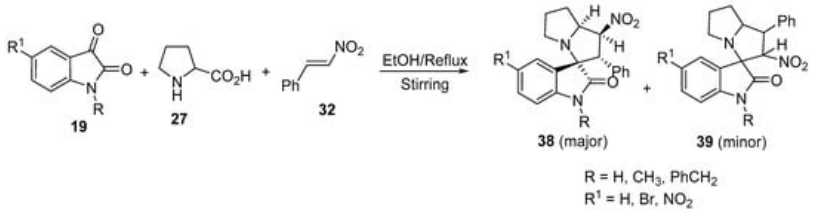
Scheme 9. Synthesis of spiro[pyrrolidin-2,3′-oxindoles] **37**.

It was assumed that, based on the secondary orbital interaction (SOI) of the electron-poor nitroalkenes **36** with the azomethine ylide, Path A was exclusively followed, as the *endo*-transition state in the reaction sequence was more energetically favorable (Scheme 10) [30].



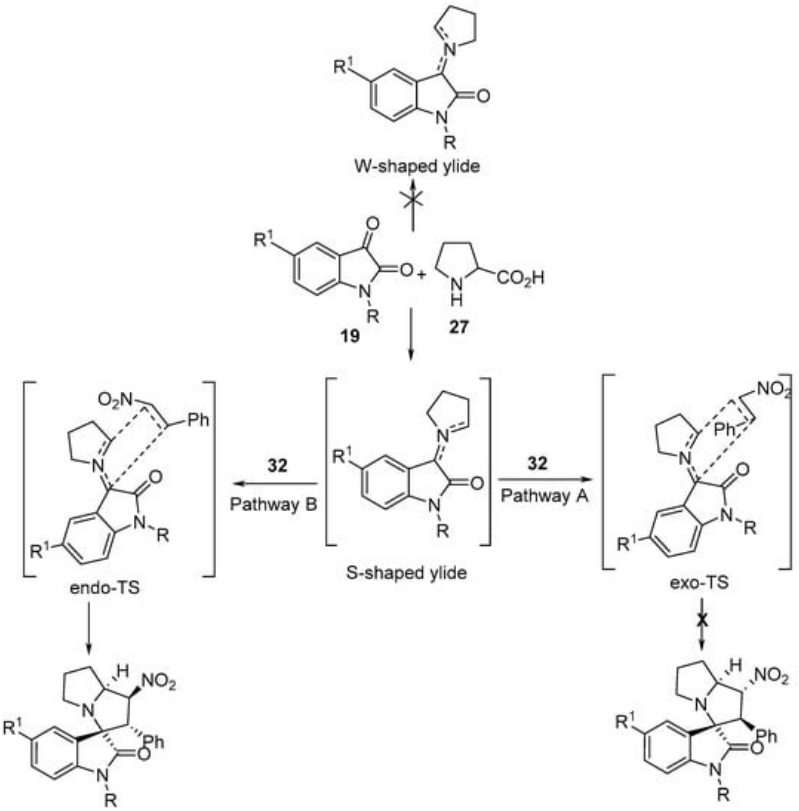
Scheme 10. Proposed mechanism for the cycloaddition of azomethine ylide (via endo′-transition state).

Spirooxindolo-nitropyrrolizines **38** (major product) and **39** (minor product) were obtained from the cycloaddition reaction of azomethine ylides, generated in situ from isatin **19**, with proline **27** and (*E*)-*ß*-nitrostyrene **32** (Scheme 11) [31]. A significant inversion in the regioselectivity was observed when the polar [3+2]-cycloaddition of the azomethine ylides was attempted with trans-β-nitrostyrene instead of (*E*)-1-phenyl-2-nitropropene.



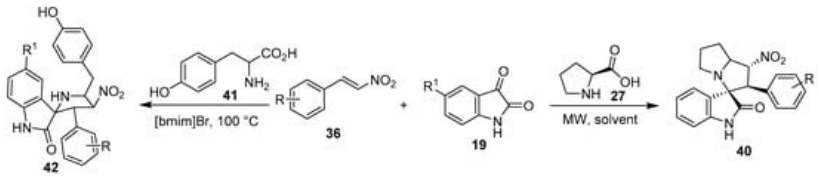
Scheme 11. Synthesis of spirooxindolo-nitropyrrolizines **38** and **39**.

It was assumed that the reaction proceeds through *S*-shaped ylide with a cycloaddition via the endo-transition state (pathway B), yielding cycloadducts **38**, and not the exo-transition state (pathway A). Computational studies (Gaussian 03) of the transition states (Density Functional Theory (DFT), B3LYP, and 6-31G(d,p) basis set) confirmed these assumptions (Scheme 12) [31].



Scheme 12. Proposed mechanism for the cycloaddition of the azomethine ylides with nitrostyrene.

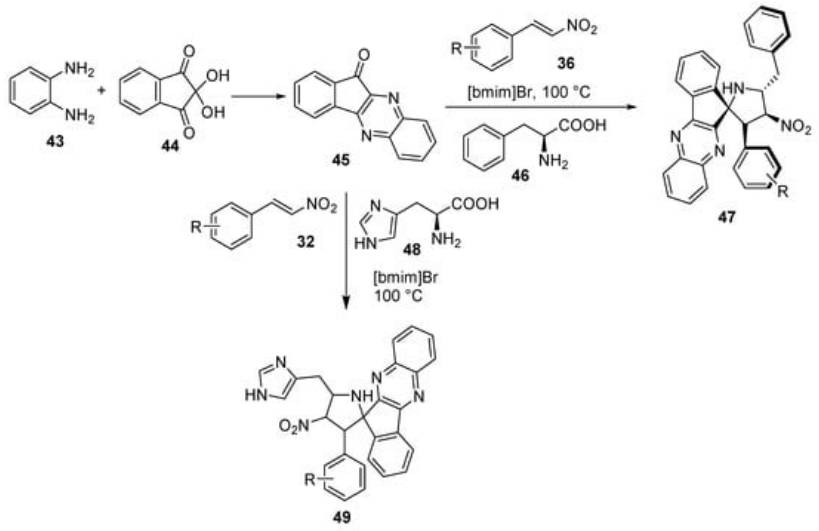
A series of spiro[indoline-3,3′-pyrrolizin]-2-ones **40** with potential anti-amyloidogenic properties useful against Alzheimer's disease were obtained by the microwave-assisted cycloaddition of nitroalkenes **36** and azomethine ylides (generated from isatin **19** and *L*-proline **27**) [32]. Analogously, spirooxindole-pyrrolidines **42** were obtained by the reaction of tyrosine **41** in an ionic liquid [bmim]Br at 100 °C. Promising antiproliferation properties were observed for some of the synthesized compounds (**42**) against human A549 (adenocarcinoma basal epithelial) and Jurkat (*T*-cell lymphoma) cell lines (MTT assay) using Camptothecin as a positive control; the compounds exhibited a safe response against the non-cancer cell lines MCF-10 (normal breast) and PCS-130-010 (lung smooth muscle). Caspase-dependent apoptosis (especially caspase-3) was mentioned as the mode of action for the observed antiproliferative activity (Scheme 13) [33].



R = H, 4-Me, 4-OMe, 2,4-$(OMe)_2$, 2,5-$(OMe)_2$, 2,6-$(OMe)_2$, 3,4-$(OMe)_2$, 4-OH-3-OMe, 4-Cl, 4-Br, 3-NO_2
R^1 = H, OCF_3

Scheme 13. Synthesis of spiro-indolines **40**, **42**.

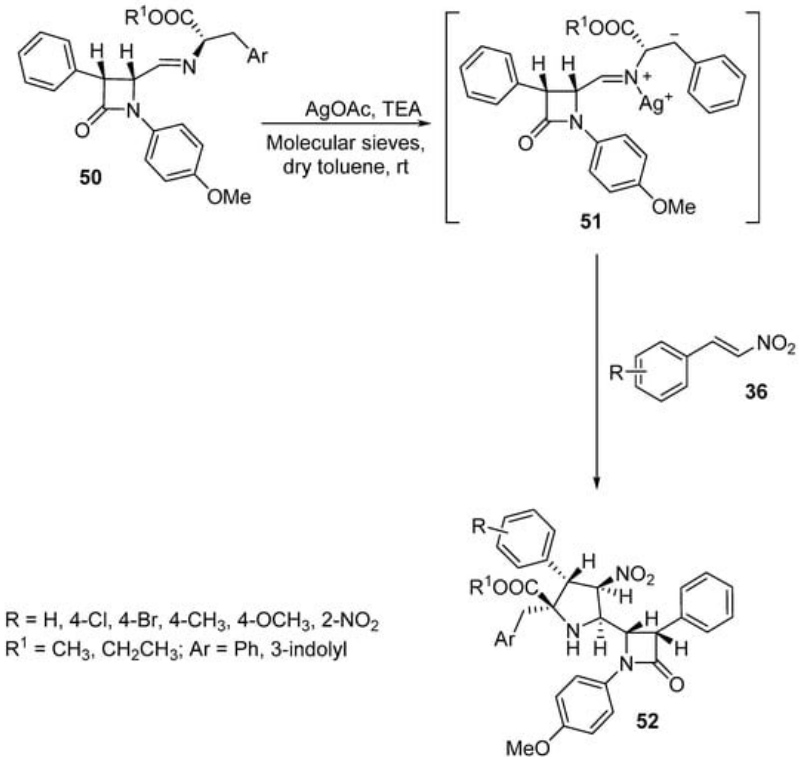
Ionic liquid chemistry was utilized to prepare 4′-nitrospiro[indeno[1,2-*b*]quinoxaline-11,2′-pyrrolidines] **47** by the cycloaddition reaction of nitroalkenes **36** with azomethine ylide (generated from indenoquinoxalinone **45** and *L*-phenylalanine **46**) in an ionic liquid [bmim]Br. Some of the synthesized agents revealed antimycobacterial properties (*Mycobacterium tuberculosis* H37Rv) with an efficacy comparable to that of ethambutol (reference standard) [34]. Similarly, spiro compounds **49** were obtained by using *L*-histidine **48** instead of *L*-phenylalanine **46** in this reaction. Some of the synthesized compounds revealed cholinesterase (acetylcholinesterase and butyrylcholinesterase)-inhibitory properties with considerable efficiencies relative to Galantamine (Scheme 14) [35].



R = H, 4-Br, 2-Cl, 4-Cl, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 2-F, 4-F, 3-NO_2, 2-furanyl, 2-pyridinyl

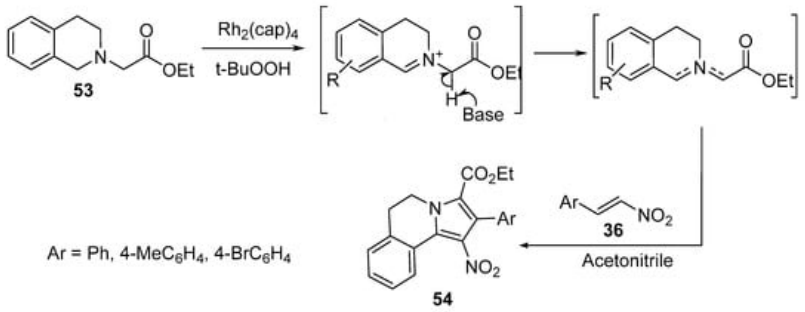
Scheme 14. Synthesis of 4′-nitrospiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidines] **47**, **49**.

Pyrrolidinyl *ß*-lactams **52** were prepared as single diastereomers by the reaction of azomethine ylides **51**, generated from β-lactam imines of α-amino ester **50**, with nitrostyrenes **36** in the presence of silver acetate and triethylamine (Scheme 15). This reaction is an example of [3+2]-cycloaddition reaction via *N*-metallo azomethine ylide [36].



Scheme 15. Synthesis of pyrrolidinyl β-lactams **52**.

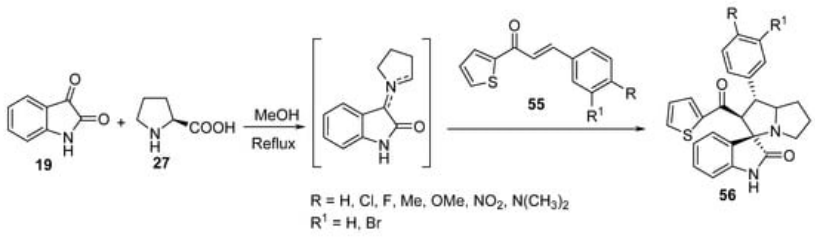
3,4-Dihydropyrrolo[2,1-*a*]isoquinolines **54** were obtained by the [3+2]-cycloaddition reaction of nitroalkenes **36** with an azomethine ylide that was efficiently generated via the dirhodium(II)caprolactamate [$Rh_2(cap)_4$] catalyzed oxidation of tetrahydroisoquinoline **53** (Scheme 16). Doyle's oxidative protocol was used to generate azomethine ylides, which were further trapped in situ via [3+2]-cycloaddition [37].



Scheme 16. Synthesis of pyrrolo[2,1-*a*]isoquinolines **54**.

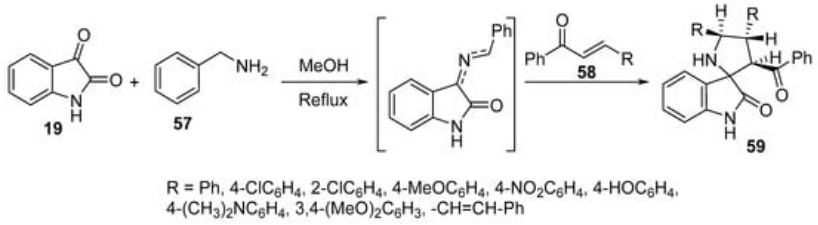
4. α,β-Unsaturated Polarophiles

Spiro[3*H*-indole-3,3′-[3*H*]pyrrolizin]-2-ones **56** were synthesized by the cycloaddition reaction of (*E*)-3-aryl-1-(thiophen-2-yl)-prop-2-en-1-ones **55** with azomethine ylide generated in situ from the condensation of isatin **19** with *L*-proline **27** (Scheme 17). Some of the synthesized spiroindoles **56** showed potential antibacterial activity against *Staphylococcus aureus* and *Salmonella typhi* (relative to Streptomycin) and antifungal activity against *Candida albicans* (relative to Amphotericin B) [38].



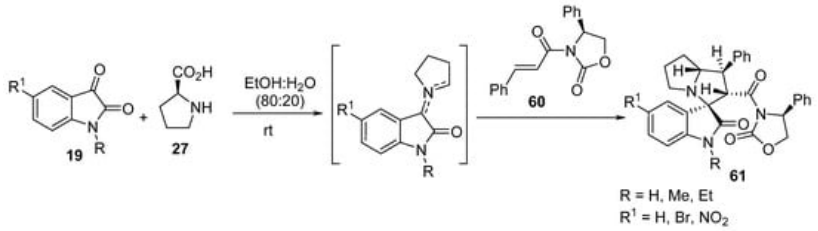
Scheme 17. Synthesis of spiro[3H-indole-3,3′-[3H]pyrrolizin]-2-ones **56**.

Spiro[pyrrolidine-2,3′-indolin]-2′-ones **59** were synthesized by the multi-component cycloaddition reaction of chalcones **58** and an azomethine ylide formed from the condensation of isatin **19** and benzylaminemine **57**. Few of the synthesized spiro-analogs **59** revealed potent inhibitory advanced glycation end (AGE) product formation in a bovine serum albumin (BSA)-glucose assay that was higher than that of aminoguanidine (standard reference). The occurrence of AGE is related to hyperglycemia observed as a complication of diabetes (Scheme 18) [39].



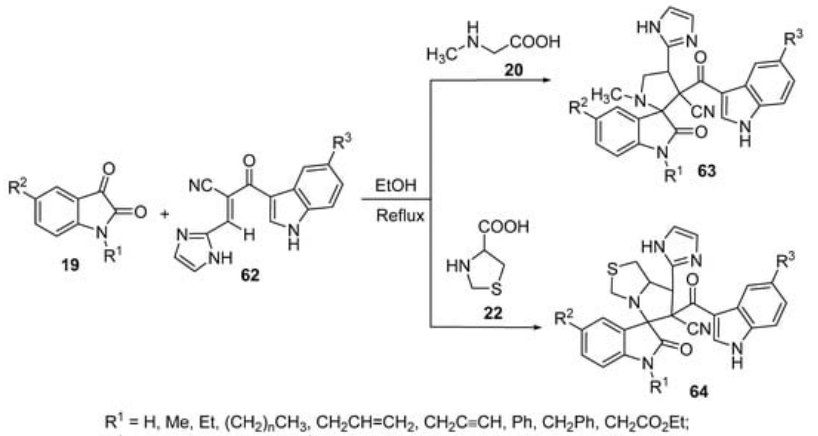
Scheme 18. Synthesis of spiro[pyrrolidine-2,3′-indolin]-2′-ones **59**.

Taghizadeh et al. reported an efficient and greener multicomponent protocol for the synthesis of regio-, diastereo-, and enantioselective spiro-oxindolopyrrolizidines **61** from optically active cinnamoyl oxazolidinone **60** and azomethine ylides that were formed from the condensation reaction of isatin **19** and *S*-proline **27** (Scheme 19) [40].



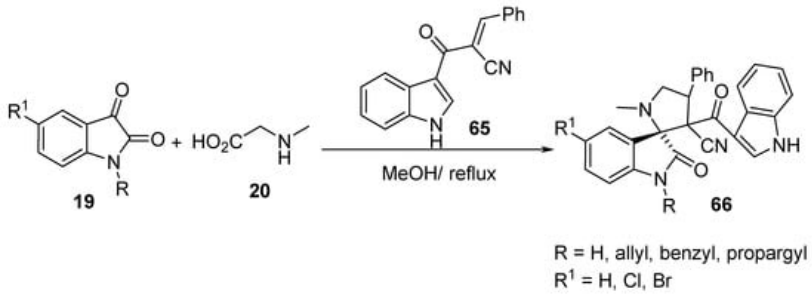
Scheme 19. Synthesis of the spiro-oxindolopyrrolizidines **61**.

Spiro[indoline-3,2′-pyrrolidines] **63** were prepared by the reaction of compound **62** containing an *α*,*β*-unsaturated ketone function with azomethine ylides obtained from isatin **19** and sarcosine **20**, while spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazoles] **64** was obtained from a similar reaction that involved thioproline **22** instead of sarcosine **20** (Scheme 20). Some of the synthesized spiro-compounds, **63** and **64,** revealed anticancer properties against the A549 lung cancer cell line (MTT assay) [41][42] and spiro-compound **63** also showed antimicrobial activity against Gram-positive (*Micrococcus luteus*, *Enterobacter aerogenes*, *Staphylococcus aureus* and *Staphylococcus aureus* “MRSA-methicillin resistant”) and Gram-negative (*Salmonella typhimurium*, *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Shigella flexneri*) bacterial strains and fungi (*Malassesia pachydermatis*, *Candida albicans*) relative to Streptomycin and Ketoconazole (used as antibacterial and antifungal standard references, respectively) [42].



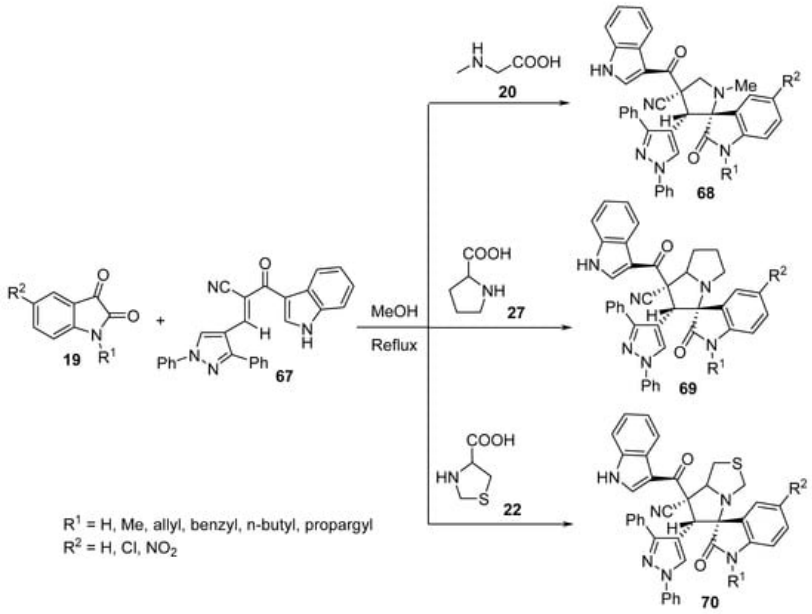
Scheme 20. Synthesis of spiro[indoline-3,2′-pyrrolidines] **63** and spiro[indoline-3,5′-pyrrolo[1,2-c]thiazoles] **64**.

Spiropyrrolidine-oxindoles **66** were prepared in appreciable yields by the cycloaddition reaction of the unsaturated 2π-electron component (*E*)-2-(1*H*-indole-3-carbonyl)-3-phenylacrylonitrile **65** and azomethine ylides obtained from the condensation of isatin **19** and sarcosine **20** (Scheme 21) [43].



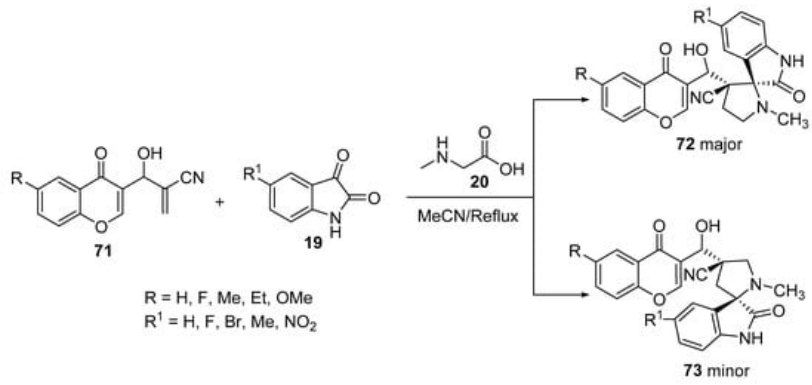
Scheme 21. Synthesis of spiropyrrolidine-oxindoles **66**.

Similarly, spiropyrrolidine–oxindoles **68**–**70** were obtained from the reaction of enone **67** with azomethine ylides derived from isatin **19** and *α*-amino acids (sarcosine **20**, proline **27** or thioproline **22**). Among all the synthesized compounds, some showed antimicrobial properties against Gram-positive and Gram-negative bacterial as well as fungal strains using Streptomycin and Ketconazole as standard references (Scheme 22) [44].



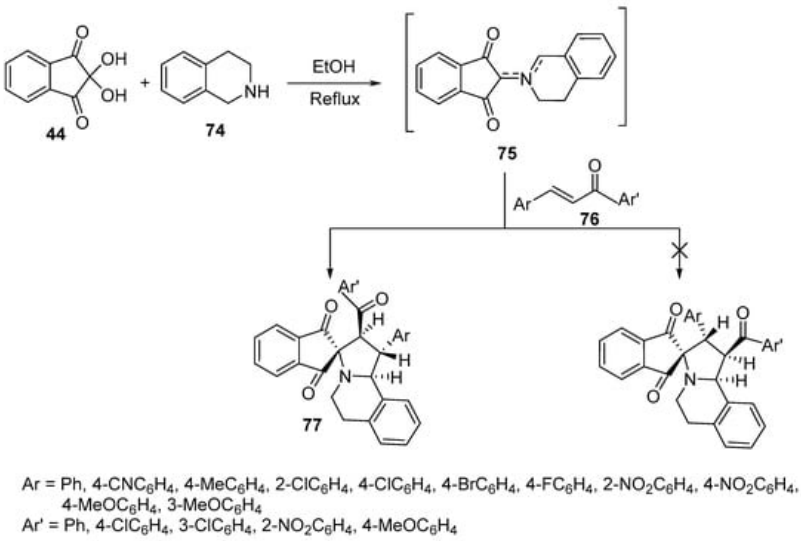
Scheme 22. Synthesis of spiropyrrolidine-oxindoles **68**–**70**.

The unsaturated 2π-electron component, 2-[hydroxyl(4-oxo-4*H*-chromen-3-yl)methyl]acrylonitrile **71,** was synthesized by the Baylis–Hillman reaction of chromene-3-aldehyde, treated with the azomethine ylides (from isatin **19** and sarcosine **20**), which afforded the corresponding regioselective spiro[pyrrolidine-oxindoles] **72** and **73** as major and minor products, respectively (Scheme 23) [45].



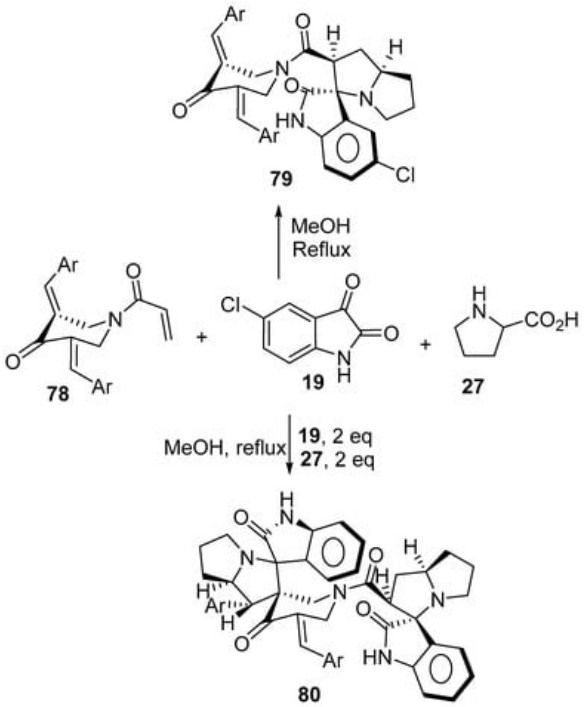
Scheme 23. Synthesis of spiro[pyrrolidine-oxindoles] **73**, **74**.

A convenient method for the selective construction of spiroindane-1,3-diones **77** relies upon the generation of unstabilized azomethine ylides from the initial condensation between ninhydrin **44** and 1,2,3,4-tetrahydroisoquinoline **74.** Subsequent azomethine ylide cycloaddition onto the conjugated double bond of chalcone **76** was exploited, giving target cycloadducts with good yields (77–94%) and diastereoselectivity (Scheme 24) [46].



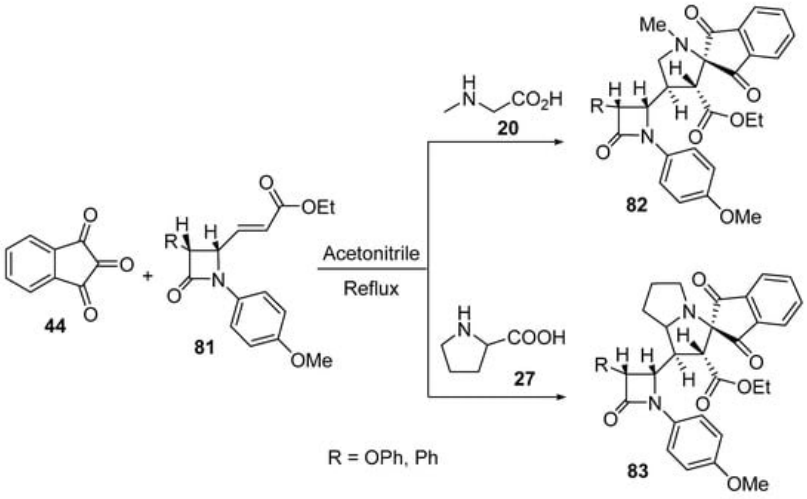
Scheme 24. Synthesis of spiroindane-1,3-diones **77**.

The reaction of azomethine ylide generated from 5-choloroisatin **19** and *L*-proline **27** as well as 1-acryloyl-4-piperidinones **78** yielded the corresponding spirooxindole-pyrrolizines **79** (yield 62–84%). Some of the synthesized cycloadducts **79** displayed cholinesterase-inhibitory properties (acetylcholinesterase and butyrylcholinestrase) with potency relative to Galantamine [47]. When the reaction was conducted in a 1:2:2 molar ratio of 1-acryloyl-4-piperidinones **78,** isatin **19,** and *L*-proline **27,** respectively, the bisspiropyrrolizines **80** were formed instead (yield 53–74%). It was found that most of the mono-spiropyrrolizines **79** (obtained using a 1:1:1 molar ratio of the reactants in yields of 73–84%) revealed higher cholinesterase enzyme (acetylcholinesterase and butyrylcholinestrase)-inhibitory activity than the bisspiropyrrolizine derivatives **80** (Scheme 25) [48].



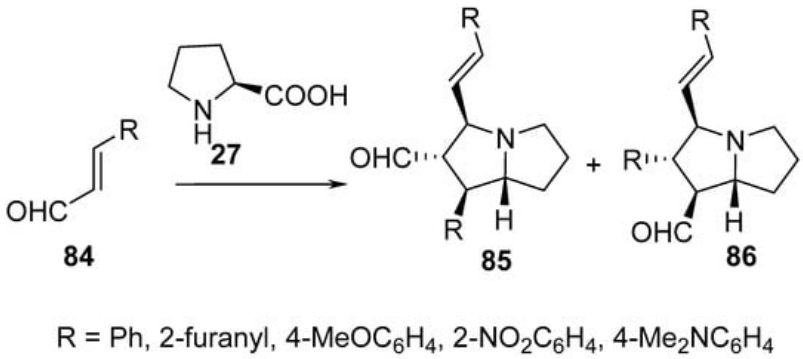
Scheme 25. Synthesis of mono-spiropyrrolizines **79** and bisspiropyrrolizines **80**.

The reaction of 3-(3-phenylazetidin-2-yl) acrylates **81** with azomethine ylide formed by the condensation of ninhydrin **44** and amino acids (sarcosine **20**/*L*-proline **27**) afforded the corresponding spiroindanopyrrolidines **82** and spiroindanopyrrolizines **83** (Scheme 26). The synthesized cycloadducts **82** and **83** showed antibacterial properties against *Proteus mirabilis*, *Proteus vulgaris*, *Salmonella typhi*, and *Staphylococcusi aureus* relative to Tetracycline (standard reference drug) [49].



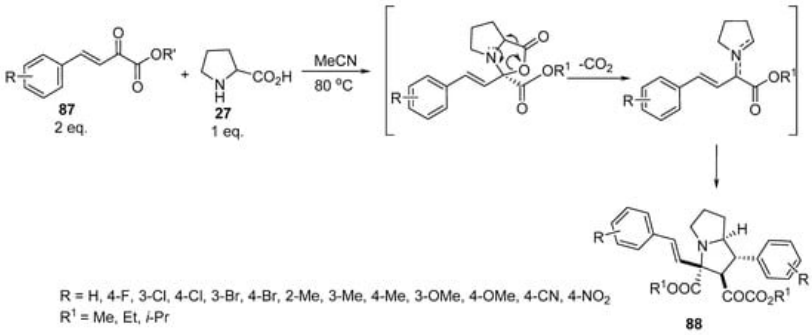
Scheme 26. Synthesis of spiroindanopyrrolidines **82** and spiroindanopyrrolizines **83**.

Cycloaddition of cinnamaldehydes **84** with azomethine ylides, generated from another cinnamaldehyde molecule **84** and *L*-proline **27**, afforded hexahydro-1*H*-pyrrolizines **85** and **86** in different ratios depending on the heating method (conventional heating, 25–80 °C vs. with microwave technique) and the solvent used (MeCN, DMF, toluene, CH_2Cl_2, DMSO) (Scheme 27) [50].



Scheme 27. Synthesis of hexahydro-1*H*-pyrrolizines **85** and **86**.

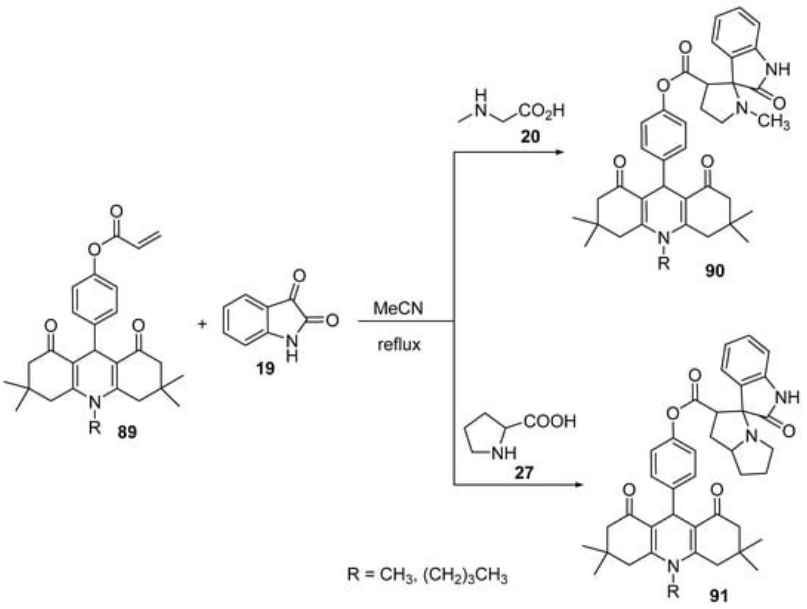
Pyrrolizidines of type **88** were obtained by reacting *β*,*γ*-unsaturated *α*-keto esters of type **87** with proline **27** in a 2:1 molar ratio. The reaction was assumed to proceed via the formation of azomethine ylides by the condensation of the starting unsaturated esters of type **87** with amino acid **27**, which, in turn, interacted with another molecule of **87** to ultimately yield pyrrolizidines of type **88** (Scheme 28) [51].



Scheme 28. Synthesis of pyrrolizidines **88**.

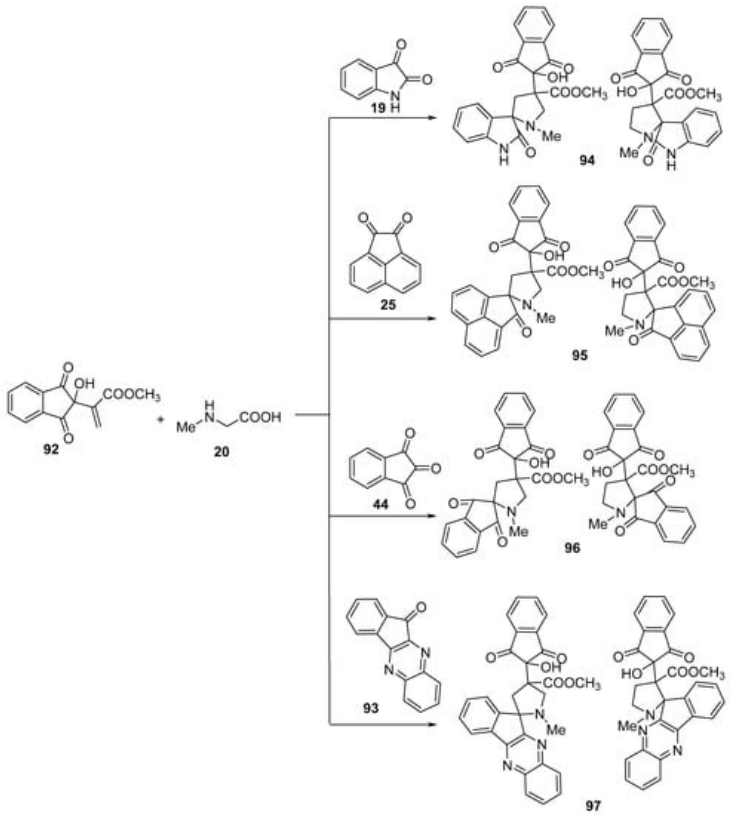
5. Acrylates

The reaction of *O*-acryloylacridinediones **89** with azomethine ylides, generated from isatin **19** and secondary amino acids (sarcosine **20**/proline **27**), afforded the corresponding spiro-pyrrolidines **90** and spiro-pyrrolizidines **91** (Scheme 29) [52].



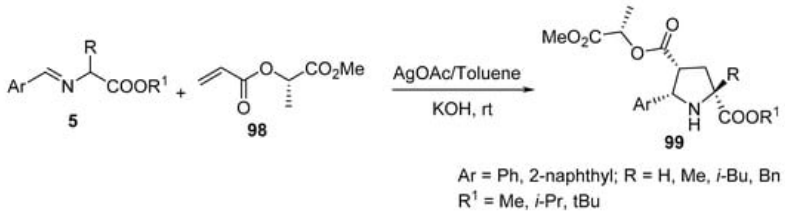
Scheme 29. Synthesis of spiro-pyrrolidines/pyrrolizidines **90/91**.

Spiropyrrolidines **94**–**97** were obtained via the reaction of methyl 2-(1*H*-inden-2-yl)acrylate **92** with azomethine ylides generated in situ by reacting ketones (isatin **19**, acenaphthenequinone **25**, ninhydrin **44,** or 11*H*-indeno[1,2-*b*]quinoxaline-11-one **93**) with sarcosine **20** (Scheme 30) [53].



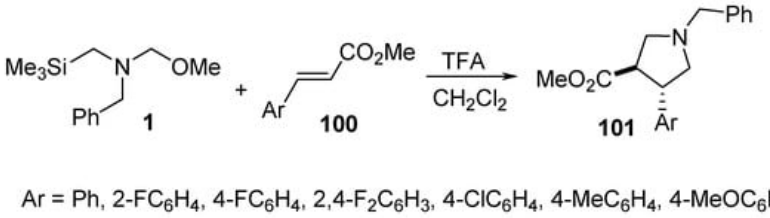
Scheme 30. Synthesis of spiropyrrolidines **94**–**97**.

The reaction of methyl lactate acrylates of type **98** with azomethine ylides, generated from imino-esters **5** in the presence of silver acetate and KOH, gave chiral proline derivatives of type **99** (Scheme 31) [54].



Scheme 31. Synthesis of chiral prolines **99**.

The reaction of *trans* arylacrylates **100** with the azomethine ylide, formed from benzyl-(methoxymethyl) [(trimethylsilyl)methyl]amine **1** in the presence of a catalytic amount of trifluoroacetic acid, afforded the corresponding *trans* pyrrolidine derivatives **101** (Scheme 32) [55].



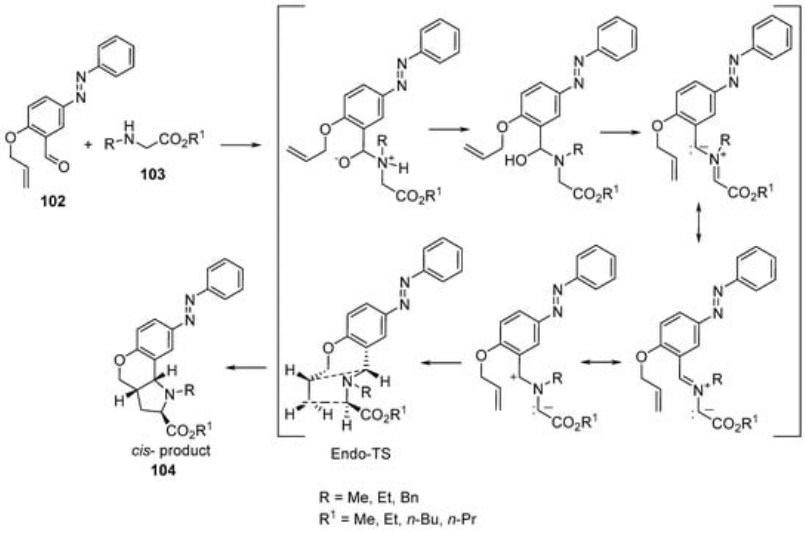
Ar = Ph, 2-FC_6H_4, 4-FC_6H_4, 2,4-$F_2C_6H_3$, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 32. Synthesis of trans pyrrolidines **101**.

6. Intramolecular Cycloaddition Reaction of Azomethine Ylides with Acyclic Unsaturated 2π-Electron Components

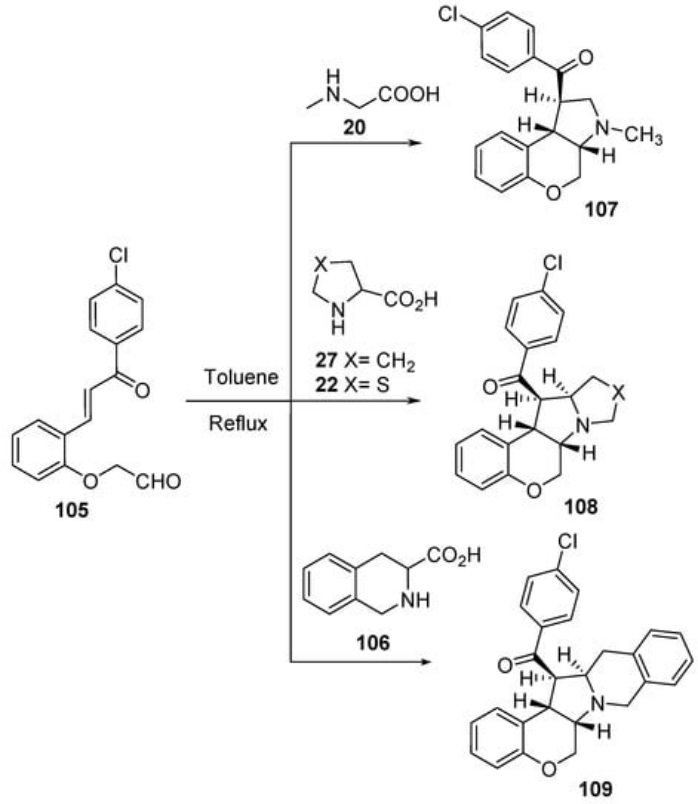
6.1. Acyclicunsaturated 2π-Electron Components Containing Olefinic and Aldehyde Groups

Azomethine ylides (formed via the reaction of *α*-amino esters **103** with *O*-allyl-5-phenyldiazenylsalicylaldehyde **102**) underwent intramolecular [3+2]-cycloaddition under microwave conditions, affording the 8-phenyldiazenylchromeno[4,3-*b*]pyrrolidines **104** (Scheme 33). The synthesized compounds showed antibacterial activity against Gram-positive (*Streptococcus pneumoniae*, *Clostridium tetani*, and *Bacillus subtilis*) and Gram-negative bacteria (*Salmonella typhi*, *Vibrio cholerae*, and *Escherichia coli*), fungi (*Aspergillus fumigatus* and *Candida albicans*), and mycobacteria (*M. Tuberculosis* H37RV) relative to the antibacterial (Ampicillin, Norfloxacin, Chloramphenicol, Ciprofloxacin), antifungal (Griseofulvin, Nystatin), and antimycobacterial (Metronidazole) standard references used [56].



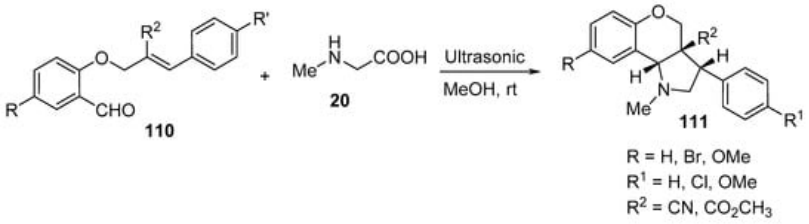
Scheme 33. Synthesis of 8-phenyldiazenylchromeno[4,3-*b*]pyrrolidines **104**.

The intramolecular cycloaddition reaction of azomethine ylides, formed from alkenyl aldehyde **105** and secondary amino acids (sarcosine **20**, *L*-proline **27**, thioproline **22,** and tetrahydroisoquinoline-3-carboxylic acid **106**), afforded the corresponding chromenopyrrole derivatives **107**–**109** (Scheme 34). The synthesized compounds showed promising antibacterial (against *S. aureus*, *B. subtilis* “Gram-positive”; *S. pneumoniae*, *E. coli*, and *Shigella* sp., *S. typhi* “Gram-negative”) and antifungal (against *Trichoderma* sp., *Aspergillus* sp. and *C. albicans*) activities against the references Tetracycline and Carbendazim (antibacterial and antifungal standard references, respectively) [57].



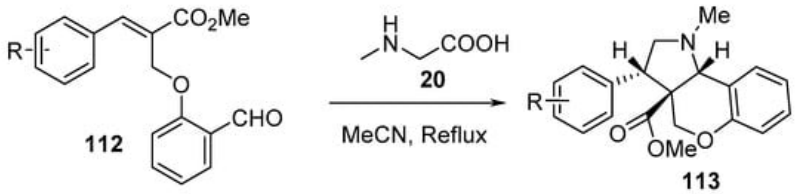
Scheme 34. Synthesis of chromenopyrrole-containing compounds **107**–**109**.

The intramolecular cycloaddition of *O*-allyl salicylaldehydes **110** and sarcosine **20** under ultrasonic irradiation in methanol at room temperature yielded the corresponding chromeno[4,3-*b*]pyrroles **111** (Scheme 35) [58].



Scheme 35. Synthesis of chromeno[4,3-*b*]pyrroles **111**.

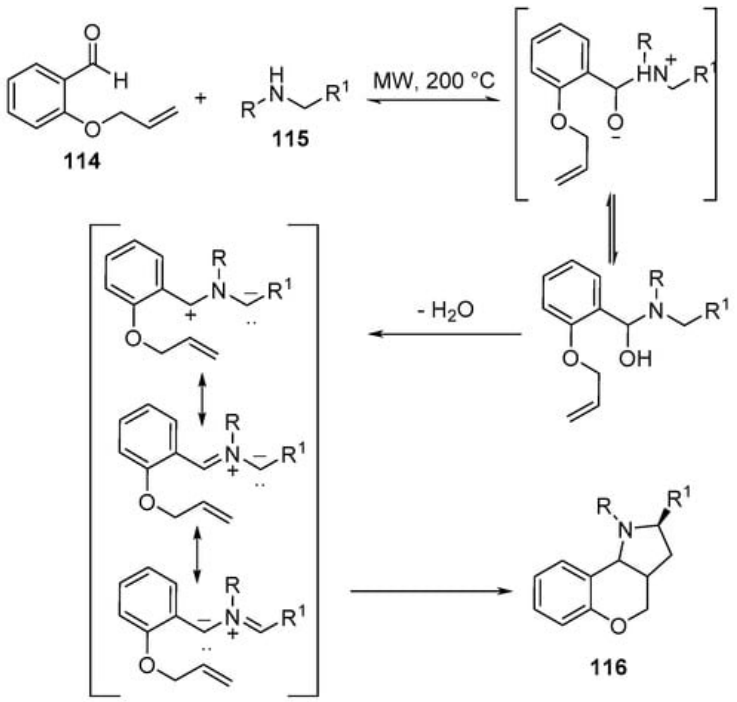
Chromeno[4,3-*b*]pyrrolidines **113** were obtained in a highly regio- and stereoselective manner by the intramolecular cycloaddition of *O*-allylic salicylaldehydes **112** and sarcosine **20** (Scheme 36) [59].



R = H, 4-Me, 4-Et, 4-*i*-Pr, 4-F, 2-Cl, 3-Cl, 4-Cl

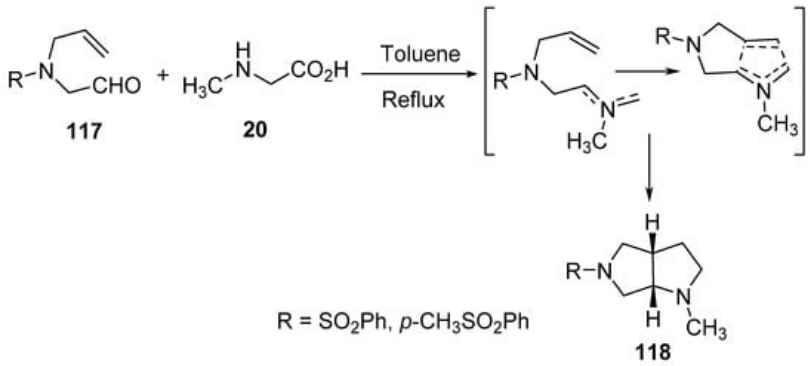
Scheme 36. Synthesis of chromeno[4,3-*b*]pyrrolidines **113**.

Similarly, hexahydrochromeno[4,3-*b*]pyrroles **116** were obtained via intramolecular [3+2}-cycloaddition of *O*-allylic salicylaldehyde **114** and amines **115** under microwave conditions (Scheme 37) [60].



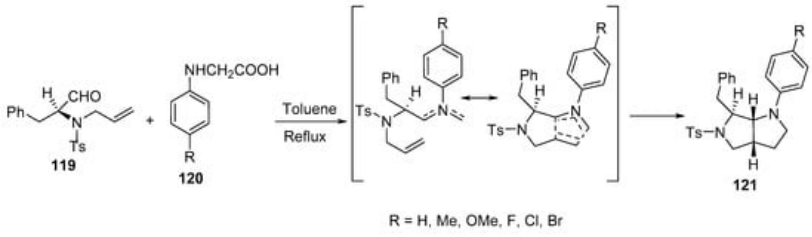
Scheme 37. Synthesis of hexahydrochromeno[4,3-*b*]pyrroles **116**.

Bicyclic pyrrolo[3,4-*b*]pyrroles **118** were obtained by the intramolecular cyclization of the generated azomethine ylides from aldehydes **117** and sarcosine **20** under refluxing conditions in toluene (Scheme 38) [61].



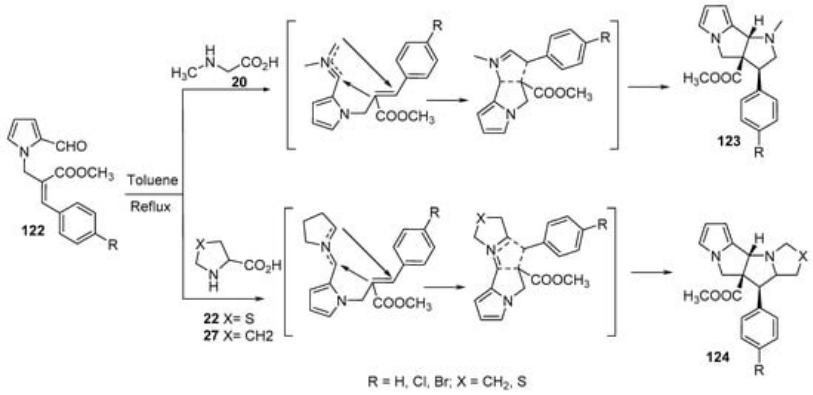
Scheme 38. Synthesis of pyrrolo[3,4-*b*]pyrroles **118**.

Octahydropyrrolo[3,4-*b*]pyrroles **121** with various substituents in their aromatic rings were synthesized by the intramolecular cycloaddition of azomethine ylides, which was formed from the reaction of alkenyl aldehyde **119** with *N*-aryl glycines **120** (Scheme 39) [62].



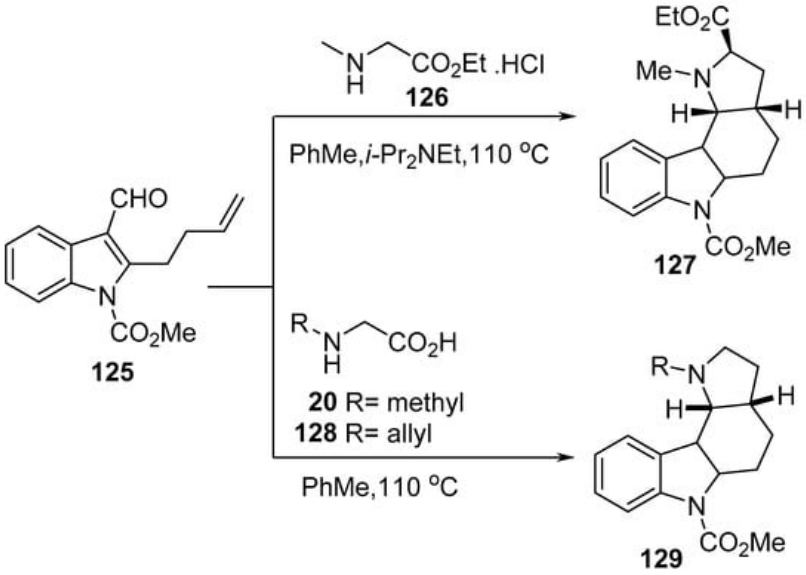
Scheme 39. Synthesis of octahydropyrrolo[3,4-*b*]pyrroles **121**.

The condensation of *N*-alkenyl aldehydes **122** with *α*-amino acids (sarcosine **20**, thioproline **22** and proline **27**) generated azomethine ylides, which underwent an intramolecular cycloaddition reaction yielding the corresponding polycyclic compounds **123** and **124** (Scheme 40) [63].



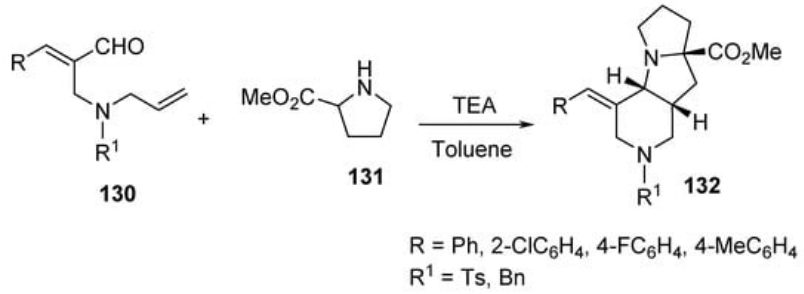
Scheme 40. Synthesis of polycyclic compounds **123** and **124**.

Similarly, the intramolecular reaction of azomethine ylide obtained from 2-butenylindole-3-carboxaldehyde **125** with *N*-methyl glycine ethyl ester hydrochloride **126** gave the indole-containing alkaloid **127**. Whereas its reaction with *N*-methyl glycine **20** or *N*-allyl glycine **128** gave the corresponding indole heterocycles of type **129** (Scheme 41) [64].



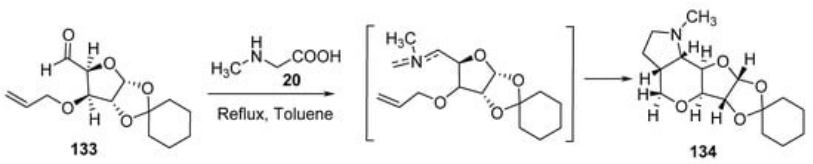
Scheme 41. Synthesis of indole-containing heterocycles **127** and **129**.

Another example of intramolecular cycloaddition was the reaction of (*E*)-2-{[allyl(benzyl)amino]methyl}cinnamaldehydes **130** with proline methyl ester hydrochloride **131** under microwave conditions, which afforded the pyrido[3,4-*b*]pyrrolizines **132** (Scheme 42) [65].



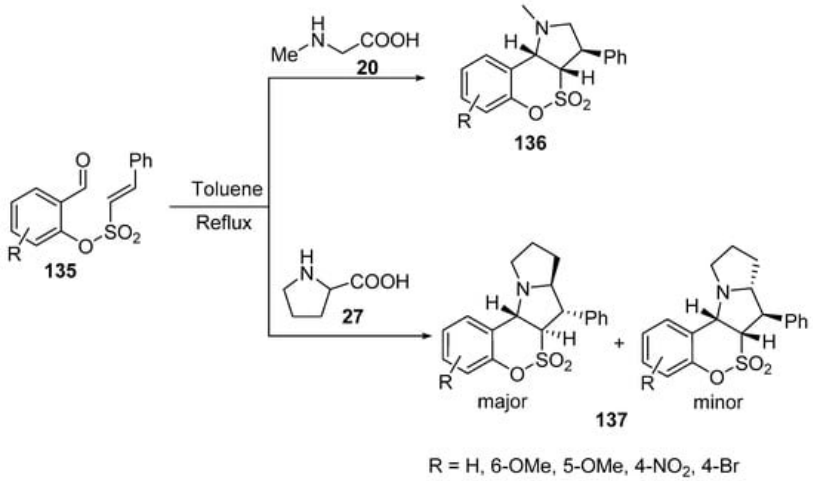
Scheme 42. Synthesis of pyrido[3,4-*b*]pyrrolizines **132**.

By using 1,2-*O*-cyclohexylidine-3-*O*-allyl-*α*-*D*-xylopentadialdo-1,4-furanose **133** (sugar-derived aldehyde) in a reaction with sarcosine **20,** furopyranopyrrolidine of type **134** was formed with high diastereoselectivity (Scheme 43) [66].



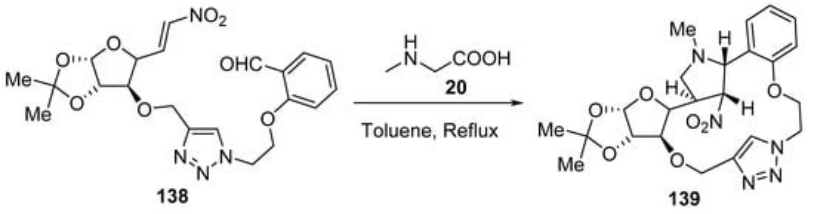
Scheme 43. Synthesis of furopyranopyrrolidine **134**.

The intramolecular [3+2]-cycloaddition of azomethine ylides, generated from 2-formylphenyl-(*E*)-2-phenylethenesulfonates **135** and sarcosine **20,** afforded the corresponding [1,2]oxathiino[4,3-*b*]pyrroles **136**. However, the reaction of derivative **135** with *L*-proline **27** gave the corresponding [1,2]oxathiino[3,4-*b*]pyrrolizines **137** as *trans–trans* (major) and *cis–trans* (minor) isomers (Scheme 44) [67].



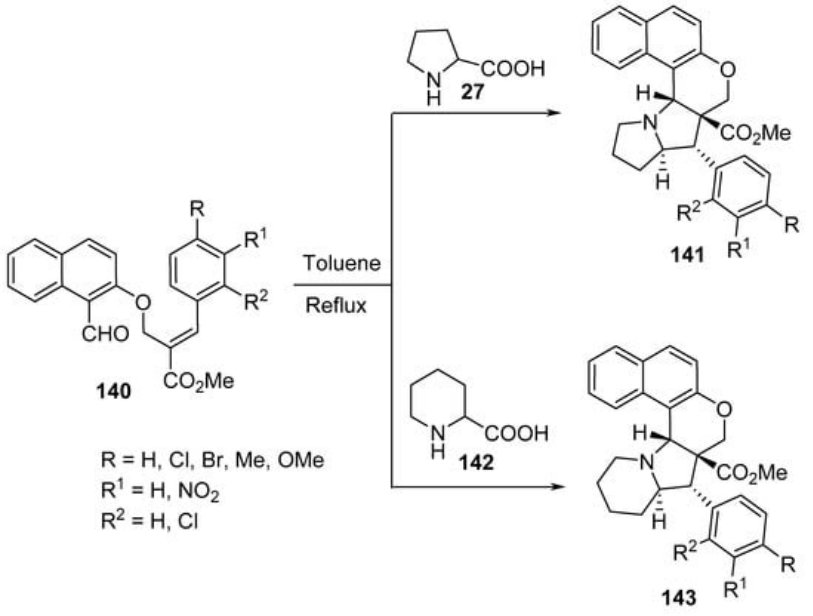
Scheme 44. Synthesis of benzo[*e*][1,2]oxathiino[4,3-*b*]pyrrole-4,4-dioxides **136** and benzo[*e*][1,2]oxathiino[3,4-*b*]pyrrolizine-6,6-dioxides **137**.

Scheme 45 shows an interesting example of a macrocycle of type **139** formation via the intramolecular cycloaddition of an azomethine ylide generated from a triazole-linked glycol-nitroalkenyl aldehyde derivative **138** and sarcosine **20** [68].



Scheme 45. Synthesis of macrocycle **139**.

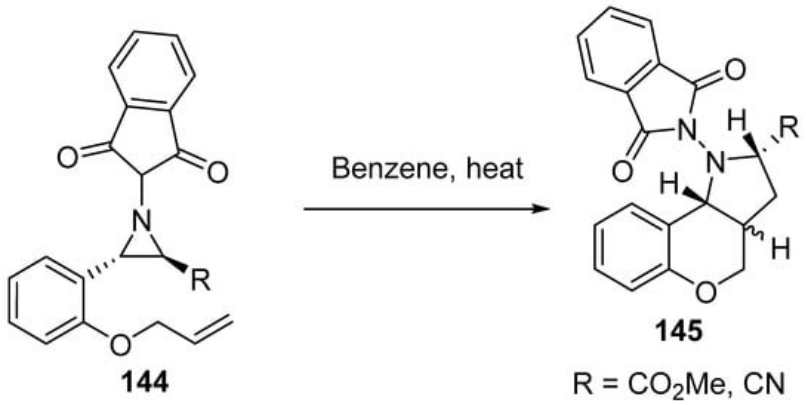
Polycyclic naphtho[2,1-*b*]pyrano-pyrrolizidine and indolizidine derivatives **141** and **143** were synthesized by the intramolecular [3+2]-cycloaddition of azomethine ylides generated from naphtho-*O*-alkenyl aldehydes **140** and *α*-amino acids (*L*-proline **27** or *DL*-pipecolinic acid **142)** (Scheme 46) [69].



Scheme 46. Synthesis of naptho-pyrano-pyrrolizidines/indolizidines **141** and **143**.

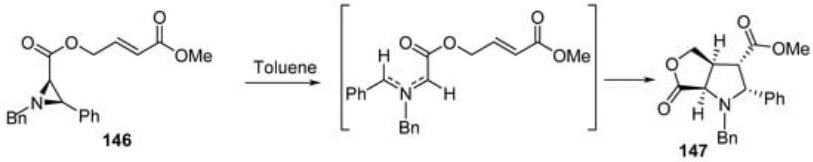
6.2. Acyclic Unsaturated 2π-Electron Components Containing Olefinic Linkage and Azirdine

Scheme 47 shows the thermolysis of aziridines **144** that led to the in situ formation of azomethine ylides, which underwent intramolecular cycloaddition, thus affording *N*-phthalimidopyrrolidine derivatives **145** as a mixture of two diastereoisomers [70].



Scheme 47. Synthesis of *N*-phthalimidopyrrolidines **145**.

Another bicyclic system of *γ*-lactone **147** was created by the intramolecular [3+2]-cycloaddition of azomethine ylide generated via the thermolysis of aziridine derivative **146** in refluxing toluene (Scheme 48) [71].



Scheme 48. Synthesis of bicyclic γ-lactone **147**.

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