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Review

Synthesis of Multi-Substituted Pyrrole Derivatives Through [3+2] Cycloaddition with Tosylmethyl Isocyanides (TosMICs) and Electron-Deficient Compounds

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Abstract: Pyrrole and its polysubstituted derivatives are important five-membered heterocyclic compounds, which exist alone or as a core framework in many pharmaceutical and natural product structures, some of which have good biological activities. The Van Leusen [3+2] cycloaddition reaction based on tosylmethyl isocyanides (TosMICs) and electron-deficient compounds as a substrate, which has been continuously developed due to its advantages such as operationally simple, easily available starting materials, and broadly range of substrates, is one of the most convenient methods to synthetize pyrrole heterocycles. In this review, we discuss the different types of two carbon synthons in the Van Leusen pyrrole reaction and give a summary of the progress of these synthesis methods in the past two decades.

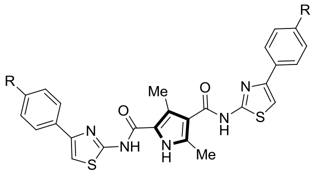
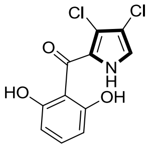
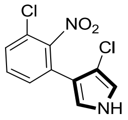
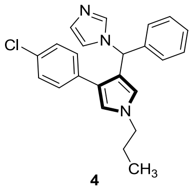
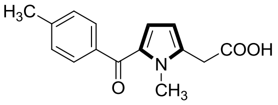
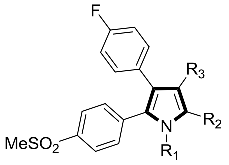
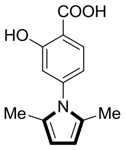
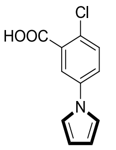
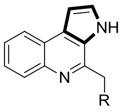
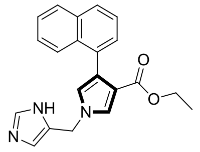
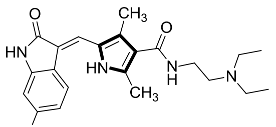
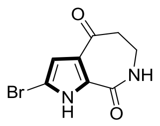
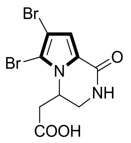
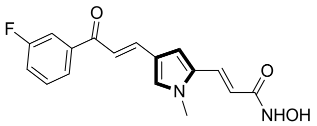
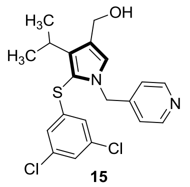
Keywords: pyrrole heterocycles; TosMICs; electron-deficient compounds; Van Leusen pyrrole synthesis; [3+2] cycloaddition

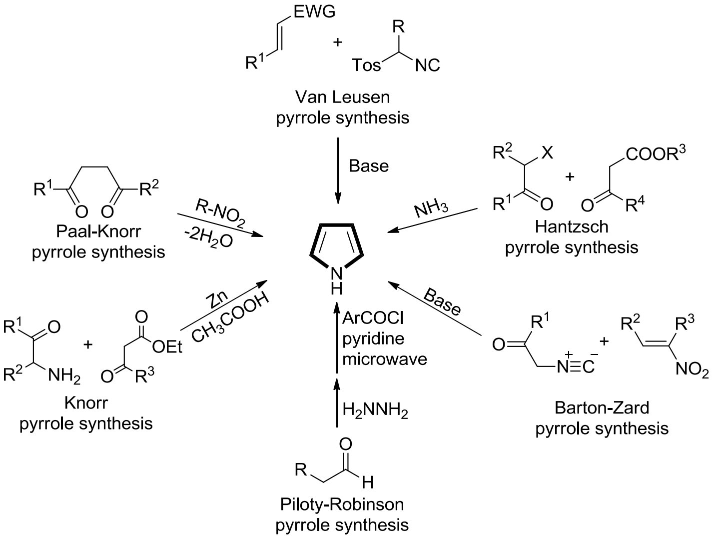
1. Introduction

Pyrrole and its polysubstituted derivatives are important five-membered heterocyclic compounds, which exist alone or as a core skeleton in many pharmaceutical and natural product structures, some of them have good bioactivity such as antibacterial [1,2], antifungal [3,4], anti-inflammatory [5,6], antiviral [7], antimalarial [8], anticancer [9,10], antiparasitic [11], etc., and can also be used as enzyme inhibitor in the organism [12,13]. Some typical pyrrole derivative chemical structures and the physiological functions are summarized in the following Table 1.

Since pyrrole and its multi-substituted derivatives play an important role in organic synthesis as well as in biology, syntheses of five-membered heterocyclic pyrrole compounds have always been valued by researchers. Over the last decades, there are many methods for synthesizing pyrrole compounds in laboratory routes [14], and the classical methods include Knorr pyrrole synthesis [15], Paal-Knorr pyrrole synthesis [16], Hantzsch pyrrole synthesis [17], Barton-Zard reaction [18], Van Leusen pyrrole synthesis [19], and Piloty–Robinson pyrrole synthesis [20]. These synthesis methods are summarized in Scheme 1.

Table 1. Some typical pyrrole derivative chemical structures and the physiological functions.

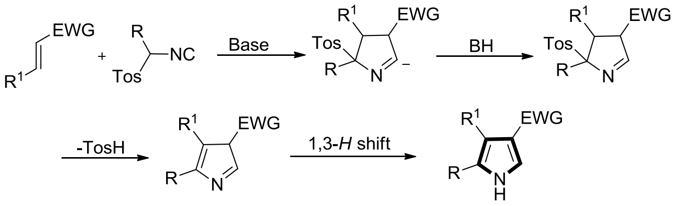
Physiological Functions	Chemical Structures	References
Antibacterial	 **1**  Pyoluteorin **2**	[1,2]
Antifungal	 Pyrrolnitrin **3**  **4**	[3,4]
Anti-inflammatory	 Tolmetin **5**  **6**	[5,6]
Antiviral	 NB-2 ClogP: 4.28 **7**  NB-64 ClogP: 315 **8**	[7]
Antimalarial	 Marinoquinoline A (R = H)) Marinoquinoline B (R =*i*-Pr) Marinoquinoline C (R = Ph) Marinoquinoline D (R = 4-HO-Ph) **9**	[8]
Anticancer	 **10**  Sunitinib **11**	[9,10]
Antiparasitic	 **12**  **13**	[11]
Enzyme inhibitor	 **14**  **15**	[12,13]



Scheme 1. Typical cycloaddition methods for pyrrole heterocycle and its derivatives.

As shown in Scheme 1, the method for synthesizing pyrrole based on the [3+2] cycloaddition reaction of TosMIC as 3-atom synthon with electron-deficient olefins is also known as the Van Leusen pyrrole synthesis. It was first reported by the Van Leusen et al. in 1972. Van Leusen and co-workers used TosMICs with ester-containing double bond compounds to synthesize a series of 3,4-disubstituted pyrrole compounds under basic conditions [19]. Subsequently, they extended the substrate scope to include electron-withdrawing groups on electron-deficient olefins, such as α,β-unsaturated cyano, sulfonyl, nitro, and sulfonyl groups, which enriched the structure diversity of the resulting pyrrole compounds [21,22]. Therefore, the Van Leusen [3+2] cycloaddition reaction is one of the most convenient methods to synthetize pyrrole heterocycles, which has been continuously developed over the ensuing years due to its advantages such as operationally simple, easily available starting materials, and broad range of substrates.

TosMIC is a colorless, odorless, stable solid that can be stored at room temperature. It is an important organic synthesis intermediate, and widely used in the synthesis of five-membered nitrogen-containing heterocycles [23]. Under the Van Leusen pyrrole synthesis reaction conditions, TosMIC loses a proton to form a carbanion under the action of a base because of the electron-withdrawing effect of the sulfone and isocyanide. The carbon anion attacks on the α,β-unsaturated compound, undergoes an intramolecular [3+2] cycloaddition reaction, and causes the leaving of the tosyl group to form the final heterocyclic compound. The mechanism of [3+2] cycloaddition reaction between TosMICs and electron-deficient alkenes to form pyrrole derivatives is shown in Scheme 2.



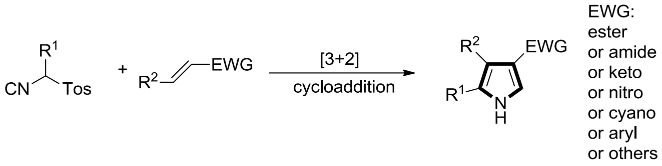
Scheme 2. Mechanism of pyrrole compounds formed by [3+2] cycloaddition between TosMICs and electron-deficient alkenes.

In recent reports, it has been found that this reaction occurs selectively at the position of a less polar double bond. The use of electron-deficient compounds having an electron-withdrawing group and a relatively stable structure, or a solvation effect in the reaction system to stabilize the structure of the electron-deficient compound, can significantly increase the rate and yield of the reactions.

In this paper, we review the research progress of the synthesis of pyrrole derivatives through the [3+2] cycloaddition reaction between TosMICs and different kinds of 2-carbon synthons based on the Van Leusen pyrrole synthesis method in the past two decades.

2. Synthesis of Pyrrole Derivatives by [3+2] Cycloaddition of TosMICs with Alkenes

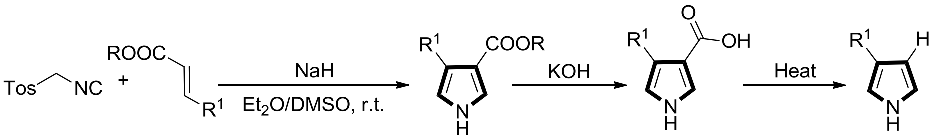
In 1972, Van Leusen and co-workers firstly reported that TosMICs can react with electron-deficient alkenes under basic conditions to produce 3-substituted pyrrole derivatives [19]. They found that there are [3+2] cycloadditions occurring in alkenes with different electron-withdrawing groups. As shown in Scheme 3, the electron-withdrawing groups may be esters, amides, ketones, nitros, cyanos, aryls, etc. [24–60]. Based on the different types of electron-withdrawing group attached to the alkenes, they are classified and described in order (Scheme 3).



Scheme 3. Synthetic protocols for polysubstituted pyrroles from TosMICs and electron-defect alkenes.

2.1. Alkenes with an Ester Group

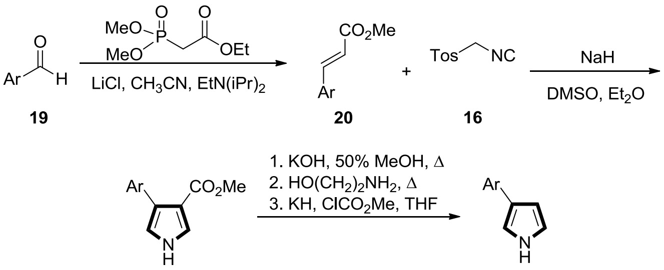
As early as in the 1990s, Van Leusen and co-workers developed a process in which TosMIC **16** reacts with a Michael acceptor to form 3,4-disubstituted pyrrole compounds **17** or 3-substituted pyrrole compounds **18**. This procedure necessarily installs the activating Z group of the Michael acceptor at the 3-position of the pyrrole ring formed (Scheme 4) [22,24].



16 **17** **18**

Scheme 4. Synthesis of 3, 4-substituted and 3-disubstituted pyrrole compounds **17** and **18**.

In 1997, the Trudell group described an expeditious method for the synthesis of 3-aryl-substituted pyrroles. The 3-arylpyrroles **22** were prepared in a short reaction sequence from the readily available aryl aldehydes **19**. The aldehydes **19** were converted into the corresponding methyl 3-arylacrylate esters **20** using a Wadsworth-Emmons olefination procedure. Treatment of **20** with TosMIC **16** afforded the 4-aryl-3-(methoxycarbonyl)-pyrroles **21**. Then the ester moieties were hydrolyzed to the corresponding carboxylic acids with excess KOH in 50% MeOH. The acid derivatives were then decarboxylated by heating in 2-ethanolamine to give the 3-arylpyrroles **22** in good yield (Scheme 5) [25].

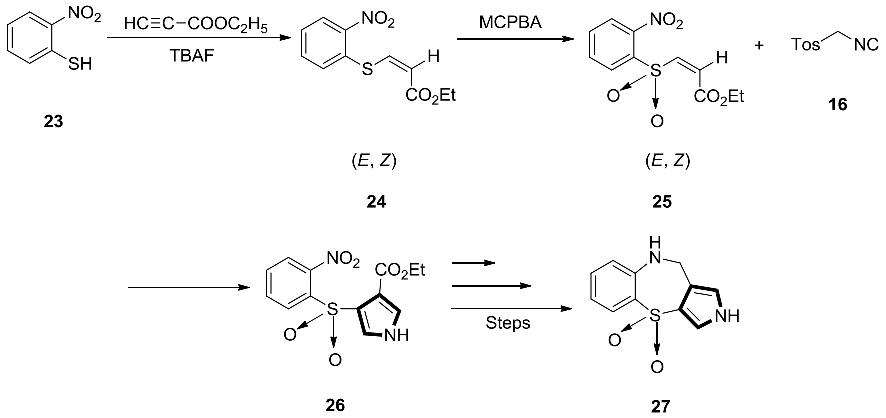


19 **20** **16** **21** **22**

Scheme 5. Synthesis of 3-arylpyrroles **22**.

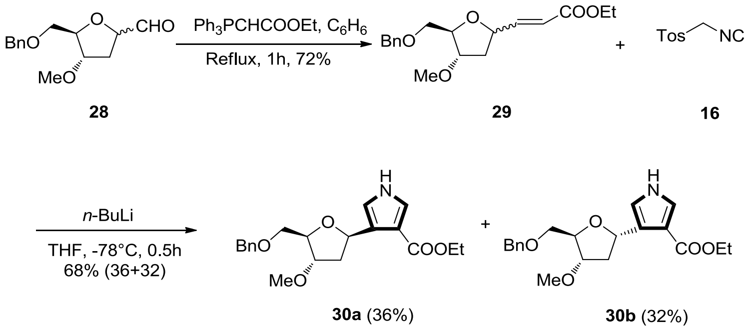
The electron neutral or electron-deficient aryl vinyl esters such as cinnamic acid esters could be successfully employed in the cyclization reaction. However, the TosMIC **16** addition reaction with **20** which possessed electron-rich substituents on the aryl ring did not yield the desired pyrroles, but rather gave intractable mixtures.

The next year, Di Santo et al. pioneered the synthesis of 2*H*-pyrrolo[3,4-*b*][1,5]pyrrolobenzothiazepine **27**. They started with tetrabutylammonium fluoride (TBAF)-catalyzed reaction of 2-nitrothiophenol **23** with ethyl 2-propynoate to afford ethyl 3-(2-nitrophenylthio)propenoate **24**. Then they performed a transformation of the sulfur derivative into the sulfone analogue by the use of *m*-chloroperbenzoic acid (MCPBA). Afterwards, the novel *E*/*Z* mixture **25** was reacted with TosMIC **16** to form ethyl 4-(2-nitrophenylsulfony1)-1*H*-pyrrole-3-carboxylate **26** as the sole product. 2*H*-pyrrolo[3,4-*b*][1,5]pyrrolobenzothiazepine **27** can be synthesized by using compound **26** as raw material (Scheme 6) [26].



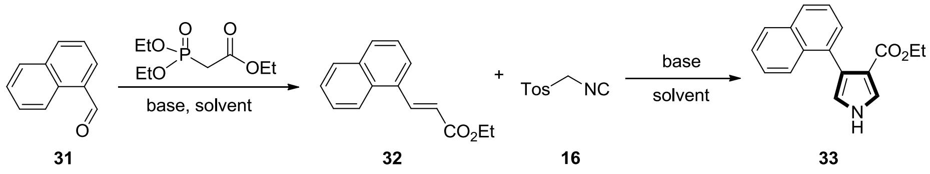
Scheme 6. Synthesis of 2*H*-pyrrolo[3,4-*b*][1,5]pyrrolobenzothiazepine **27**.

In 2007, Krishna's group found that aldehyde **28** on treatment with (ethoxycarbonylmethylene)-triphenylphosphorane in refluxing benzene was converted to the α,β-unsaturated ester **29** (72%), and treatment of **29** with potassium salt of TosMIC **16** afforded the corresponding pyrrole C-nucleosides **30a** (36%) and **30b** (32%) (Scheme 7) [27].



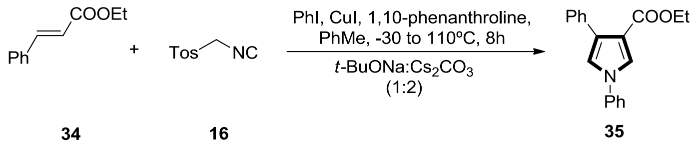
Scheme 7. Synthesis of pyrrole *C*-nucleosides **30a** and **30b**.

In 2008, Shin's group developed a synthesis of ethyl 4-substituted-1*H*-pyrrole-3-carboxylates **33** from aldehyde **31**, in which they synthesized α,β-unsaturated ester **32** from aromatic or aliphatic aldehydes by the Horner-Wadsworth-Emmons reaction and subsequently reacted it with TosMIC **16** in the presence of sodium *t*-amylate in toluene. In this reaction, the solvent, toluene, can be used in both reaction and crystallization, which makes it more practical and greener (Scheme 8) [28].



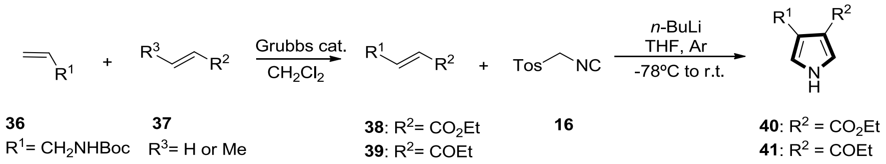
Scheme 8. Synthesis of ethyl 4-substituted-1*H*-pyrrole-3-carboxylate **33.**

Hu's group developed a procedure for the preparation of *N*-arylated 3,4-disubstituted pyrroles **35** from alkenes in the same year. They found that these compounds can be obtained when a mixture of ethyl 3-phenylacrylate **34**, TosMIC **16**, PhI, CuI, and 1,10-phenanthroline in toluene was treated with 3.0 equivalents of base at −30 °C for 10 min and then the resultant mixture was refluxed until the intermediate was completely exhausted. When a (1:2) mixture of *t*-BuONa to Cs_2CO_3 was used as base, **35** was obtained as a single product. In this procedure, *t*-BuONa served as a base for Van Leusen pyrrole synthesis and Cs_2CO_3 for the *N*-arylation, respectively (Scheme 9) [29].



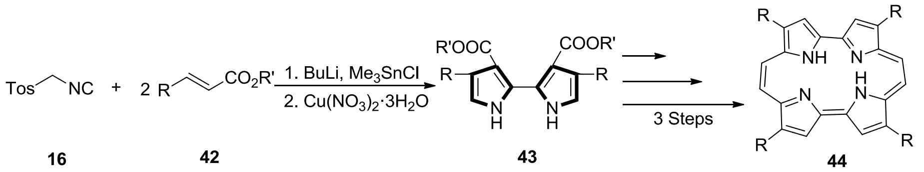
Scheme 9. Synthetic route of *N*-arylated 3,4-disubstituted pyrrole **35**.

In 2009, Poulard et al. designed a synthetic route for 3,4-disubstituted pyrrole compounds **40**, in which the 1,2-disubstituted Michael acceptors **38** are prepared by cross-methylation with compounds **36** and **37** that were used to react with TosMIC **16** to obtain **40**. Under the same conditions, compounds **41** can be also obtained when the R^2 group was the ketone carbonyl-substituted Michael acceptor **39** (Scheme 10) [30].



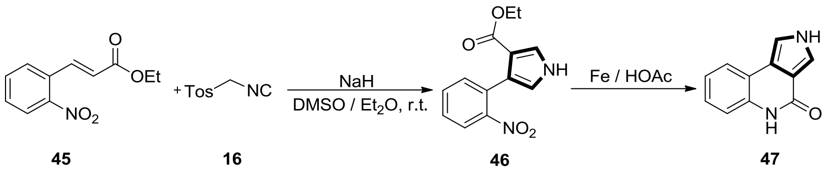
Scheme 10. Synthesis of 3,4-disubstituted pyrrole compounds **40** and **41**.

In the same year, the Sánchez-García group reported that 2,2′-bipyrroles compounds **43** were synthesized through the reaction of enesters **42** and TosMIC **16**. 2,7,12,17-tetraarylporphycenes **44** can be synthesized by using compounds **43** as raw materials. Porphycenes are of great value in the chemical industry and in biomedicine. During this reaction, there will also be a monopyrrole product formed, but if post-treated with dilute ammonia, the bipyrrole compound can be precipitated in ethyl acetate (Scheme 11) [31].



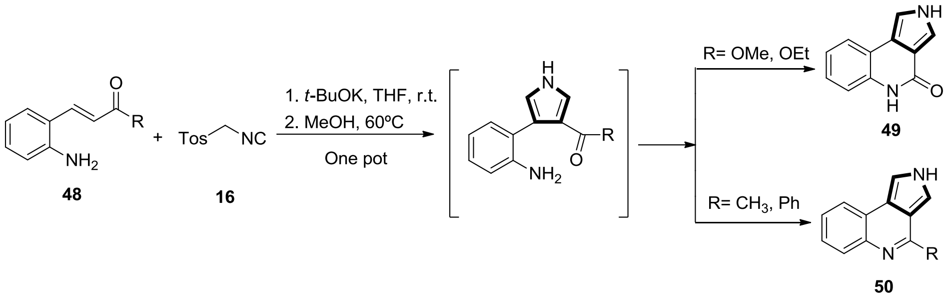
Scheme 11. Synthesis of 2,2′-bipyrrole compounds **43**.

In 2012, Di Santo et al. described the formation of a pyrrole derivative **46** from (*E*)-ethyl-3-(2-nitrophenyl)acrylate **45** and TosMIC **16** under basic conditions. Then, nitro reduction and intramolecular cyclization into a lactam were further performed to synthesize 2*H*-pyrrolo[3,4-*c*]quinoline compound **47** (Scheme 12) [32].



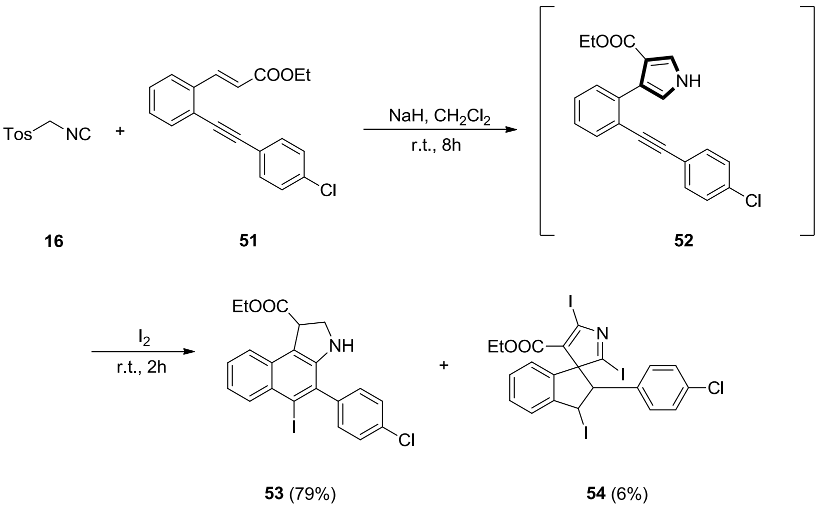
Scheme 12. Synthetic route of pyrrole derivative **47**.

In 2014, the Ji group found that 2-aminoaryl acrylate **48** and TosMIC **16** undergo [3+2] cycloaddition under basic condition and could effectively synthesize pyrrolo[3,4-*c*]quinolinone **49** or pyrrolo[3,4-*c*]quinolines **50**. It is worth mentioning that the reacted pyrrole intermediate will both undergo an intramolecular condensation reaction of the ester or ketone with the amine during the formation of the quinoline ring. The reactions have good efficiency and practicality, and the yields can reach up to 73% (Scheme 13) [33].



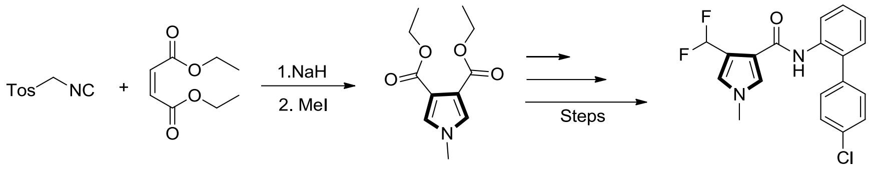
Scheme 13. Synthesis of pyrrolo[3,4-*c*]quinolinone **49** and pyrrolo[3,4-*c*]quinolines **50**.

In 2015, our group developed an expedient and divergent tandem one-pot synthesis of benz[*e*]indole derivative **53** (79%) and spiro[indene-1,3′-pyrrole] derivative **54** (6%) from alkyne-tethered chalcones/cinnamates **51** and TosMIC **16**. The formation of intermediate **52** in this reaction involves a [3+2] cycloaddition with TosMIC **16** and electron-deficient ester **51** (Scheme 14) [34]. To our knowledge this reaction is the first example of intramolecular electrophilic cyclizations of alkynes with in-situ generated pyrroles.



Scheme 14. Synthesis of benz[*e*]indole derivative **53** and spiro[indene-1,3′-pyrrole] derivative **54**.

In 2018, the Lamberth group reported a new synthesis route of pyrrolocarboxamide compounds **57**. They firstly used diethyl maleate **55** as starting material, which was converted with TosMIC **16** into the 3,4-dicarbethoxy-substituted pyrrole **56**. Then, after a series of reactions on the substituents, pyrrole carboxamide compound **57** was synthesized (Scheme 15) [35].

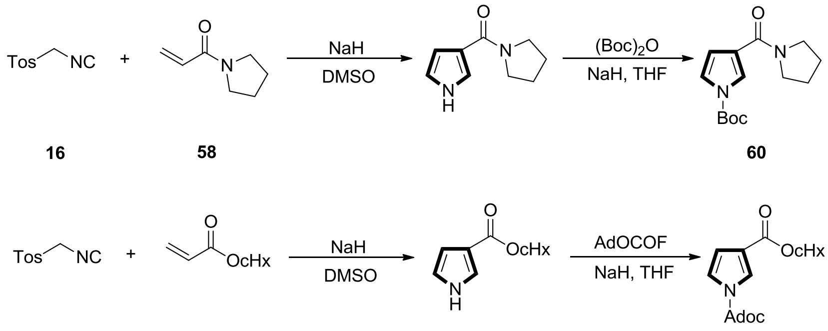


16 **55** **56** **57**

Scheme 15. Synthesis of pyrrole carboxamide compound **57.**

2.2. Alkenes with an Amide Group

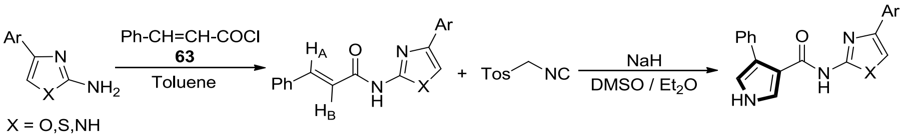
Donohoe and co-workers continued to expand the reaction to TosMIC **16** with acrylic acid pyrrolidide **58** to generate two pyrroles in reasonable yields in 1998. The compound was subsequently protected under standard conditions to yield the *N*-Boc pyrrole **60**. Under the similar conditions, *N*-Adoc pyrrole **61** could be obtained from cyclohexyl acrylate **59** and TosMIC **16**, respectively (Scheme 16) [36].



16 **59** **61**

Scheme 16. Synthesis of *N*-Boc pyrrole **60** or *N*-Adoc pyrrole **61**.

In 2011, Padmavathi et al. condensed cinnamoyl chloride **63** with an aromatic heterocyclic compound **62** containing an amino group to prepare a series of aromatic heterocyclic cinnamic acid amide compounds **64**. Then, these electron-deficient alkenes were reacted with TosMIC **16** in the presence of NaH, DMSO and diethyl ether to prepare a series of 4′-phenyl-*N*-(4-heteroaryl-2-yl)-1′*H*-pyrrole-3′-carboxamide compounds **65**. According to a bioassay, compounds **65** have certain antibacterial activity against Gram-negative bacteria, and most of the compounds have the effect of inhibiting spore germination (Scheme 17) [37].

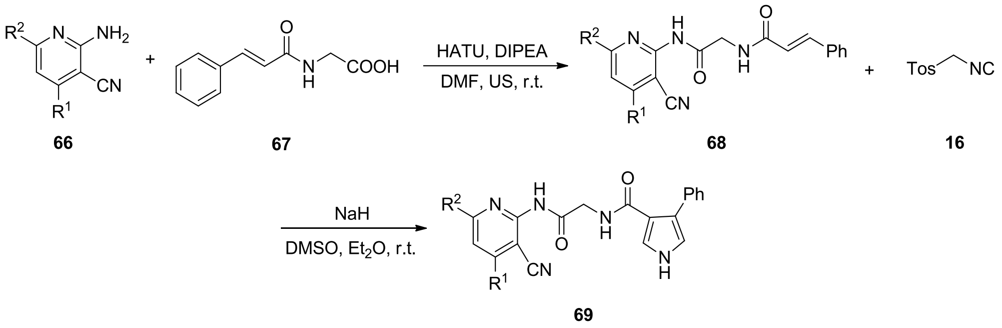


X = O,S,NH

62 **64** **16** **65**

Scheme 17. Synthesis of 4′-phenyl-*N*-(4-heteroaryl-2-yl)-1′*H*-pyrrole-3′-carboxamide compounds **65**.

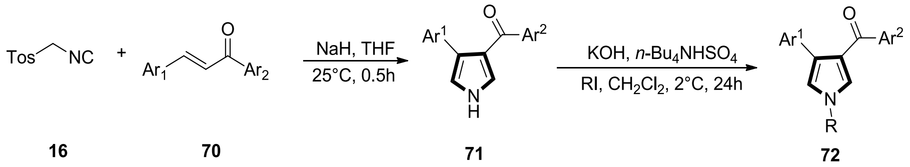
In 2017, Adivireddy et. al. developed a synthesis of pyridinylcarbamoylmethyl pyrrolyl compounds **69**. In this route, the synthetic intermediate (*E*)-*N*-((4-(aryl)-3-cyano-6-(aryl)pyridin-2-ylcarbamoyl)methyl)cinnamamide **68** was prepared by the condensation of 2-amino-4,6-diaryl-pyridine-3-carbonitrile **66** with 2-(cinnamamido)acetic acid **67** in the presence of *o*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluraniumhexafluorophosphate (HATU) and *N*,*N*-diisopropyl-ethylamine (DIPEA) in DMF under ultrasonication at room temperature. Then occurs the reaction of **68** with TosMIC **16** in the presence of NaH and in a solvent mixture of ether and dimethylsulfoxide (2:1) produced *N*-((4-(aryl)-3-cyano-6-(aryl) pyridin-2-ylcarbamoyl)methyl)-4-phenyl-1*H*-pyrrole-3-carboxamide **69**. The bis amido linked aromatized heterocycles pyrrolyl pyridines **69** exhibited excellent radical scavenging activity (Scheme 18) [38].



Scheme 18. Synthesis of pyridinylcarbamoylmethyl pyrrolyl compounds **69**.

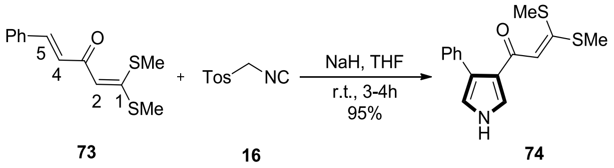
2.3. Alkenes with a Keto Group

In 2000, Dannhardt and co-workers reported that 1,3-diarylprop-2-en-1-ones **70** and TosMIC **16** were dissolved in THF as solvent to produce 3-aroyl-4-arylpyrroles **71** in the presence of NaH at room temperature for 0.5 h. Then compounds **71** were alkylated at the pyrrole nitrogen to afford an *N*-substituted aryl-aroyl-pyrroles **72** (Scheme 19) [39].



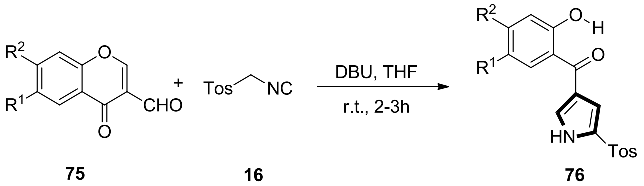
Scheme 19. Synthesis of 3-aroyl-4-arylpyrroles **71** and *N*-substituted aryl-aroyl-pyrroles **72**.

The [3+2] cycloaddition of TosMIC with unsymmetrically substituted divinyl ketones occurs selectively on the less polar double bond. In 2007, the Rao group found that TosMIC **16** and cinnamoylketene dithioacetal **73** can selectively synthesize 3,3-bis(methylthio)-1-(4-aryl-1*H*-pyrrol-3-yl)prop-2-en-1-one **74** via [3+2] cycloaddition. This reaction occurs selectively on the less polar 4-position ene bond (Scheme 20) [40].



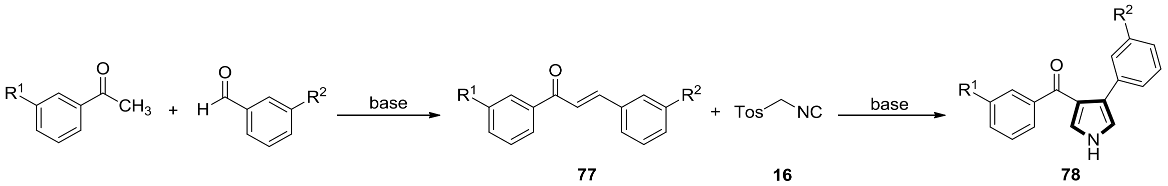
Scheme 20. Synthesis of 3, 3-bis(methylthio)-1-(4-aryl-1*H*-pyrrol-3-yl)prop-2-en-1-one compound **74**.

In the same year, Terzidis et al. reported that chromone-3-carboxaldehydes **75** were allowed to react with equimolar amounts of TosMIC **16** in the presence of DBU, in the aprotic nonpolar solvent THF at room temperature. As a result 2-tosyl-4-(2-hydroxybenzoyl)pyrroles **76** were isolated in good yield (Scheme 21) [41].



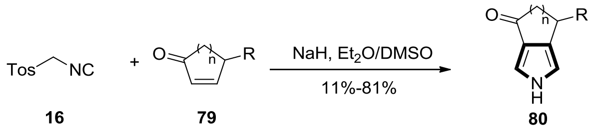
Scheme 21. Synthesis of 2-tosyl-4-(2-hydroxybenzoyl)pyrroles **76**.

In 2009, the Pérez group synthetized a series of pyrrole derivatives **78** by using TosMIC **16** with α,β-unsaturated carbonylic compounds **77**, which were obtained through Claisen-Schmidt condensation from the respective acetophenones and benzaldehydes substituted in *m*-position (Scheme 22) [42].



Scheme 22. Synthetic route of pyrrole derivatives **78**.

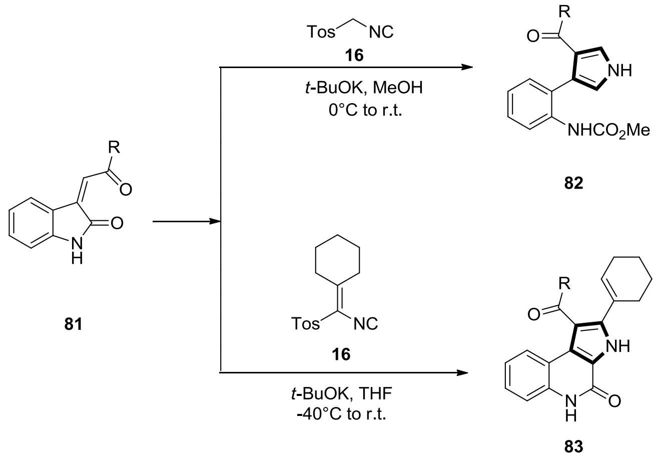
In 2012, Kelly et al. found that the cyclic α,β-unsaturated ketone **79** can be used as a Michael acceptor for 1,3-dipolar cycloaddition to form pyrrole. The 3,4-fused cycloalkanopyrroles **80** were synthesized by reaction of **79** with TosMIC **16** and sodium hydride in a 3:1 solution of diethyl ether and dimethyl sulfoxide at room temperature, but the yield of the cyclization appeared to depend on the base-sensitivity of the Michael acceptor (Scheme 23) [43].



R= CH_2CO_2Me, CH_2CO_2Bn

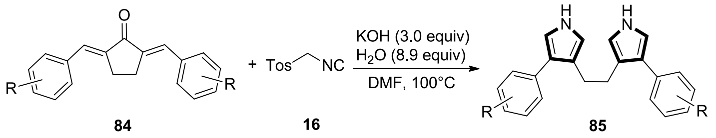
Scheme 23. Synthesis of 3,4-fused cycloalkanopyrroles **80**.

Similar reactions can occur with TosMIC derivatives. In 2013, the Ji group reported the reaction of TosMIC **16** with (*Z*)-3-(2-oxo-2-ethylidene)indolin-2-one derivatives **81** to give pyrrole derivatives **82**, and developed a simple and convenient synthetic approach to access of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one derivatives **83** by the reaction of **81** with functionalized TosMIC derivatives **16** under basic conditions (Scheme 24) [44].



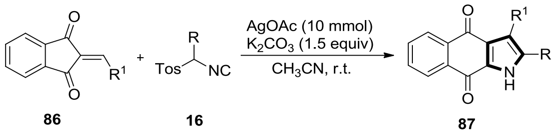
Scheme 24. Synthesis of disubstituted pyrroles **80** and 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one derivatives **83**.

In the following year, Ji et al. also discovered a method for synthesizing bridged 3,3′-dipyrrole derivatives **85** by the reaction of dienone derivatives **84** with TosMIC **16**. In addition to the classical [3+2] cycloaddition reaction, this reaction also involves C-C bond cleavage caused by traces of water in the system. They also captured a spirocyclic intermediate, which is providing a new idea for the study of the construction of bispirocyclic compounds by isonitrile (Scheme 25) [45].



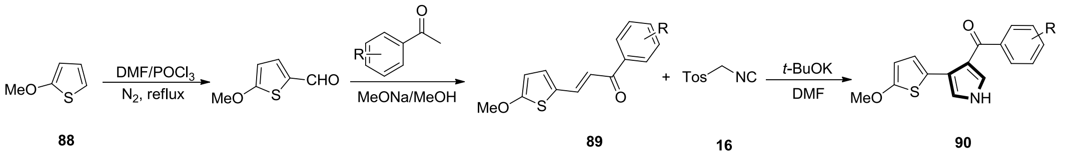
Scheme 25. Synthesis of bridged 3,3′-dipyrrole derivatives **85.**

In 2016, our group described a silver-catalyzed tandem reaction of TosMIC derivatives **16** with 2-methyleneindene-1,3-diones **86** to produce benzo[*f*]indole-4,9-diones compounds **87**. The reaction undergoes a domino [3+2]-cycloaddition/imidoyl anion cyclization/ring opening of cyclo-propanolate/aromatization and three C-C bonds are formed successively. The pyrrole ring is constructed while expanding a carbon atom to the original carbon ring (Scheme 26) [46].



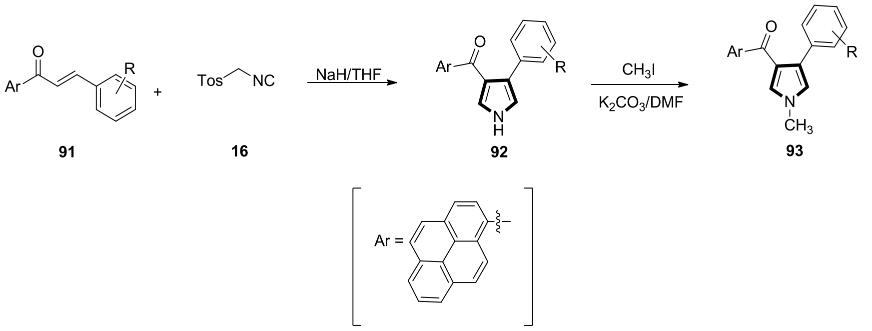
Scheme 26. Synthesis of benzo[*f*]indole-4,9-diones compounds **87**.

In 2017, Mao and co-workers reported a synthesis of 4-substituted thienyl pyrrole compounds **90** via Vilsmeier-Haack formylation, aldol condensation and Van Leusen pyrrole synthesis using 2-methoxythiophene **88** as starting material. Compounds **90** have good selectivity and inhibition to tumor cells (Scheme 27) [47].



Scheme 27. Synthesis of 4-substituted thienyl pyrrole compounds **90.**

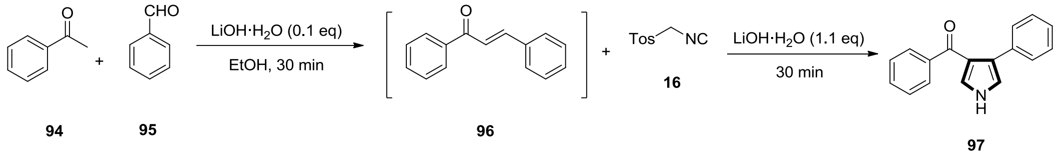
In 2017, Shanmugam et al. described that chalcone **91** and TosMIC **16** undergo [3+2] cycloaddition under mild conditions to synthesize 3-aroyl-4-arylpyrrole compounds **92**. A new substituted carbamoylpyrrole **93** exhibiting moderate antibacterial activity against gram-positive bacteria and gram-negative bacteria was then synthesized by a substitution reaction with methyl iodide (Scheme 28) [48].



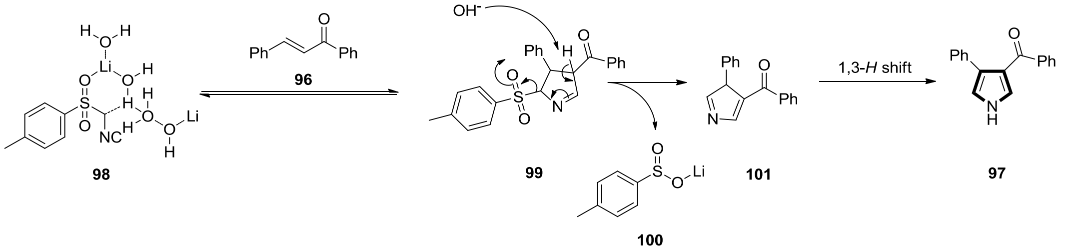
Scheme 28. Synthesis of 3-aroyl-4-arylpyrrole compounds **93**.

Solvation or dynamic solvent effects can affect the rate of [3+2] cycloaddition reaction between TosMIC and aromatic ketones. In 2013, Nair's group discovered a lithium hydroxide mediated 3,4-disubstituted pyrrole synthesis method [49]. As shown in Scheme 29, acetophenone **94** was reacted with benzaldehyde **95** in the presence of $LiOH{\cdot}H_2O$ in ethanol medium to afford 1,3-diphenylprop-2-enone **96** by an aldol condensation between the enolate and the electrophile. Then, TosMIC **16** and an additional equivalent of $LiOH{\cdot}H_2O$ were added to the same system. As the reaction progressed, a white solid precipitated from the reaction medium, the product obtained was filtered, washed with water and ethanol, and characterized as phenyl(4-phenyl-1*H*-pyrrol-3-yl)methanone **97**. In this reaction system, due to the small size of Li^+ ion, $LiOH{\cdot}H_2O$ has obvious covalent character, which slows down the release of OH^-. At the same time, a solvation effect occurs in the polar solvent to increase the yield.

A plausible mechanism for the reaction is depicted in Scheme 30. $LiOH{\cdot}H_2O$ abstracts a proton from the methylene group of TosMIC to generate a carbanion which can be stabilized by the sulfonyl group. The intermediate 1,3-dipole undergoes [3+2] cycloaddition reaction to provide the cycloadduct **100**. Elimination of lithium *p*-toluenesulfinate under the action of a base to produce a C-3 substituted pyrrole derivative **101**. Finally, 1,3-hydride shift occurs to afford the product **97**. The *β*-substituent of the electrophile ends up at the C-4 position of the pyrrole ring.

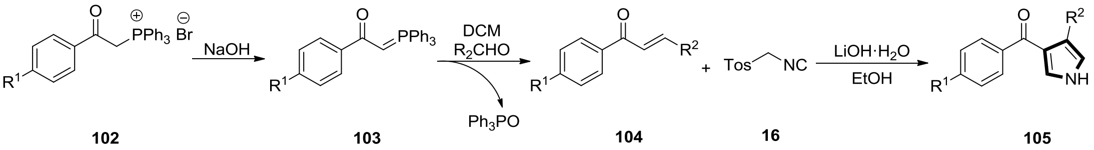


Scheme 29. Synthesis of phenyl(4-phenyl-1*H*-pyrrol-3-yl)methanone **97**.



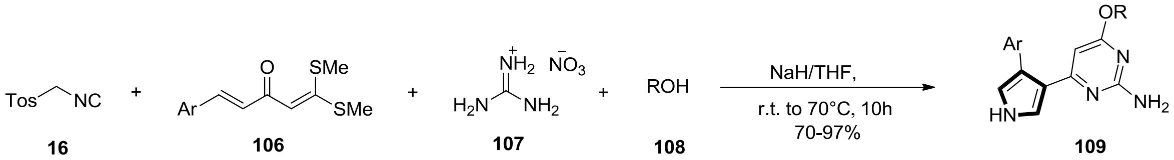
Scheme 30. A plausible mechanism for the [3+2] cycloaddition reaction for TosMIC with $LiOH{\cdot}H_2O$.

In 2016, Nair and co-workers also reported an aroyl-substituted pyrroles **105** synthetic route from phosphonium salt **102** as starting material. The phosphonium salt was neutralized with aqueous NaOH and extracted with dichloromethane to afford 1-phenyl-2-(triphenyl-phosphoranylidene)ethenone **103**. Further the compound was reacted with isobutyraldehyde in dichloromethane to generate the corresponding α,β-unsaturated ketone **104**. Upon completion of the reaction, dichloromethane was evaporated and the reaction mixture was triturated with hexane to remove triphenylphosphine oxide. Moreover, they found that $LiOH{\cdot}H_2O$ gave good yields of the desired product as compared to NaOH and KOH. This might be due to better coordination power of lithium (Scheme 31) [50].



Scheme 31. Synthesis of aroyl-substituted pyrroles **105**.

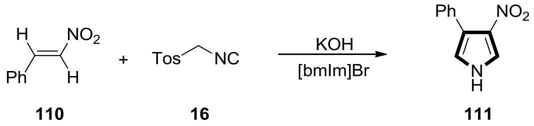
Multi-component Van Leusen pyrrole synthesis can also occur in alkenes with aromatic ketones. In 2014, the Shanmugam research group found that cinnamoylketene dithioacetal **106** undergo multi-component cycloaddition with TosMIC **16**, guanidine nitrate **107** and alkyl alcohol **108** in the presence of NaH/THF to furnish the target 6-pyrrolylpyrimidines **109** in excellent yields of 70–97% (Scheme 32) [51]. Because of the electron donating characteristics of the two methyl sulfanyl groups and the structural features of α,β-unsaturated carbonyl group, the arylvinyl double bond is more polarized than the ketene acetal double bond, which causes TosMIC **16** to selectively react at the arylvinyl double bond.



Scheme 32. Synthesis of 6-pyrrolylpyrimidines **109.**

2.4. Alkenes with a Nitro Group

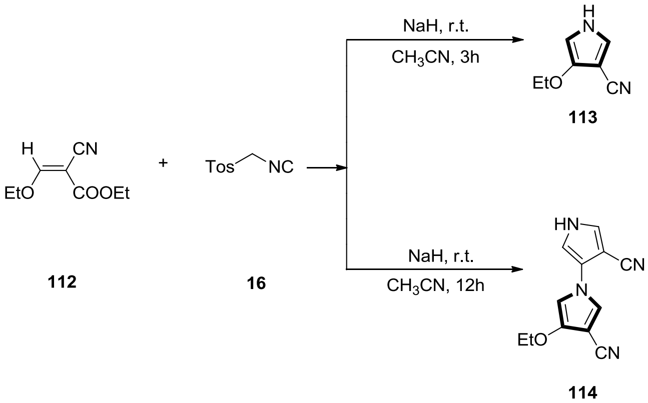
In 2009, Xiaoqi Yu and co-workers reported that 4(3)-substituted 3(4)-nitro-1*H*-pyrrole **111** can be synthesized from nitroene **110** and TosMIC **16** in the presence of the ionic liquid 1-butyl-3-methylimidazolium bromide ([bmIm]Br). This reaction can be widely applied to aromatic, aliphatic or heterocyclic substituted nitroolefins, and the recovered ionic liquid can be repeatedly used as a solvent without significantly reducing the yield (Scheme 33) [52].



Scheme 33. Synthesis of 4(3)-substituted 3(4)-niropyrrole **111**.

2.5. Alkenes with a Cyano Group

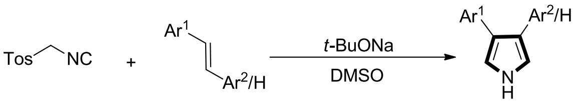
In 2012, the Yongping Yu group reported that two equivalents of a cyano-substituted trisubstituted alkene **112** and TosMIC **16** were dissolved in anhydrous acetonitrile as a solvent and reacted in the presence of NaH at room temperature for 3 h to form disubstituted pyrrole derivatives **113**. And the 1,3′-bipyrrole **114** is obtained if the reaction time is extended to 12 h (Scheme 34) [53,54]. In the experiments, researchers also found that when keto and ester groups are simultaneously present in alkenes, due to the higher reactivity, keto group can be eliminated more easily than ester groups alone. In addition, group with larger steric hindrance can reduce the reactivity when they are present on alkenes.



Scheme 34. Synthesis route of 3,4-disubstituted pyrrole derivatives **113** and 1,3′-bipyrrole compound **114**.

2.6. Alkenes with an Aryl Group

In 2002, Smith and co-workers developed a method for the one-step synthesis of 3-aryl and 3,4-diarylpyrroles **116** with good yields by readily available aryl or diaryl alkenes **115** with TosMIC **16** (Scheme 35) [55]. They found that the stronger the electron-withdrawing ability of the aryl group attached to the alkene in the substrate, the lower the temperature required for the reaction, the shorter the reaction time, and the higher yield. At the same time, the steric hindrance of the aryl group will act as a deterrent to the reaction. This phenomenon is particularly evident when the aryl group is ortho-substituted.

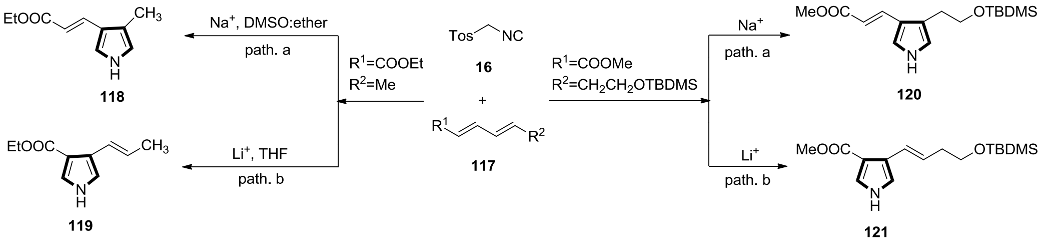


16 **115** **116**

Scheme 35. Synthesis of 3-aryl and 3,4-diaryl-(1*H*)-pyrroles **116**.

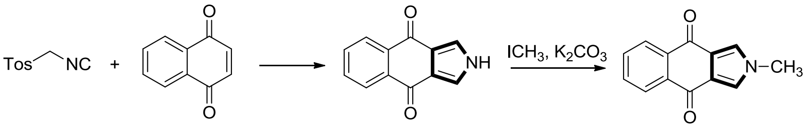
2.7. Other Alkene Synthons

Magnus et al. reported the effect of metal ion on the conjugate addition of TosMIC **16** anions to ethyl sorbate **117** in 1987. The sodium salt of TosMIC **16** in DMSO:ether reacted with **117** to afford pyrrole **118** (pathway a) in 80% yield, whereas the lithium salt of TosMIC **16** in THF afforded the addition adduct **119** in 61% yield (pathway b) (Scheme 36, left) [56]. On the basis of the research, Ganem and co-workers reported that condensation of **117** with the sodium anion of TosMIC in DMSO: ether gave regioisomers **120** in 1997. While using $LiN(TMS)_2$ in THF at −78 °C, pyrrole derivate **121** was obtained as the only detectable product. The combination of more polar solvent and more highly dissociated anion favored reaction at the terminally polarized δ-position of dienoate **117**, leading to the desired 1,6-addition product (Scheme 36, right) [57].



Scheme 36. The effect of metal ion on the conjugate addition of TosMIC **16** anions to ethyl sorbate **117**.

Quinone can be also used for the Van Leusen pyrrole synthesis. In 1996, Di Santo et al. reported a synthesis of 2*H*-benz[*f*]isoindole-4,9-dione **123** from TosMIC **16** that reacts with Michael acceptor 1,4-naphthoquinone **122**. *N*-Methylation of the latter compound with iodomethane in the presence of anhydrous potassium carbonate afforded 2-methyl-2*H*-benz[*f*]isoindole-4,9-dione **124** (Scheme 37) [58].

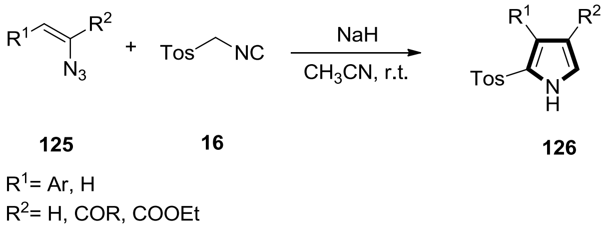


16 **122** **123** **124**

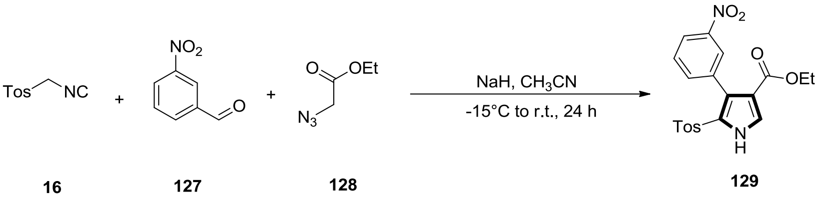
Scheme 37. Synthesis of 2-methyl-2*H*-benz[*f*]isoindole-4,9-dione **124**.

In 2012, Yongping Yu and co-workers reported synthesis of polysubstituted pyrroles **126** from TosMIC **16** and vinyl azides **125** under mild conditions in the presence of base (Scheme 38) [59]. Additionally, they developed a Van Leusen three-component reaction as a synthesis of 2,3,4-trisubstituted pyrrole **129**, where a mixture of 3-nitrobenzaldehyde **127** and ethyl 2-azidoacetate

128 was stirred under the Knoevenagel condensation conditions using NaH as the base for 2 h at −15 °C, followed by addition of TosMIC **16**. The reaction mixture was then stirred at room temperature for 24 h to give the desired product **129** (Scheme 39) [59].

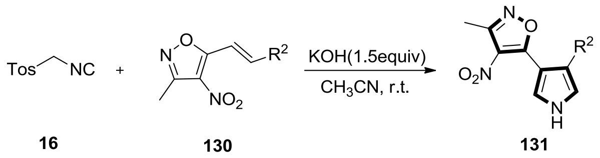


Scheme 38. Synthesis of polysubstituted pyrroles **126**.

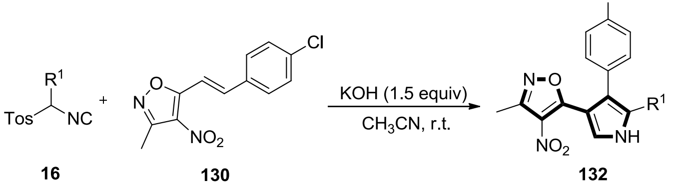


Scheme 39. Synthesis of 2,3,4-trisubstituted pyrrole **129**.

In 2017, our research group discovered that TosMIC **16** can undergo a [3+2] cycloaddition reaction with a styrylisoxazole compounds **130** to construct a series of 3-isoxazole disubstituted pyrrole derivatives **131** (Scheme 40) [60]. Under the same optimized reaction condition, the synthesis of the 3-isoxazole trisubstituted pyrrole derivatives **132** was achieved by using the TosMIC derivatives **16** (Scheme 41) [60]. This transformation is operationally simple, high-yielding, and displays broad substrate scope.



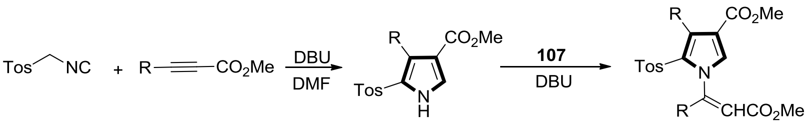
Scheme 40. Synthesis of 3-isoxazole disubstituted pyrroles derivatives **131**.



Scheme 41. Synthesis of 3-isoxazole trisubstituted pyrrole derivatives **132**.

3. Synthesis of Pyrrole Derivatives by [3+2] Cycloaddition of TosMICs with Alkynes

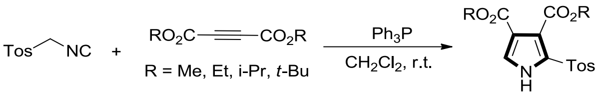
Similar to alkenes, alkynes can also undergo [3+2] cycloaddition with TosMIC to synthesize pyrrole derivatives. As early as in 1979, Saikachi and co-workers found that acetylene ester **133** (2 equiv each) and TosMIC **16** can produce 2,3,4-trisubstituted pyrrole compounds **134** in the presence of DBU. The 1,2,3,4-tetrasubstituted pyrrole compounds **135** can be synthesized by another one-step addition reaction (Scheme 42) [61].



16 133 134 135

Scheme 42. Synthesis of 2,3,4-trisubstituted pyrrole derivatives **134** and 1,2,3,4-tetrasubstituted pyrrole derivatives **135**.

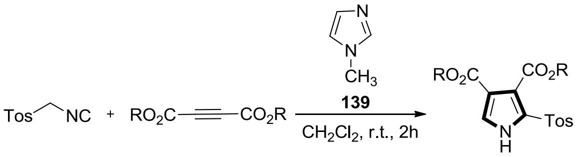
In 2006, Alizadeh et al. found that dialkyl acetylenedicarboxylates **136** react with TosMIC **16** in the presence of Ph_3P to form dialkyl 2-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylates **137**. In this reaction, the nucleophilic addition of Ph_3P to the acetylenic esters further increases the reactivity of the substrate as an electron-withdrawing group (Scheme 43) [62].



16 136 137

Scheme 43. Synthesis of 2,3,4-trisubstituted pyrrole derivatives **137**.

In 2011, the Adib group developed a protocol that is different with respect to the common shortcomings such as long reaction time, low yield, expensive raw materials, and harsh reaction conditions. A mixture of TosMIC **16**, and a dialkyl acetylenedicarboxylate **138**, in the presence of a catalytic amount of 1-methylimidazole **139** undergoes a smooth addition reaction in anhydrous CH_2Cl_2 at room temperature to afford 2,3,4-trisubstituted pyrroles **140** in yields of 90–95% (Scheme 44) [63].



16 138 140

Scheme 44. Synthesis of 2,3,4-trisubstituted pyrrole derivatives **140**.

4. Conclusions

In summary, the Van Leusen [3+2] cycloaddition reaction based on TosMICs and electron-deficient compounds is involved in the construction of pyrrole and its derivatives because of its advantages such as simple and convenient synthesis substrate, diverse products, etc., and will play an increasingly important role in the synthesis of bioactive pyrrole derivatives in the pharmaceutical synthesis. In recent years, some research progress has been made, which provides new ideas for the synthesis of polysubstituted pyrrole ring framework. In the future, there will be a focus on developing more types and higher selectivity 2-carbon synthons in subsequent research to increase the expansion of the reaction.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Idhayadhulla, A.; Kumar, R.S.; Nasser, A.J.A. Synthesis, Characterization and Antimicrobial Activity of New Pyrrole Derivatives. *J. Mex. Chem. Soc.* **2011**, *55*, 218–223.

2. Massa, S.; Artico, M.; Corelli, F.; Mai, A.; Di Santo, R.; Cortes, S.; Marongiu, M.E.; Pani, A.; La Colla, P. Synthesis and Antimicrobial and Cytotoxic Activities of Pyrrole-Containing Analogues of Trichostatin A. *J. Med. Chem.* **1990**, *33*, 2845–2849. [CrossRef] [PubMed]
3. Gordee, R.S.; Matthews, T.R. Systemic Antifungal Activity of Pyrrolnitrini. *Appl. Microbiol.* **1969**, *17*, 690–694. [PubMed]
4. Di Santo, R.; Tafi, A.; Costi, R.; Botta, N.; Artico, M.; Corelli, F.; Forte, M.; Caporuscio, F.; Angiolella, L.; Palamara, A.T. Antifungal Agents. 11. N-Substituted Derivatives of 1-[(Aryl)(4-aryl-1*H*-pyrrol-3-yl)methyl]-1*H*-imidazole: Synthesis, Anti-Candida Activity, and QSAR Studies. *J. Med. Chem.* **2005**, *48*, 5140–5153. [CrossRef] [PubMed]
5. Hyneck, M.L.; Smitch, P.C.; Munafo, A.; Mcdonagh, A.F.; Benet, L.Z. Disposition and irreversible plasma protein binding of tolmetin in humans. *Clin. Pharmacol. Ther.* **1988**, *44*, 107–114. [CrossRef] [PubMed]
6. Wilkerson, W.W.; Copeland, R.A.; Covington, M.; Trzaskos, J.M. Antiinflammatory 4,5-Diarylpyrroles. 2. Activity as a Function of Cyclooxygenase-2 Inhibition. *J. Med. Chem.* **1995**, *38*, 3895–3901. [CrossRef] [PubMed]
7. Jiang, S.B.; Lu, H.; Liu, S.W.; Zhao, Q.; He, Y.X.; Debnath, A.K. *N*-Substituted Pyrrole Derivatives as Novel Human Immunodeficiency Virus Type 1 Entry Inhibitors That Interfere with the gp41 Six-Helix Bundle Formation and Block Virus Fusion. *Antimicrob. Agents Chemother.* **2004**, *48*, 4349–4359. [CrossRef] [PubMed]
8. Okanya, P.W.; Mohr, K.I.; Gerth, K.; Jansen, R.; Müller, R. Marinoquinolines A-F, Pyrroloquinolines from *Ohtaekwangia kribbensis* (Bacteroidetes). *J. Nat. Prod.* **2011**, *74*, 603–608. [CrossRef] [PubMed]
9. Lee, H.; Lee, J.; Lee, S.K.; Shin, Y.; Jung, W.; Kim, J.H.; Park, K.; Kim, K.; Cho, H.S.; Ro, S.; et al. A Novel Class of Highly Potent, Selective, and Non-Peptidic Inhibitor of Ras Farnesyltransferase (FTase). *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3069–3072. [CrossRef]
10. Paludetto, M.N.; Bijani, C.; Puisset, F.; Bernardes-Génisson, V.; Arellano, C.; Robert, A. Metalloporphyrin-Catalyzed Oxidation of Sunitinib and Pazopanib, Two Anticancer Tyrosine Kinase Inhibitors: Evidence for New Potentially Toxic Metabolites. *J. Med. Chem.* **2018**, *61*, 7849–7860. [CrossRef] [PubMed]
11. Scala, F.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O.; Tierney, M.; Kaiser, M.; Tasdemir, D. Bromopyrrole Alkaloids as Lead Compounds against Protozoan Parasites. *Mar. Drugs* **2010**, *8*, 2162–2174. [CrossRef] [PubMed]
12. Ragno, R.; Simeoni, S.; Rotili, D.; Caroli, A.; Botta, G.; Brosch, G.; Massa, S.; Mai, A. Class II-selective histone deacetylase inhibitors. Part 2: Alignment-independent GRIND 3-D QSAR, homology and docking studies. *Eur. J. Med. Chem.* **2008**, *43*, 621–632. [CrossRef] [PubMed]
13. Di Sanro, R.; Tafi, A.; Costi, R.; Artico, M.; Miele, G.; Lavecchia, A.; Novellino, E.; Bergamini, A.; Cancio, R.; Maga, G. Arylthiopyrrole (AThP) Derivatives as Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors: Synthesis, Structure-Activity Relationships, and Docking Studies (Part 1). *Chem. Med. Chem.* **2006**, *1*, 1367–1378. [CrossRef] [PubMed]
14. Ono, N.; Okujima, T. Synthesis of Pyrroles and Their Derivatives from Isocyanides. In *Isocyanide Chemistry*, 1st ed.; Nenajdenko, V.G., Ed.; Wiley-VCH: Weinheim, Germany, 2012; pp. 385–429.
15. Knorr, L. Synthese von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635–1642.
16. Paal, C. Synthese von Thiophen- und Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367–371. [CrossRef]
17. Hantzsch, A. Neue Bildungsweise von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474–1476. [CrossRef]
18. Barton, D.H.R.; Kervagoret, J.; Zard, S.Z. A useful synthesis of pyrroles from nitroolefins. *Tetrahedron* **1990**, *46*, 7587–7598. [CrossRef]
19. Van leusen, A.M.; Siderius, H.; Hoogenboom, B.E.; Van Leusen, D. A new and simple synthesis of the pyrrole ring system from Michael acceptors and tosylmethylisocyanides. *Tetrahedron Lett.* **1972**, *13*, 5337–5340. [CrossRef]
20. Milgram, B.C.; Eskildsen, K.; Richter, S.M.; Scheidt, W.R.; Scheidt, K.A. Microwave-Assisted Piloty−Robinson Synthesis of 3,4-Disubstituted Pyrroles. *J. Org. Chem.* **2007**, *72*, 3941–3944. [CrossRef] [PubMed]
21. Moskal, J.; Van Leusen, A.M. A New Synthesis of Indoles by Electrocyclic Ring Closure of Dialkenylpyrroles. Synthesis of Alkenylpyrroles from 1-Tosylalkenyl Isocyanides and Michael Acceptors. *J. Org. Chem.* **1986**, *51*, 4131–4139. [CrossRef]
22. Ten Have, R.; Leusink, F.R.; Van Leusen, A.M. An Efficient Synthesis of Substituted 3(4)-Nitropyrroles from Nitroalkenes and Tosylmethyl Isocyanides. *Synthesis* **1996**, *7*, 871–876. [CrossRef]

23. Tandon, V.K.; Rai, S. *p*-Toluenesulfonylmethyl isocyanide: A versatile synthon in organic chemistry. *Sulfur Rep.* **2003**, *24*, 307–385.
24. Dijkstra, H.P.; Ten Have, R.; Van Leusen, A.M. A Direct Synthesis of 2-(Trimethylstannyl)pyrroles from Michael Acceptors and Stannylated Tosylmethyl Isocyanide. *J. Org. Chem.* **1998**, *63*, 5332–5338. [CrossRef]
25. Pavri, N.P.; Trudell, M.L. An Efficient Method for the Synthesis of 3-Arylpyrroles. *J. Org. Chem.* **1997**, *62*, 2649–2651. [CrossRef] [PubMed]
26. Di Santo, R.; Costi, R.; Massa, S.; Artico, M. Pyrrole-Annulated Heterocyclic Systems. Synthesis of 2H-Pyrrolo[3,4-b][1,5]benzothiazepine 4,4-Dioxide Derivatives. *Synth. Commun.* **1998**, *28*, 2517–2530. [CrossRef]
27. Krishna, P.R.; Ramana Reddy, V.V.; Srinivas, R. A new synthetic route to oxazole and pyrrole 2-deoxy-C-ribosides. *Tetrahedron* **2007**, *63*, 9871–9880. [CrossRef]
28. Chang, J.H.; Shin, H. Practical One-Pot Syntheses of Ethyl 4-Substituted-1*H*-Pyrrole-3-Carboxylates from Aldehydes. *Org. Process Res. Dev.* **2008**, *12*, 291–293. [CrossRef]
29. Zhu, R.; Xing, L.X.; Liu, Y.T.; Deng, F.K.; Wang, X.Y.; Hu, Y.F. Practical one-pot sequential procedure for the preparation of *N*-arylated 3,4-disubstituted pyrroles from alkenes. *J. Organomet. Chem.* **2008**, *693*, 3897–3901. [CrossRef]
30. Poulard, C.; Cornet, J.; Legoupy, S.; Dujardin, G.; Dhal, R.; Huet, F. Synthesis of Polysubstituted Pyrroles. *Lett. Org. Chem.* **2009**, *6*, 359–361. [CrossRef]
31. Sánchez-García, D.; Borrell, J.I.; Nonell, S. One-Pot Synthesis of Substituted 2,2′-Bipyrroles. A Straightforward Route to Aryl Porphycenes. *Org. Lett.* **2009**, *11*, 77–79. [CrossRef] [PubMed]
32. Furlotti, G.; Alisi, M.A.; Apicella, C.; de Joannon, A.C.; Cazzolla, N.; Costi, R.; Crucitti, G.C.; Garrone, B.; Iacovo, A.; Magarò, G.; et al. Discovery and Pharmacological Profile of New 1*H*-Indazole-3-carboxamide and 2*H*-Pyrrolo[3,4-*c*]quinoline Derivatives as Selective Serotonin 4 Receptor Ligands. *J. Med. Chem.* **2012**, *55*, 9446–9466. [CrossRef] [PubMed]
33. Lu, X.M.; Li, J.; Cai, Z.J.; Wang, R.; Wang, S.Y.; Ji, S.J. One pot synthesis of pyrrolo[3,4-*c*]quinolinone/pyrrolo[3,4-*c*]quinoline derivatives from 2-aminoarylacrylates/2-aminochalcones and tosylmethyl isocyanide (TosMIC). *Org. Biomol. Chem.* **2014**, *12*, 9471–9477. [CrossRef] [PubMed]
34. Zhang, X.; Feng, C.J.; Jiang, T.; Li, Y.F.; Pan, L.; Xu, X.X. Expedient and Divergent Tandem One-Pot Synthesis of Benz[*e*]indole and Spiro[indene-1,3′-pyrrole] Derivatives from Alkyne-Tethered Chalcones/Cinnamates and TosMIC. *Org. Lett.* **2015**, *17*, 3576–3579. [CrossRef] [PubMed]
35. Walter, H.; Lamberth, C.; Corsi, C. Synthesis of fungicidally active succinate dehydrogenase inhibitors with novel difluoromethylated heterocyclic acid moieties. *Monatshefte Chem.* **2018**, *149*, 791–799. [CrossRef]
36. Donohoe, T.J.; Guyo, P.M.; Harji, R.R.; Heiliwell, M. The Birch reduction of 3-substituted pyrroles. *Tetrahedron Lett.* **1998**, *39*, 3075–3078. [CrossRef]
37. Padmavathi, V.; Prema kumari, C.; Venkatesh, B.C.; Padmaja, A. Synthesis and antimicrobial activity of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles. *Eur. J. Med. Chem.* **2011**, *46*, 5317–5326. [CrossRef] [PubMed]
38. Gudi, Y.; Gundala, S.; Venkatapuram, P.; Adivireddy, P.; Chippada, A.R.; Allagadda, R. Synthesis and Antioxidant Activity of a New Class of Pyridinylcarbamoylmethyl Pyrrolyl/Pyrazolylcarboxamides. *J. Heterocycl. Chem.* **2017**, *54*, 3498–3509. [CrossRef]
39. Dannhardt, G.; Kiefer, W.; Krämer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. The pyrrole moiety as a template for COX-1/COX-2 inhibitors. *Eur. J. Med. Chem.* **2000**, *35*, 499–510. [CrossRef]
40. Rao, H.S.P.; Sivakumar, S. Aroylketene dithioacetal chemistry: Facile synthesis of 4-aroyl-3-methylsulfanyl-2-tosylpyrroles from aroylketene dithioacetals and TosMIC. *Beilstein J. Org. Chem.* **2007**, *3*, 31. [PubMed]
41. Terzidis, M.; Tsoleridis, C.A.; Stephanidou-Stephanatou, J. Reaction of chromone-3-carboxaldehydes with TOSMIC: Synthesis of 4-(2-hydroxybenzoyl)pyrroles. *Tetrahedron* **2007**, *63*, 7828–7832. [CrossRef]
42. Hormaza, A.; Pérez, O.F.A. Síntesis de una nueva serie de pirroles vía cicloadición. *Rev. Soc. Quím. Perú* **2009**, *75*, 12–16.
43. Kelly, J.M.; Leeper, F.J. Synthesis of 3,4-fused cycloalkanopyrroles by 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2012**, *53*, 819–821. [CrossRef]
44. Wang, R.; Wang, S.Y.; Ji, S.J. Chemoselective synthesis of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one derivatives from 3-phenacylideneoxindoles and substituted tosylmethyl isocyanide (TosMIC). *Tetrahedron* **2013**, *69*, 10836–10841. [CrossRef]

45. Wang, R.; Wang, S.Y.; Ji, S.J. Water promoted C–C bond cleavage: Facile synthesis of 3,3-bipyrrole derivatives from dienones and tosylmethyl isocyanide (TosMIC). *Org. Biomol. Chem.* **2014**, *12*, 1735–1740. [CrossRef] [PubMed]
46. Zhang, L.J.; Zhang, X.M.; Lu, Z.C.; Zhang, D.W.; Xu, X.X. Accessing benzo[f]indole-4,9-diones via a ring expansion strategy: Silver-catalyzed tandem reaction of tosylmethyl isocyanide (TosMIC) with 2-methyleneindene-1,3-diones. *Tetrahedron* **2016**, *72*, 7926–7930. [CrossRef]
47. Zhao, K.; Wang, S.; Zhan, X.Q.; Liu, Z.L.; Mao, Z.M. Synthesis and Anti-tumor Activity of 4-(Methoxyl thienyl)-3-(substituted benzoyl)pyrroles. *Chin. J. Org. Chem.* **2017**, *37*, 943–953. [CrossRef]
48. Divakar, M.A.; Shanmugam, S. Live cell imaging of bacterial cells: Pyrenoylpyrrole-based fluorescence labeling. *Chem. Biol. Drug Des.* **2017**, *90*, 554–560.
49. Sharma, R.; Kumar, K.; Chouhan, M.; Grover, V.; Nair, V.A. Lithium hydroxide mediated synthesis of 3,4-disubstituted pyrroles. *RSC Adv.* **2013**, *3*, 14521–14527. [CrossRef]
50. Kumar, K.; More, S.S.; Goyal, S.; Gangar, M.; Khatik, G.L.; Rawal, R.K.; Nair, V.A. A convenient synthesis of 4-alkyl-3-benzoylpyrroles from α,β-unsaturated ketones and tosylmethyl isocyanide. *Tetrahedron Lett.* **2016**, *57*, 2315–2319. [CrossRef]
51. Dhanalakshmi, P.; Shanmugam, S. Convenient one-pot multicomponent strategy for the synthesis of 6-pyrrolylpyrimidines. *RSC Adv.* **2014**, *4*, 29493–29501.
52. Qin, J.; Zhang, J.; Wu, B.; Zheng, Z.G.; Yang, M.; Yu, X.Q. Efficient and Mild Protocol for the Synthesis of 4(3)-Substituted 3(4)-Nitro-1*H*-pyrroles and 3-Substituted 4-Methyl-2-tosyl-1*H*-pyrroles from Nitroolefins and Tosylmethyl Isocyanide in Ionic Liquids. *Chin. J. Chem.* **2009**, *27*, 1782–1788. [CrossRef]
53. Qiu, F.L.; Wu, J.W.; Zhang, Y.H.; Hu, M.; Yu, F.; Zhang, G.L.; Yu, Y.P. A Novel Synthesis of Multisubstituted Pyrroles via Trisubstituted Olefins and TosMIC Derivatives. *Lett. Org. Chem.* **2012**, *9*, 305–308.
54. Qiu, F.L.; Wu, J.W.; Zhang, Y.H.; Hu, M.; Yu, Y.P. One-pot cascade approach to 1,3'-bipyrrole derivatives from trisubstituted olefins with tosylmethyl-isocyanide (TosMIC). *Tetrahedron Lett.* **2012**, *53*, 446–448. [CrossRef]
55. Smith, N.D.; Huang, D.; Cosford, N.D.P. One-Step Synthesis of 3-Aryl- and 3,4-Diaryl-(1*H*)-Pyrroles Using Tosylmethyl Isocyanide (TOSMIC). *Org. Lett.* **2002**, *4*, 3537–3539. [CrossRef] [PubMed]
56. Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y.S.; Ananthanarayan, T.P. Studies on the synthesis of the antitumor agent CC-1065. Synthesis of the unprotected cyclopropapyrroloindole A portion using the 3,3′-bipyrrole strategy. *J. Am. Chem. Soc.* **1987**, *109*, 2706–2711. [CrossRef]
57. De Leon, C.Y.; Ganem, B. A New Approach to Porphobilinogen and its Analogs. *Tetrahedron* **1997**, *53*, 7731–7752. [CrossRef]
58. Di Santo, R.; Costi, R.; Massa, S.; Artico, M. Synthesis of Pyrrolo [3,4-*c*][1] benzazepine-4,10(2*H*, 5*H*)-dione, a Model System Useful for the Design of 11-Oxosibiromycinone Analogues. *Synth. Commun.* **1996**, *26*, 1839–1847. [CrossRef]
59. Chen, W.T.; Shao, J.A.; Li, Z.; Giulianotti, M.A.; Yu, Y.P. Synthesis of 2,3,4-trisubstituted pyrroles via a facile reaction of vinyl azides and tosylmethyl isocyanide. *Can. J. Chem.* **2012**, *90*, 214–221. [CrossRef]
60. Zhang, X.M.; Xu, X.X.; Zhang, D.W. [3+2] Cycloaddition of Tosylmethyl Isocyanide with Styrylisoxazoles: Facile Access to Polysubstituted (isoxazol-5-yl)pyrroles. *Molecules* **2017**, *22*, 1131. [CrossRef] [PubMed]
61. Saikachi, H.; Kitagawa, T.; Sasaki, H. Reaction of Tosylmethyl Isocyanide with Methyl 3-Substituted Propiolates as Acetylenic Michael Acceptors. *Chem. Pharm. Bull.* **1979**, *27*, 2857–2861. [CrossRef]
62. Alizadeh, A.; Masrouri, H.; Rostamnia, S.; Movahedi, F. One-Step Synthesis of Dialkyl 2-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylates by Reaction of Acetylenedicarboxylates with 'Tosylmethyl Isocyanide' (TsMIC) and Triphenylphosphine. *Helv. Chim. Acta* **2006**, *89*, 923–926. [CrossRef]
63. Adib, M.; Mohammadi, B.; Sheikhi, E.; Bijanzadeh, H.R. 1-Methylimidazole-catalyzed reaction between tosylmethyl isocyanide and dialkyl acetylenedicarboxylates: An efficient synthesis of functionalized pyrroles. *Chin. Chem. Lett.* **2011**, *22*, 314–317. [CrossRef]