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Pyrrolo[1,2-*b*]pyridazines: synthesis and application perspective

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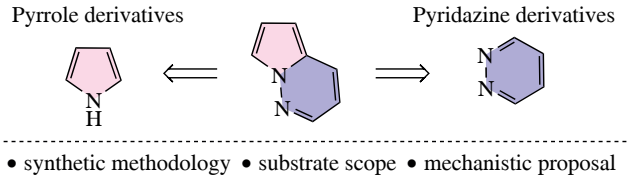
Pyrrolo[1,2-*b*]pyridazines continue to attract significant interest due to their diverse biological activities. This review explores various synthetic approaches to constructing the pyrrolo[1,2-*b*]pyridazine scaffold and examines its applications. Covering key advancements in pyrrolo[1,2-*b*]-pyridazine chemistry reported between 2008 and 2024, we highlight their role in the development of practically relevant compounds. By emphasizing recent progress in this field, we aim to inspire further research and innovation in the synthesis and application of these heterocyclic systems.



Keywords: pyrrole, pyridazine, pyrrolo[1,2-*b*]pyridazines, synthetic methodology, cyclization, 1,3-dipolar cycloaddition.

1. Introduction

Pyrrolo[1,2-*b*]pyridazines, a class of nitrogen-bridged heterocycles, are recognized as privileged scaffolds in both materials science and medicinal chemistry. In particular, they serve as potent inhibitors of kinase enzymes including Janus kinase 3 (JAK1/3),[1] interleukin-1 receptor-associated kinase (IRAK),[2] and poly(ADP-ribose)polymerase 1 (PARP-1),[3] which are promising targets for the treatment of rheumatoid arthritis.[4] Furthermore, these heterocycles display antimicrobial[5,6] and anticancer[7] activities and function as antagonists of corticotropin-releasing factor 1 (CRF1) receptors[8] (Figure 1). Additionally, these compounds exhibit remarkable properties for optoelectronic applications, such as biosensors, lasers, electroluminescent materials, and semiconductor devices.[9–11] Given their multifaceted applications, the development of new synthetic methodologies to access pyrrolo[1,2-*b*]pyridazines remains a vital area of research.

The first review on pyrrolopyridazines was published in 2008.[12] Since then, two additional reviews have partially covered the synthesis of these compounds.[13,14] Over the years, more than 30 related publications have emerged, making it timely to consolidate and analyze the accumulated knowledge to drive

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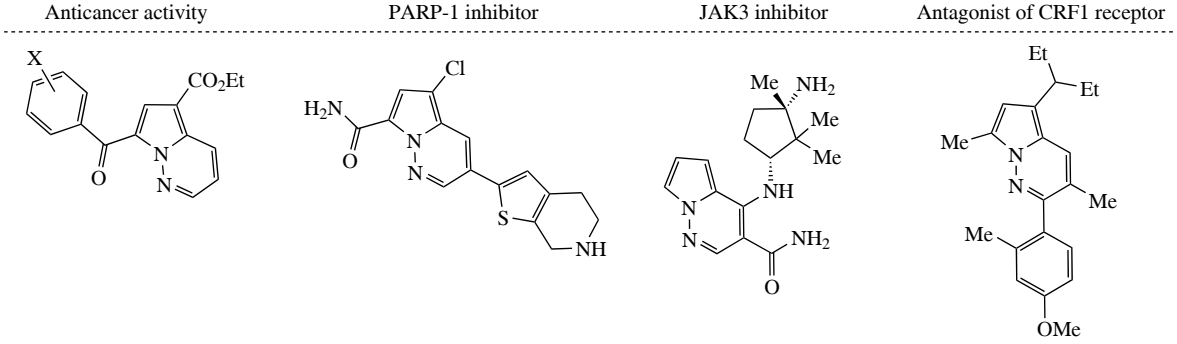
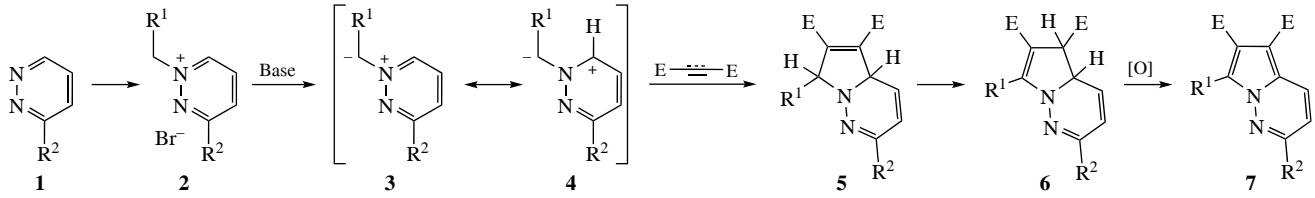


Figure 1 Represented examples of valuable molecules containing pyrrolo[1,2-*b*]pyridazine scaffold.



Scheme 1 Proposed mechanism for the formation of pyrrolo[1,2-*b*]pyridazines **7**.

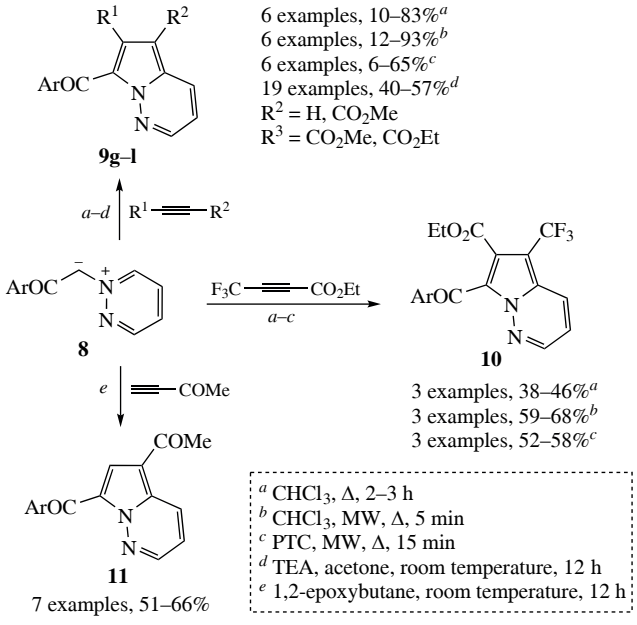
further research in this field. Synthetic approaches in this review are categorized into two main strategies based on the starting materials: (1) synthesis from pyridazines and (2) synthesis from pyrroles. This review also describes the physicochemical properties and biological profiles of pyrrolopyridazines, highlighting their potential applications across various fields.

2. Syntheses starting from substituted pyridazines

2.1. 1,3-Dipolar cycloaddition

One of the principal methods for synthesizing pyrrolo[1,2-*b*]-pyridazines involves the 1,3-dipolar cycloaddition of pyridazinium ylides with dipolarophiles, including activated alkenes, alkynes, or their analogues. The reactive ylide is typically generated *in situ* from the corresponding salts **2** (Scheme 1).

The reaction between diazinium ylides and acetylenic esters has been successfully utilized to synthesize a broad range of substituted pyrrolopyridazines **9**, which exhibit notable *in vitro* activity against Gram-positive bacteria (Scheme 2).[5] Notably, incorporation of a trifluoromethyl group into the pyridazine core

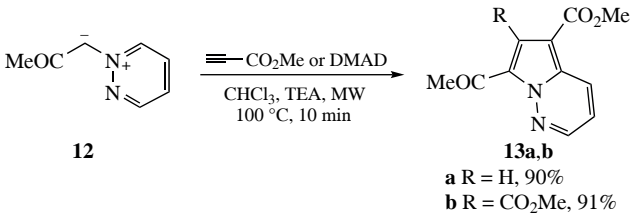


Scheme 2 Synthesis of 7-aroylpyrrolo[1,2-*b*]pyridazines **9**–**11**.

of compound **10** has been shown to enhance *in vitro* antimicrobial activity.[6] In addition, microwave irradiation (MW) has been demonstrated to significantly accelerate these reactions, reduce energy consumption, and improve product yields.

A series of pyrrolo[1,2-*b*]pyridazines **11** were synthesized by employing 1-butyn-3-one as an acetylenic dipolarophile in 1,2-epoxybutane at room temperature.[15] Remarkable, the 1,3-dipolar cycloaddition of various pyridazinium ylides with ethyl propiolate remains a widely adopted approach for conctructing pyrrolo[1,2-*b*]pyridazine frameworks. In 2019, pyrrolopyridazines exhibiting potent antiproliferative activity were synthesized using a similar strategy.[7]

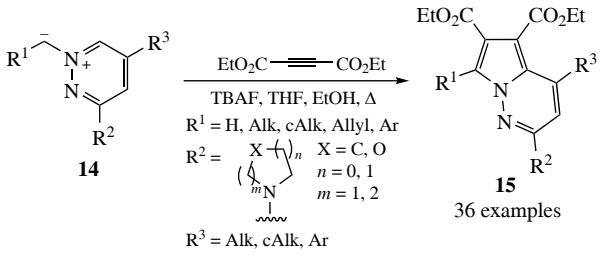
Luminescent pyridazines **13** were prepared *via* a similar reaction between diazinium ylide **12** and the corresponding dipolarophile (Scheme 3). A comparison between conventional heating and microwave irradiation revealed that MW significantly reduced reaction times and improved the yields of the target compounds.[9] Additionally, the first solid-phase synthesis of fluorescent pyrrolopyridazines using activated alkynes under both MW and conventional heating conditions has been reported.[10,11]



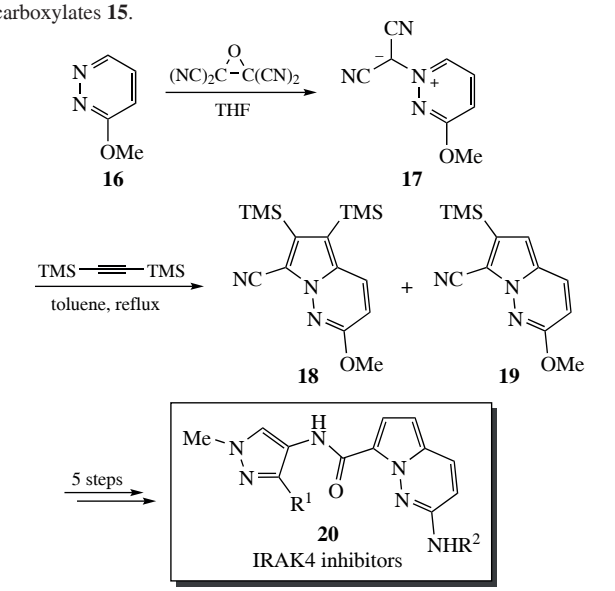
Scheme 3 Synthesis of 7-acetylpyrrolo[1,2-*b*]pyridazines **13**.

Fox's research group identified a novel structural class of diacylglycerol acyltransferase 1 (DGAT1) inhibitors featuring a pyrrolopyridazine core. Substituted pyrrolopyridazines **15** were synthesized *via* a well-established sequence: *N*-alkylation of 3,5-disubstituted pyridazines with various halides yielded the corresponding salts, which were converted to ylides **14** and subsequently underwent 1,3-dipolar cycloaddition with diethyl acetylenedicarboxylate, to furnish the target compounds **15** (Scheme 4).[16]

Key pyridazinium ylides can also be prepared *via* the reaction of the corresponding pyridazine with tetracyanoethylene oxide. The subsequent reaction of the resulting ylide **17** with non-activated bis(trimethylsilyl)acetylene as a dipolarophile



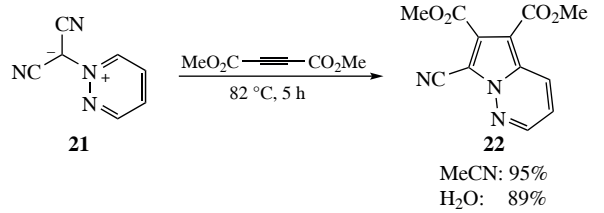
Scheme 4 Synthesis of diethyl pyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylates **15**.



Scheme 5 Synthesis of substituted pyrrolo[1,2-*b*]pyridazine-7-carbonitriles **18** and **19**.

yields a mixture of pyrrolo[1,2-*b*]pyridazines **18** and **19**. Further protodesilylation furnishes pyrrolo[1,2-*b*]pyridazine-7-carbonitrile, which serves as a crucial intermediate in the synthesis of a series of IRAK4 inhibitors **20** (Scheme 5).[2]

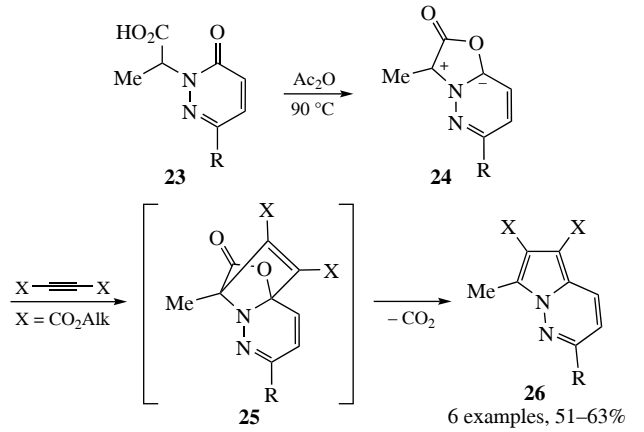
Dimethyl 7-cyanopyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate (**22**) was synthesized *via* the reaction of dicyano(pyridazin-1-ium-1-yl)methanide (**21**) with dimethyl acetylenedicarboxylate (DMAD) under 'on-water' conditions. The authors demonstrated that the efficiency of this reaction is contingent upon the solubility of the dipolarophile in water (Scheme 6).[17]



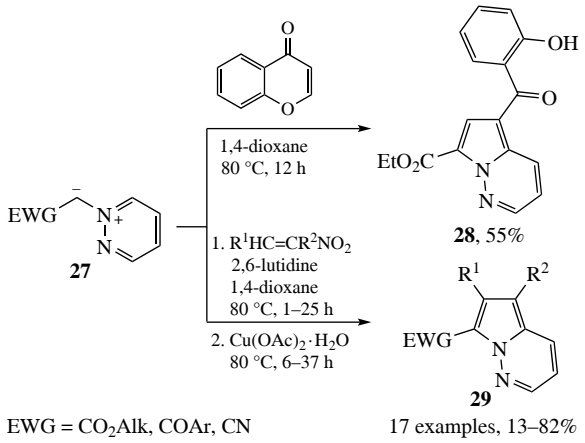
Scheme 6 Synthesis of 7-cyanopyrrolo[1,2-*b*]pyridazine **22**.

It has been demonstrated that azomethine ylides, generated *in situ* from the reaction of 2-[2(3*H*)-pyridazinon-1-yl]-propanoic acid (**23**) with acetic anhydride, act as effective 1,3-dipolar species (Scheme 7). Specifically, the reaction of the bicyclic mesoionic compound **24** with an acetylenic dipolarophile yields an unstable intermediate **25**, which undergoes decarboxylation under the reaction conditions, affording highly functionalized pyrrolo[1,2-*b*]pyridazines **26**.[18] More recently, by employing a similar synthetic strategy, the authors successfully synthesized antitumor pyrrolo[1,2-*b*]-pyridazines from pyridazinone acids.[19]

In addition to alkynes, alkenes also serve as effective electron-deficient partners in 1,3-dipolar cycloaddition reactions. Notably,



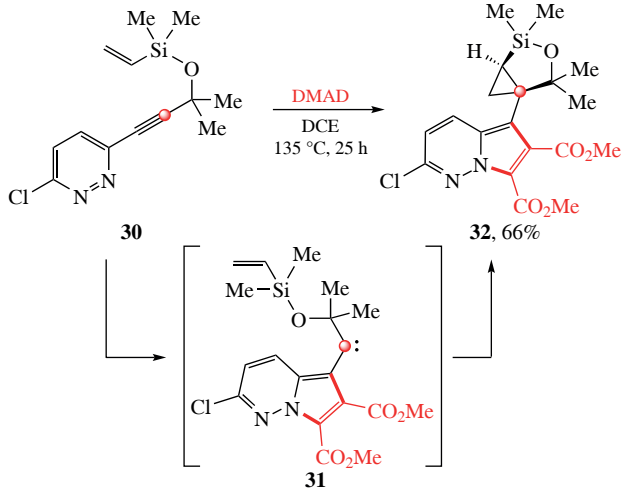
Scheme 7 Synthesis of highly functionalized pyrrolo[1,2-*b*]pyridazines **26**.



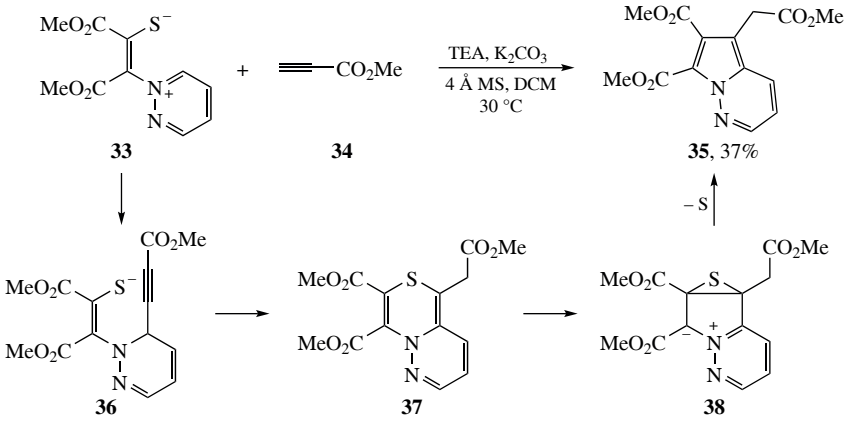
Scheme 8 Synthesis of functionalized pyrrolo[1,2-*b*]pyridazines **28**, **29**.

pyrrolo[1,2-*b*]pyridazine **28** was obtained in 55% yield from the reaction of pyridazinium salt **27** with 4*H*-chromen-4-one under heating in 1,4-dioxane (Scheme 8).[20] Furthermore, oxidative [3+2] annulation reactions between nitroalkenes and pyridazinium ylides **27**, mediated by $Cu(OAc)_2 \cdot H_2O$, provided access to functionalized pyrrolo[1,2-*b*]pyridazines **29**.[21]

An intriguing metal-free intramolecular cyclopropanation has recently been described.[22] Notably, alkynyl-substituted pyridazine **30** reacts with electron-deficient DMAD, generating a transient carbene **31** that undergoes intramolecular cyclopropanation, ultimately yielding highly functionalized pyrrolo[1,2-*b*]pyridazine **32** (Scheme 9). Furthermore, the authors demonstrated that this methodology could be applied to



Scheme 9 Synthesis of 2,5,6,7-tetrasubstituted pyrrolo[1,2-*b*]pyridazine **32**.

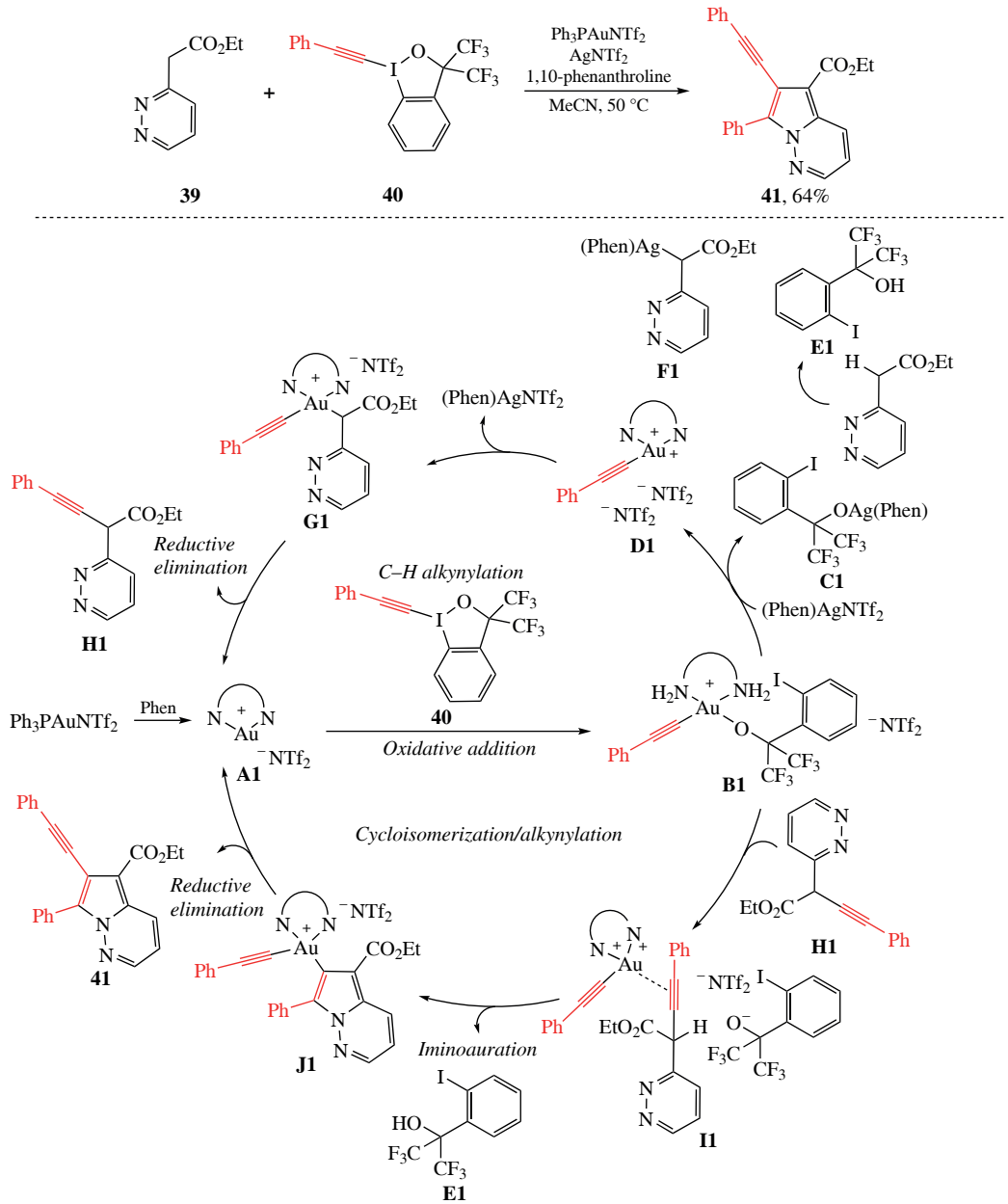


Scheme 10 Synthesis of dimethyl pyrrolo[1,2-*b*]pyridazine-6,7-dicarboxylate **35**.

the synthesis of related pyridazines without the construction of the cyclopropane ring.[23]

2.2. Formal [4+1] pathway

Versatile pyridinium 1,4-zwitterionic thiolates, readily generated from sulfur, DMAD, and pyridazine, have been utilized in the synthesis of pyrrolo[1,2-*b*]pyridazines. A triethylamine-mediated cyclization of the 1,4-zwitterionic thiolate **33** with methyl propiolate **34** affords pyrrolo[1,2-*b*]pyridazine **35** under mild conditions, albeit in low yield (Scheme 10). The authors propose that the transformation proceeds *via* a formal [4+1] annulation, initiated by an acetylide attack on the starting



Scheme 11 Au/Ag-catalyzed cascade synthesis of ethyl pyrrolo[1,2-*b*]pyridazine-5-carboxylate **41**.

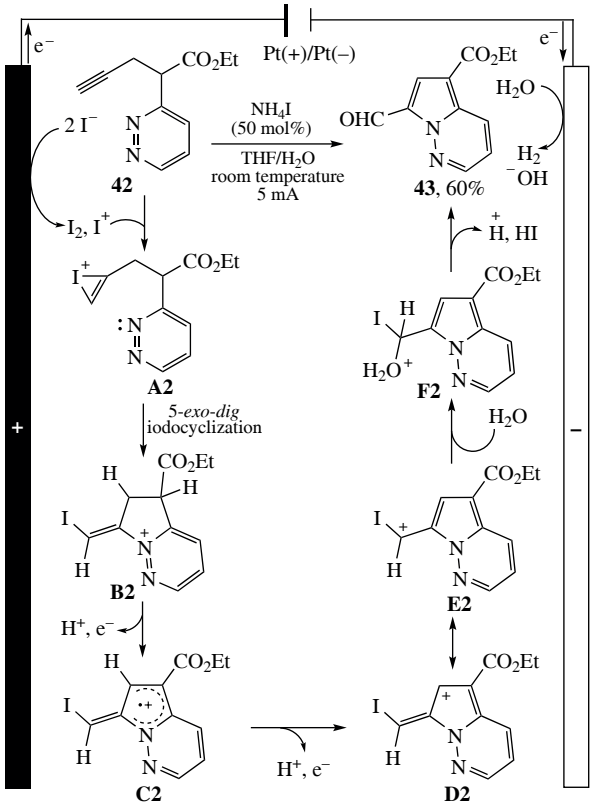
pyridazine **33** to form intermediate **36**. A subsequent nucleophilic attack by sulfur on the activated acetylenic moiety generates pyridazino[6,1-*c*][1,4]thiazine **37**. Finally, spontaneous ring contraction and sulfur extrusion complete the formation of the desired pyrrolo[1,2-*b*]pyridazine **35**.[24]

2.3. Au/Ag-catalyzed cascade

The cascade C(sp^3)–H alkynylation/iminoauration of ethyl 2-(pyridazin-3-yl)acetate (**39**) with the hypervalent iodine(III) reagent **40** was achieved using a bimetallic Au/Ag-catalyst, affording ethyl pyrrolo[1,2-*b*]pyridazine-5-carboxylate **41** (Scheme 11). The proposed reaction mechanism involves two Au^I/Au^{III} catalytic cycles. In the first cycle, the Au^I species **A1** undergoes oxidative addition with reagent **40** to form an Au^{III} alkynyl complex **B1**. The transfer of an alkoxy anion from **B1** to Ag^I initiates C–H functionalization, generating Ag^{III} species **F1**. Subsequent transmetalation between the Au^{III} complex **D1** and Ag^I species **F1** yields Au^{III} complex **G1**, which then undergoes reductive elimination to form 2-propargylpyridazine **H1** and regenerating the Au^I species **A1**, thus completing the first catalytic cycle. In the second cycle, the Au^{III} alkynyl complex **B1** activates the triple bond of 2-propargylpyridazine **H1**, facilitating an intramolecular nucleophilic attack by the pyridazine nitrogen. This step leads to cyclization of the pyrrolo[1,2-*b*]pyridazine core and simultaneous release of alcohol **E1**. A final reductive elimination completes the cycle, yielding the desired product **41**. The developed reaction was found to be highly adaptable to a range of diazaheterocyclic substrates, including those derived from pyrazine and pyrimidine.[25]

2.4. Electrochemical synthesis

In 2022, Guo and co-workers developed an environmentally friendly method for synthesizing ethyl 7-formylpyrrolo[1,2-*b*]-pyridazine-5-carboxylate (**43**) *via* an electrochemically initiated intramolecular 1,2-amino oxygenation of alkyne **42** (Scheme 12). The reaction begins with the formation of an intermediate iodonium ion **A2**, which undergoes an intramolecular 5-*exo*-*dig* iodocyclization to yield a vinyl iodide intermediate **B2**. This intermediate then undergoes deprotonation, followed by anodic oxidation, generating a radical cation **C2**. A subsequent deprotonation and a second anodic oxidation step result in the formation of a carbocation **D2**, which underwent nucleophilic attack by H_2O to form intermediate **F2**. Finally, protonation and HI elimination afford the desired product **43**.[26]

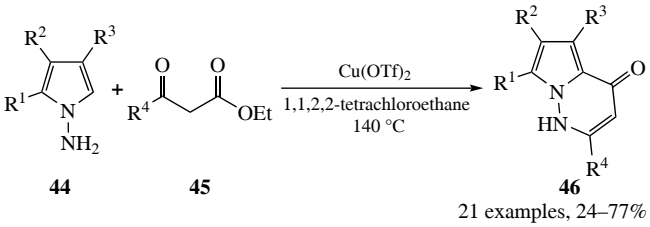


Scheme 12 Electrochemically-initiated formation of pyrrolo[1,2-*b*]-pyridazine **43**.

3. Syntheses starting from substituted pyrroles

3.1. Metal-catalyzed approaches

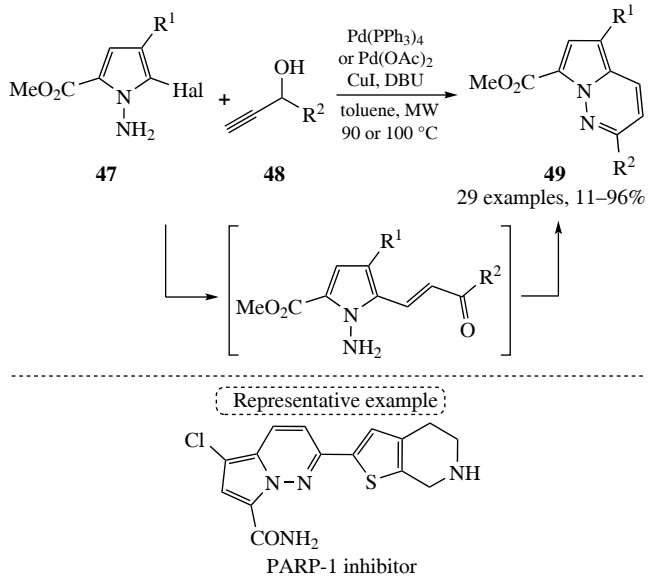
The first Cu^{II}-catalyzed tandem synthesis of 2-substituted pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones **46** *via* a Conrad–Limpach-type reaction was developed, starting from 1-aminopyrroles **44** and β-dicarbonyl compounds **45**. The resulting products **46** serve as valuable intermediates in the synthesis of various pyrrolo[1,2-*b*]pyridazines, with potential applications in drug development and materials science (Scheme 13).[27]



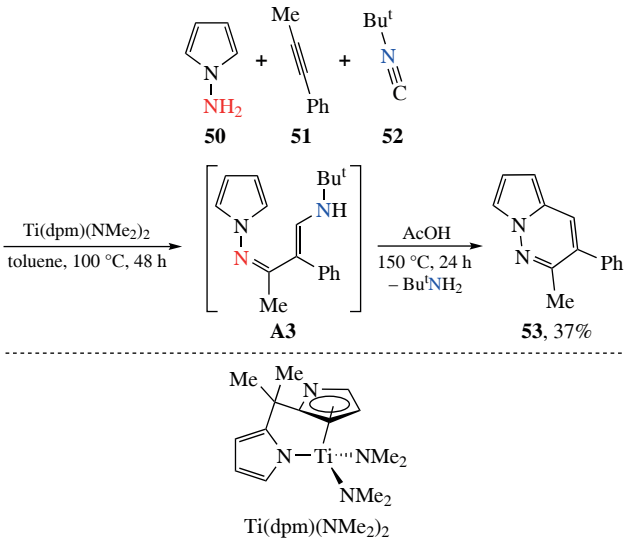
Scheme 13 Cu^{II}-catalyzed tandem synthesis of pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones **46**.

In 2013, Chunhao's research group reported a domino coupling–isomerization–condensation sequence for the synthesis of pyrrolo[1,2-*b*]pyridazines **49** (Scheme 14). Utilizing Pd/Cu catalysts, they achieved the cyclization of (hetero)aryl propargyl alcohols **48** with 1-amino-2-halopyrroles **47** to furnish pyrrolo[1,2-*b*]pyridazines **49**. This cascade transformation proceeds *via* the formation of an enone intermediate, which then undergoes an intramolecular amine–ketone condensation to yield the target product **49**.[28] Notably, some of the synthesized pyrrolo[1,2-*b*]pyridazines exhibited potent PARP-1 inhibitory activity.[6]

Odom *et al.* reported an efficient Ti-catalyzed three-component coupling reaction of *N*-aminopyrrole (**50**),



Scheme 14 Synthesis of methyl pyrrolo[1,2-*b*]pyridazine-7-carboxylates **49**.



Scheme 15 Ti-catalyzed synthesis of pyrrolo[1,2-*b*]pyridazine **53**.

1-phenylpropyne (**51**), and *tert*-butylisonitrile (**52**) to afford 2-methyl-3-phenylpyrrolo[1,2-*b*]pyridazine (**53**) (Scheme 15). The reaction proceeds through catalytic hydroamination, cycloaddition and *tert*-butylamine elimination during aromatization.[29]

In 2023, Wang and colleagues reported an efficient Au^I-catalyzed synthesis of 2-aminopyrrolo[1,2-*b*]pyridazines **56**. This strategy involves a chemoselective Au^I-catalyzed hydroamination/hydroarylation cascade, using 1-aminopyrroles **54** and non-symmetrical 1,3-diynamides **55**. The reaction proceeds smoothly in the presence of XPhosAuCl/AgNTf$_2$ following the mechanism proposed in Scheme 16. Initially, the Au-catalyzed intermolecular hydroamination of 1,3-diynamide **55** with 1-aminopyrrole **54** yields an enyne **A4**, which undergoes proton transfer to form intermediate **B4**. Au-complexation of the remaining triple bond in **C4** then promotes intramolecular hydroarylation *via* electrophilic aromatic substitution, generating intermediate **D4**. Finally, aromatization furnishes 2-aminopyrrolo[1,2-*b*]pyridazine **56**. Notably, these products exhibit fluorescence in both solution and solid states.[30]

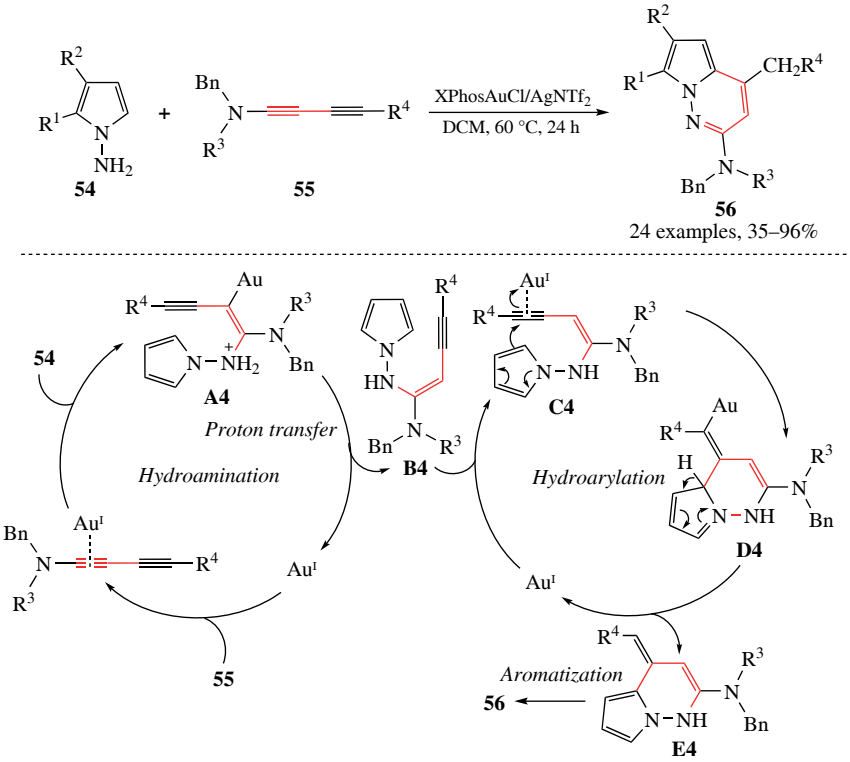
Ellman's research group reported a Rh^{III}-catalyzed dual C–H activation in the reaction of aldohydrazones **57** with alkynes **58**, affording pyrrolo[1,2-*b*]pyridazines **59** in good yields (Scheme 17).[31] The proposed mechanism proceeds *via* two concerted metalation–deprotonation steps to form a five-membered rhodacycle **A5**. Subsequent coordination of alkyne **58a** with this intermediate generates the vinyl rhodium species **C5**. Finally, reductive elimination releases the target product **59a**.

3.2. Acid-catalyzed cyclizations

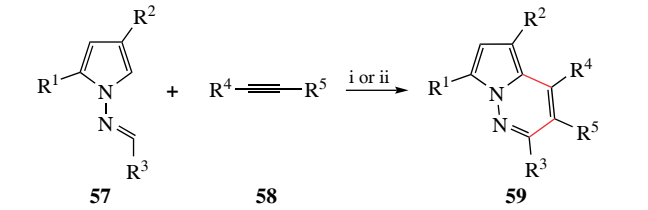
Weigelt *et al.* described the acid-mediated condensation of benzoylpyruvates with various binucleophiles, affording fused heterocycles in good yields. The developed method demonstrates tolerance for 1*H*-pyrrol-1-amine (**50**) in an acid-catalyzed reaction proceeding *via* the formation of a Li chelate complex **60**. The authors reported the formation of the corresponding ethyl pyrrolo[1,2-*b*]pyridazine-2-carboxylates **61** (Scheme 18).[32]

A straightforward method for synthesizing polysubstituted pyrrolo[1,2-*b*]pyridazines **64** from commercially available chalcones and 1*H*-pyrrol-1-amine derivatives **62** in the presence of *p*-toluenesulfonic acid (*p*-TSA) has been developed (Scheme 19).[33] The reaction commences with the hydrolysis and decarboxylation of carbamate **A6**, yielding alkenylimine **C6** *via* condensation with a chalcone. Intermediate **C6** then undergoes cyclization to form a 4,5-dihydropyrrolo[1,2-*b*]pyridazine *via* a nucleophilic attack on the pyrrole ring, accompanied by isopropyl group migration. Finally, aromatization is achieved upon refluxing with *p*-TSA.

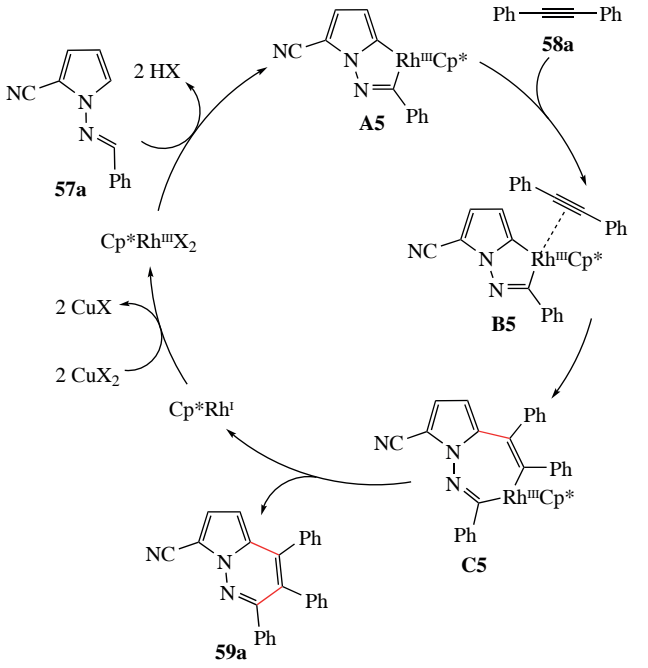
In 2017, Hynes Jr. *et al.* developed a method for preparing an effective dual JAK1/3 inhibitor using 6-bromo-4-hydroxypyrrolo[1,2-*b*]pyridazine-3-carbonitrile (**67**) as a key intermediate (Scheme 20). The 4-hydroxypyrrolo[1,2-*b*]-pyridazine **67** was synthesized from 1-aminopyrrole **65** and 1,1-diethoxypropionitrile **66** in the presence of *p*-TsOH,



Scheme 16 Au^I-catalyzed synthesis of 2-aminopyrrolo[1,2-*b*]pyridazines **56**.

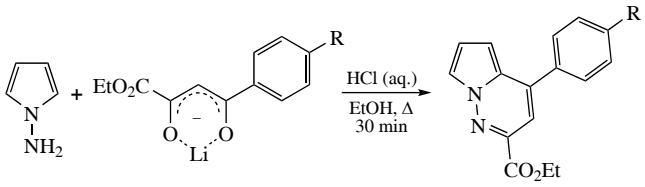


i, $[Cp^*RhCl_2]_2$, $Cu(OAc)_2$, 1,4-dioxane, 140 °C, 1 h, 17 examples, 39–88%;
ii, $[Cp^*RhCl_2]_2$, AgOAc, PivOH, THF, 120 °C, 16 h, 5 examples, 40–79%



Scheme 17 Rh^{III}-catalyzed synthesis of pyrrolo[1,2-*b*]pyridazines **59**.

followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[34] Subsequently, this method was further optimized to enhance the potency of JAK1/3 inhibitors.[4]



Scheme 18 Synthesis of pyrrolo[1,2-*b*]pyridazines **61**.

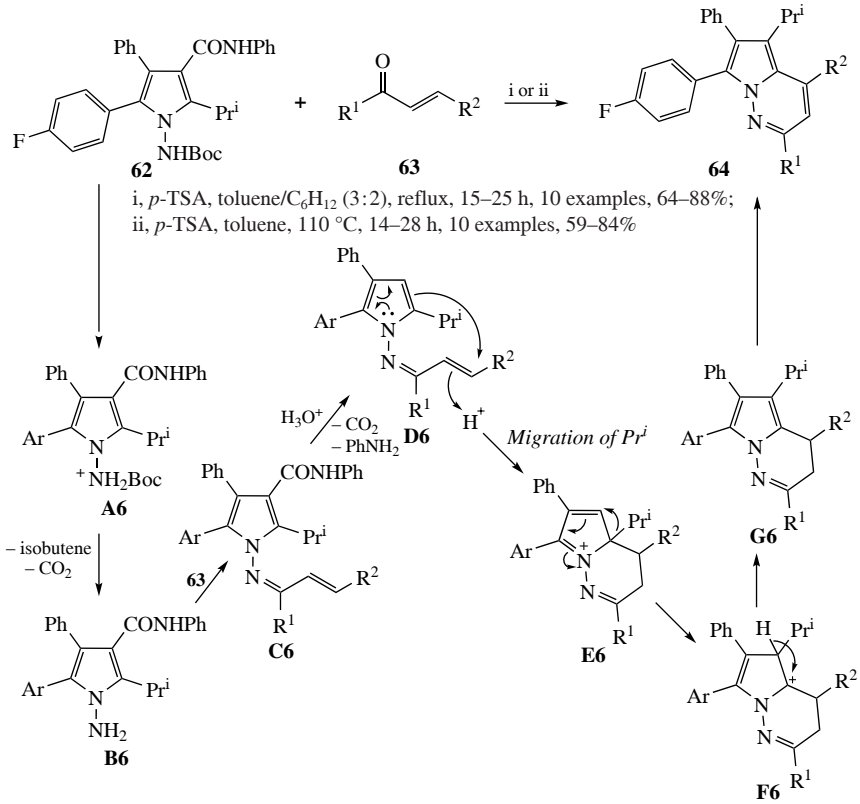
The condensation of 1-aminopyrrole **68** with β-ketoesters **69** in boiling toluene, catalyzed by *p*-TsOH, affords 4-hydroxypyrrolo[1,2-*b*]pyridazines **70** (Scheme 21). These products serve as valuable intermediates for synthesizing potential antagonists of corticotropin-releasing factor 1 (CRF1) receptors.[8]

3.3. Cyclodehydration

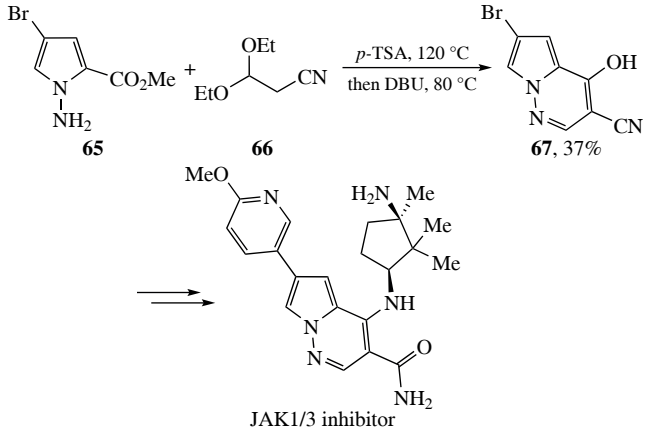
3-Phenylpyrrolo[1,2-*b*]pyridazin-2(1*H*)-one (**72**) was obtained in low yield from pyrrole **50** *via* *N*-acylation with phenylacetyl chloride, affording intermediate **71**, which subsequently underwent cyclization in the presence of 1,1-di-*tert*-butoxy-*N*,*N*-dimethylmethanamine (Scheme 22).[35]

4. Conclusions

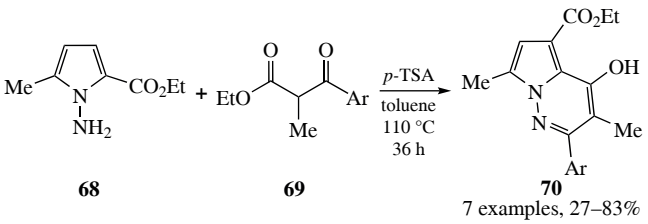
This review provides an updated overview of the construction of pyrrolo[1,2-*b*]pyridazine scaffolds through two synthetic strategies, classified based on the starting materials: pyridazine or pyrrole derivatives. Owing to the significant practical importance of pyrrolopyridazine derivatives, substantial progress has been made in this field since 2008. As of 2024, the most prevalent approach for synthesizing pyrrolo[1,2-*b*]pyridazines involves the 1,3-dipolar cycloaddition of pyridazinium ylides with dipolarophiles. Several effective methodologies have been developed, including transition metal catalysis, acid catalysis, electrochemically initiated processes, and other strategies. Given the continued advancement of heterocyclic chemistry, pyrrolo[1,2-*b*]pyridazine-based



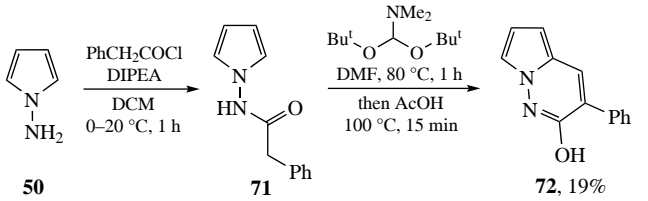
Scheme 19 Acid-catalyzed cascade synthesis of polysubstituted pyrrolo[1,2-*b*]pyridazines **64**.



Scheme 20 Synthesis of pyrrolopyridazines – JAK1/3 inhibitors.



Scheme 21 Synthesis of 4-hydroxypyrrolo[1,2-*b*]pyridazines **70**.



Scheme 22 Synthesis of pyrrolo[1,2-*b*]pyridazin-2(1*H*)-one **72**.

compounds are expected to maintain their prominence in both materials science and medicinal chemistry.

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