Res Chem Intermed (2016) 42:5617–5637
DOI 10.1007/s11164-015-2391-9

Recent developments in the heterocyclic ketene aminal-based synthesis of heterocycles

Peng Hui Yang[1]

Received: 28 September 2015 / Accepted: 11 December 2015 / Published online: 11 January 2016

Abstract Small poly-functionalized heterocycles are frequently found in pharmacophores and play important roles in drug discovery. Heterocyclic ketene aminals (HKAs) are versatile building blocks for the synthesis of a variety of heterocyclic compounds. In recent years, there has been significant progress in the chemistry of HKAs. All previous work focused on the developments of HKAs in reaction type. This review focused on the developments of HKA-based synthesis of various heterocyclic nuclei since 2002. We believe this will give some insights and help to bring about new ideas for further research.

Keywords HKAs · Heterocycle · Synthesis · MCRs

Introduction

Poly-functionalized heterocycles are frequently found in pharmacophores and play important roles in drug discovery. Heterocyclic ketene aminals (HKAs), also referred to as cyclic ketene *N*,*N*-acetals or cyclic 1,1-enediamines, are powerful and versatile building blocks in synthetic organic chemistry [1]. Due to the conjugation of the amino group and the electron-withdrawing group, the nucleophilicity of α-carbon is highly enhanced. As the amino group can serve as the second nucleophilic center, HKAs are often used to react with bis-electrophiles to construct various types of heterocyclic compounds. Bis-electrophiles, such as ethyl bromoacetate [2, 3], unsaturated carbonyl compounds [4–10], keto esters [11] and active carbonyl compounds [12], have been utilized successfully for fused heterocyclic preparation.

✉ Peng Hui Yang
yaph2001@iccas.ac.cn

[1] College of Chemistry and Chemical Engineering, Xi'an Shiyou University, Xi'an 710065, China

In recent years, there has been significant progress in the chemistry of HKAs. All previous work focused on the developments of HKAs in reaction type [1, 13]. This microreview focused on the developments of HKA-based synthesis of various heterocyclic nuclei since 2002. We believe this review will give some insights and help to bring about new ideas for further research.

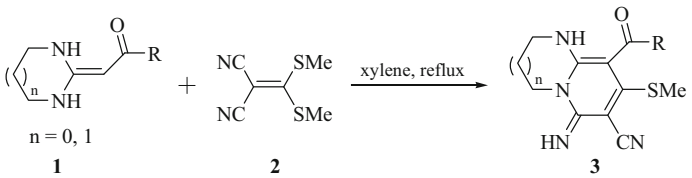
Synthesis of pyridine- or pyridone-fused 1,3-diazaheterocycles

Bicyclic pyridine or pyridone motifs are of general interest in medicinal chemistry with therapeutic properties. When HKAs react with 1,3-biselectrophiles, such as unsaturated carboxylic acid esters, acrylonitrile, itaconic anhydride, etc., pyridine- or pyridone-fused 1,3-diazaheterocycles were usually produced as a result. In 2007, our group developed a simple method for the synthesis of polyfunctionalized pyridine-fused 1,3-diazaheterocycles **3** via reaction of HKAs **1** with bis(-methylthio)methylene malononitrile **2** (Scheme 1) [14]. The reaction proceeded in a cascade way following a sequence of Michael addition, elimination and annulation by nucleophilic addition of the secondary amino group to the nitrile group. The yields of the reactions were largely dependent on the ring size of the HKAs. Six-membered HKAs usually gave good to excellent yields.

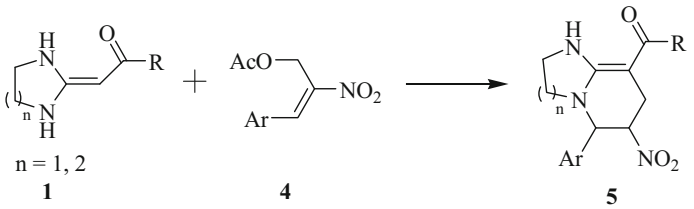
In 2008, a novel method for the synthesis of tetrahydropyridine-fused 1,3-diazaheterocycles **5** was developed by our group via reaction of HKAs **1** with Baylis–Hillman acetates **4** (Scheme 2) [15]. The reaction results were strongly dependent on the conditions. Product **5** was obtained as the sole product when the solvent was switched from polar tetrahydrofuran (THF) to nonpolar CH_2Cl_2 with the decrease of temperature to 0 °C.

2-[3-oxoisobenzofuran-1(3*H*)-ylidene]malononitrile **6** was an ideal 1,3-biselectrophile containing an exocyclic double bond for the synthesis of spiro compounds. An efficient route for the synthesis of polyfunctionalized spiro dihydropyridine-fused 1,3-diazaheterocycles **7** (Scheme 3) [16] was developed by the reaction of HKAs with compound **6**.

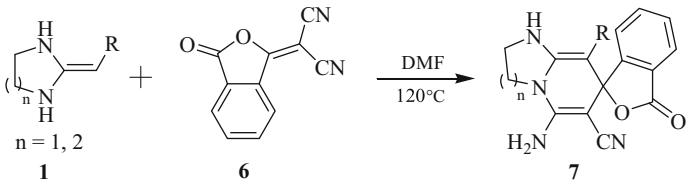
With the emergence of high-throughput screening, multicomponent reactions (MCRs) are gaining importance in synthetic organic chemistry, especially in pharmaceutical chemistry. 1,3-Biselectrophiles may be in a clear form, or they can be created in situ. In 2006, our group first reported the one-pot synthesis of dihydropyridone-fused 1,3-diazaheterocycles **8** employing HKAs, Meldrum's acid and aldehyde as components (Scheme 4) [17]. The reaction started with the



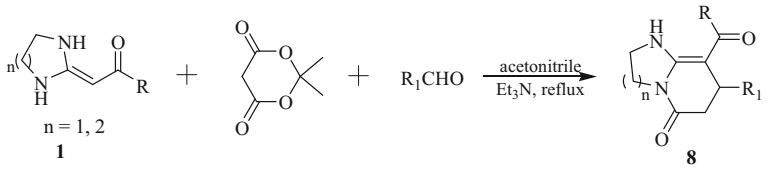
Scheme 1 Synthesis of pyridine-fused 1,3-diazaheterocycles



Scheme 2 Synthesis of tetrahydropyridine-fused 1,3-diazaheterocycles



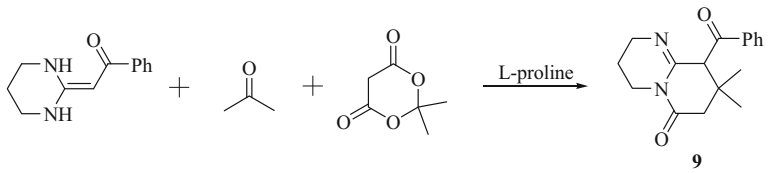
Scheme 3 Synthesis of spiro dihydropyridine-fused 1,3-diazaheterocycles



Scheme 4 One-pot synthesis of dihydropyridone-fused 1,3-diazaheterocycles

condensation of Meldrum's acid with the aldehyde to afford alkylidene Meldrum's acid, which then reacted with HKAs via an aza–ene reaction, imine–enamine tautomerization, cyclocondensation and decarboxylation to afford the final product **8**. The structures of the aldehydes had an obvious influence on the reactivity and yields.

When acetone was used as a carbonyl component, compound **9** [18] was produced by employing L-proline as a catalyst (Scheme 5). In the tautomerization of amidine and enamine, most HKA derivatives adopt the enamine form according to



Scheme 5 Synthesis of amidine-formed HKA derivatives

their spectrum. Interestingly, due to a steric effect, compound **9** existed exclusively as the amidine form rather than the enamine form.

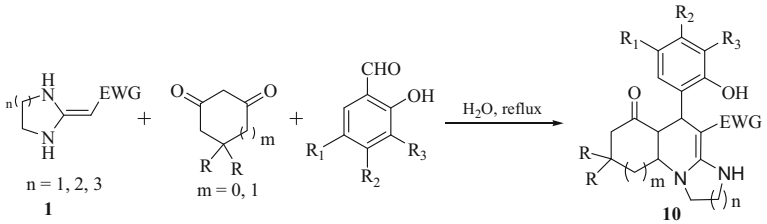
Following a similar strategy, heating a mixture of HKAs with 1,3-cyclohexanedione derivatives and salicylaldehyde derivatives in water afforded polycyclic 1,4-dihydropyridine derivatives **10** (Scheme 6) in high yield [19]. Alternatively, a four-component reaction of aromatic aldehydes, diamines, nitro ketene dithioacetal and cyclic 1,3-diones or malononitrile afforded octahydro-imidazo[1,2-*a*] quinolin-6-ones **11** (Scheme 7) [20] or polyfunctionalized 1,4-dihydropyridine-fused 1,3-diazaheterocycles **12** (Scheme 8) [21] in good yields. When HKAs were treated with aldehydes and 2-hydroxy-1,4-naphthoquinone under solvent-free conditions, benzo[*g*]imidazo[1,2-*a*]quinolinediones **13** were formed via Et_3N-catalyzed annulation (Scheme 9) [22].

Thus, refluxing a mixture of different types of HKAs, isatins and ethyl trifluoroacetate (Scheme 10) [23] or indan-1,3-dione (Scheme 11) [24] catalyzed by piperidine or p-toluenesulfonic acid (p-TSA) afforded structurally diverse spirooxindoles. Alternatively, a four-component reaction of 1,n-diamines, nitro ketene dithioacetal, isatin derivatives and malononitrile in the presence of 10 mol% of piperidine under reflux in ethanol produced highly functionalized spirooxindole derivatives **16** (Scheme 12) [25].

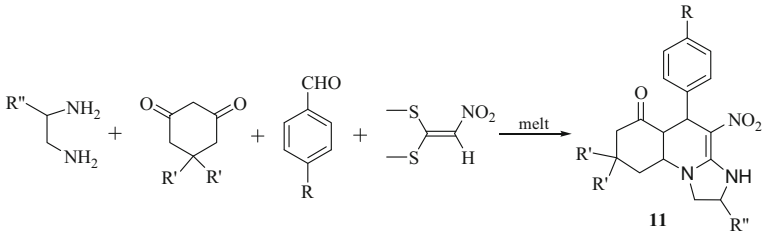
2-(2-Chloroaroyl)methyleneimidazolidines **17** represent a class of polyfunctional scaffolds with **4** reactive sites. The halogen atom on the aromatic ring may act as potential leaving group subjected to an intramolecular S_{NAr} reaction. When treated with 1 equiv of K_2CO_3 in dimethylformamide (DMF) at 100 °C, the three-component condensation products **18** or **19** were subject to intramolecular nucleophilic aryl substitution to afford tetracyclic benzo[*b*]imidazo[1,2,3-*ij*] [1, 8] naphthyridines (Scheme 13) [26, 27].

In 2011, Li's group reported 2-(2-chloroaroyl)methyleneimidazolidines **22** could react with allenic esters **23** to afford imidazo(pyrido)[1,2-*a*]pyridines **24** [28] via 1,4-diazabicyclo[2.2.2] octane (DABCO)-catalyzed tandem annulation, and imidazo(pyrido)[3,2,1-*ij*] [1, 8]-naphthyridines **25** (Scheme 14) were formed when treating with 1 equiv of K_2CO_3 in DMF at 100 °C.

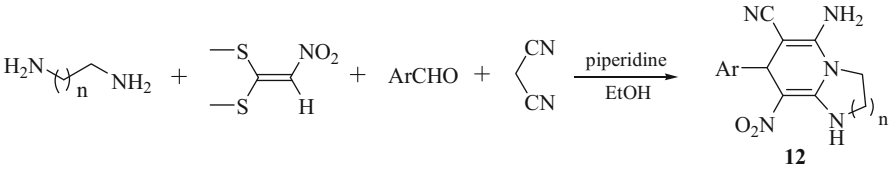
They also developed an efficient four-component protocol to synthesize imidazo[1,2-*a*]pyridines **27** and imidazo[1,2,3-*ij*] [1, 8] naphthyridine derivatives **28** (Scheme 15) from HKAs **26**, aldehydes, diketene **29**, and amines via cascade reactions [29]. Six sequential reactions including diketene ring-opening,



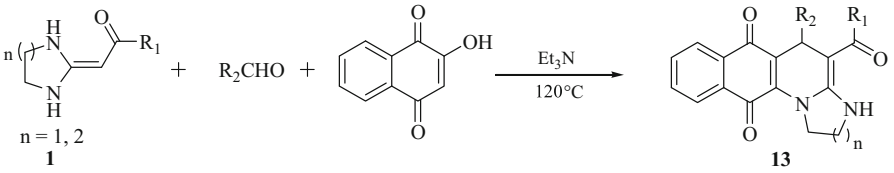
Scheme 6 Synthesis of polycyclic 1,4-dihydropyridine derivatives



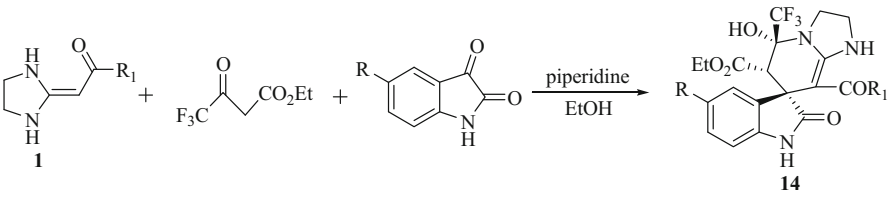
Scheme 7 Synthesis of octahydro-imidazo[1,2-*a*]quinolin-6-ones



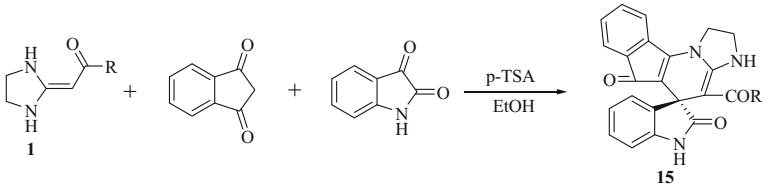
Scheme 8 Synthesis of polyfunctionalized 1,4-dihydropyridine-fused 1,3-diazaheterocycles



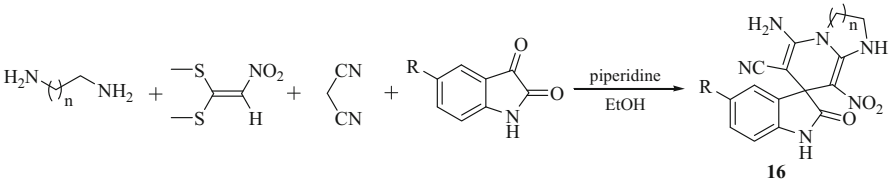
Scheme 9 Synthesis of benzo[*g*]imidazo[1,2-*a*]quinolinediones



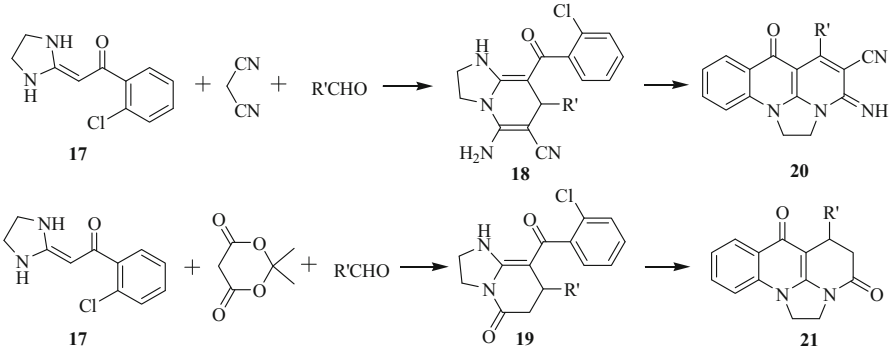
Scheme 10 Synthesis of structurally diverse spirooxindoles



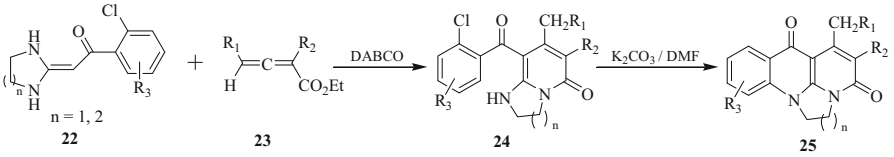
Scheme 11 Synthesis of structurally diverse spirooxindoles



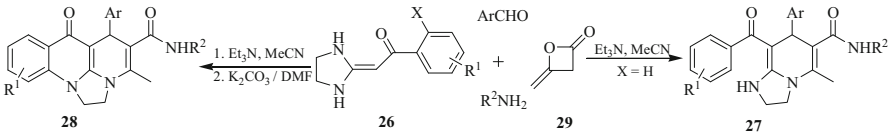
Scheme 12 Synthesis of spirooxindoles derivatives



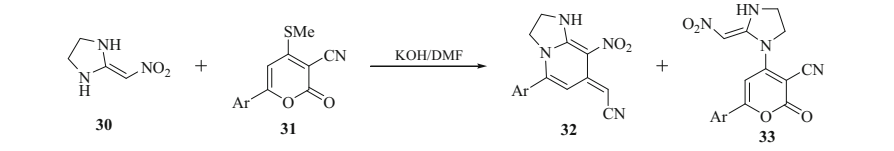
Scheme 13 Synthesis of benzo[*b*]imidazo[1,2,3-*ij*] [1, 8] naphthyridines



Scheme 14 Synthesis of imidazo(pyrido)[3,2,1-*ij*] [1, 8] naphthyridines



Scheme 15 Construction of imidazo[1,2-*a*]pyridines and imidazo[1,2,3-*ij*] [1, 8] naphthyridines



Scheme 16 Synthesis of imidazo[1,2-*a*]pyridine and pyranone derivative

Knoevenagel condensation, aza–ene reaction, imine–enamine tautomerization, cyclocondensation and intramolecular S_{NAr} were involved in the one-pot preparation.

Ram [30] reported when HKAs **30** were treated with suitably functionalized 2*H*-pyran-2-one **31**, almost equal amounts of imidazo[1,2-*a*]pyridine **32** and pyranone derivative **33** (Scheme 16) were obtained. However, when aroyl-substituted HKAs **1** were used, the bicyclic intermediate **34** underwent photocyclization to afford tetracyclic aza-anthracenones **35** (Scheme 17) [31].

In 2010, Xu and coworkers reported dissolution of compounds **36** in acetonitrile at room temperature led to the formation of two highly congested hexahydroimidazo[1,2-*a*]pyridine derivatives **37** and **38** (Scheme 18) formed by aza-Diels–Alder reaction [32].

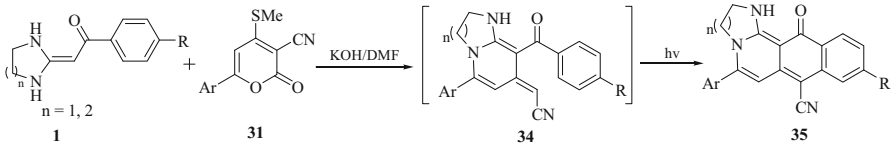
Junjappa [33] reported heating a mixture of HKAs **39** with 1,3-biselectrophiles itaconic anhydride afforded functionalized bicyclic 1,2,3,4-tetrahydropyridones **40** (Scheme 19) in good yield. Alizadeh described an efficient synthesis of highly substituted pyrido[1,2-*a*]-fused 1,3-diazaheterocycles (Schemes 20, 21) via reaction between nitroketene aminals generated in situ from the addition of various diamines to nitroketene dithioacetal and itaconic anhydride [34] or dibenzylideneacetone [35]. Similar three-component reaction of diamines, nitroketene dithioacetal and alkyl prop-2-ynoates afforded 2-oxopyridine-fused 1,3-diazaheterocycles **41** (Scheme 22) [36].

An efficient synthesis of 1,4-dihydropyridine-fused 1,3-diazaheterocycles **42** (Scheme 23) was developed by reaction of nitroketene aminals generated in situ from the addition of various diamines to nitroketene dithioacetal and 2-iminochromenes in good yield [37].

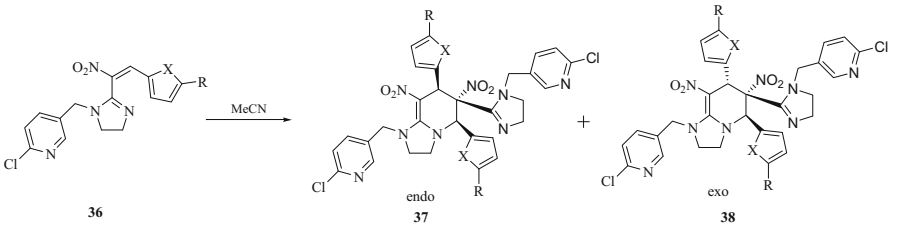
β-Keto ester enol tosylates **43** reacted with HKAs **39** as a 1,3-biselectrophiles in the presence of a base to afford bicyclic pyridones **44** (Scheme 24) in excellent yields [38]. The reaction probably proceeded via a sequence of Michael addition, elimination, imine–enamine tautomerization and cyclocondensation.

Lin's group developed an efficient synthesis of highly substituted bicyclic pyridines **45** (Scheme 25) by clocondensation of HKAs **39**, triethoxymethane, and ethyl trifluoroacetate under solvent-free and catalyst-free conditions in excellent yields [39]. It was found HKA with various substituents and different ring sizes were all good substrates for the one-pot cyclocondensation reaction.

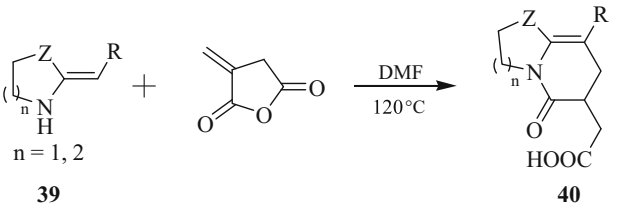
One-pot reaction of HKAs **1**, triethoxymethane and nitroalkenes **46** in the absence of catalyst and solvent gave dihydropyridine-fused diazaheterocycles **47** (Scheme 26) in high yield [40].



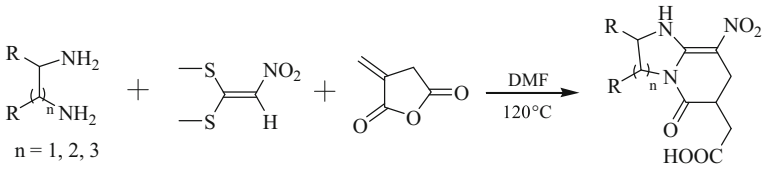
Scheme 17 Synthesis of aza-anthracenones



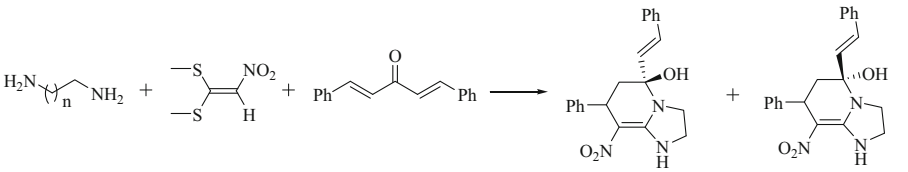
Scheme 18 Synthesis of hexahydroimidazo[1,2-*a*]pyridine derivatives



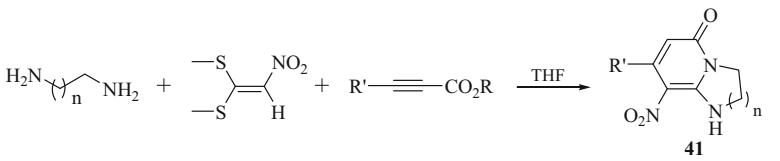
Scheme 19 Synthesis of bicyclic 1,2,3,4-tetrahydropyridones



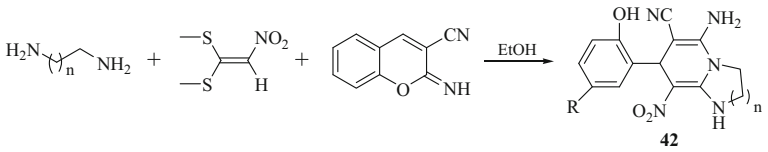
Scheme 20 Synthesis of pyrido[1,2-*a*]-fused 1,3-diazaheterocycles



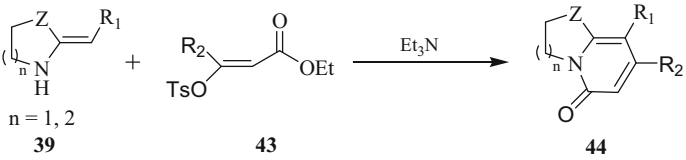
Scheme 21 Synthesis of highly substituted pyrido[1,2-*a*]-fused 1,3-diazaheterocycles



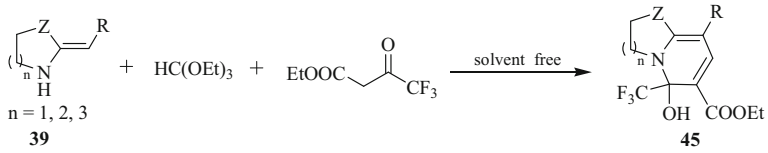
Scheme 22 Synthesis of 2-oxopyridine-fused 1,3-diazaheterocycles



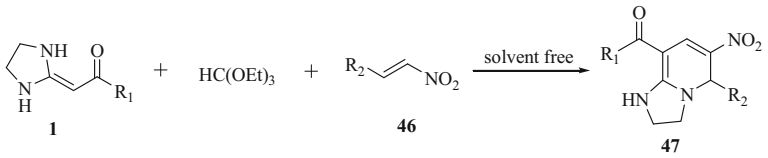
Scheme 23 Synthesis of 1,4-dihydropyridine-fused 1,3-diazaheterocycles



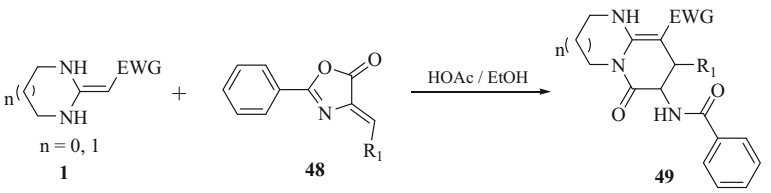
Scheme 24 Synthesis of bicyclic pyridones



Scheme 25 Synthesis of bicyclic pyridines



Scheme 26 Synthesis of dihydropyridine-fused diazaheterocycles



Scheme 27 Synthesis of bicyclic pyridone derivatives

In 2013, they also found HKAs **1** reacted with 4-arylmethylene-2-phenyloxazol-5(4H)-ones **48** in the presence of acetic acid to give bicyclic pyridone derivatives **49** (Scheme 27) [41]. Acid catalysts were essential for the reaction.

In 2014, an efficient method for synthesis of pyrrolo[3,4-*e*]pyridine derivatives **51** (Scheme 28) was developed by reaction of HKAs **1** with 2,3-dioxopyrrolidines **50** [42]. The reaction proceeded smoothly in a short time under catalyst-free conditions. A mechanism involving aza–ene, imine–enamine tautomerization followed by cyclization was proposed.

Synthesis of fused pyrrole derivatives

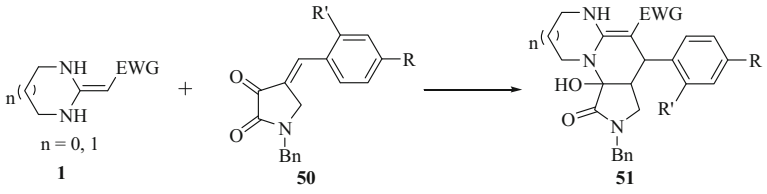
The pyrrole nucleus is featured in many natural products and drugs. When HKAs reacted with 1,2-bis-electrophiles, such as alkyl glyoxylate, *N*-alkyl maleimide, etc., multi-functional fused pyrroles were usually produced as a result. When HKAs **1** were treated with *N*-alkyl maleimide **52** in EtOH at room temperature, bicyclic pyrrolidinone **53** was formed via aza–ene and imine–enamine tautomerization followed by lactamization (Scheme 29) [43]. The reaction proceeded smoothly under catalyst-free conditions. It was interesting to note ring sizes had an effect on the outcome of the reaction and six-membered HKAs were proved to be the most reactive.

Lin's group reported HKAs **1** reacted with arylglyoxal monohydrates **54** and cyclohexane-1,3-diones **55** in water–ethanol medium under catalyst-free conditions [44]. The kinetically controlled product **56** was synthesized within 1 h (Scheme 30), and would transform into thermodynamically controlled products **57** over an additional 5 h (Scheme 31).

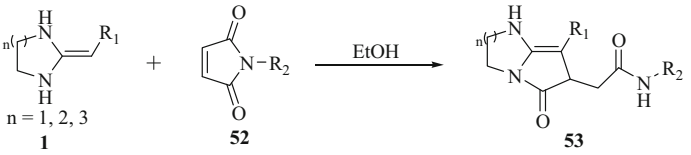
Similarly, HKAs **1** reacted with arylglyoxal monohydrates **54** and 1,3-diphenylpropane-1,3-dione under catalyst-free conditions [45] in ethanol to yield multi-functional fused pyrroles **58** in high yield (Scheme 32).

Thus, refluxing a mixture of HKAs **1**, arylglyoxal monohydrate **54**, and indoles **59** in ethanol in the presence of acetic acid led to the formation of highly functionalized bicyclic pyrrole derivatives **60** (Scheme 33) [46].

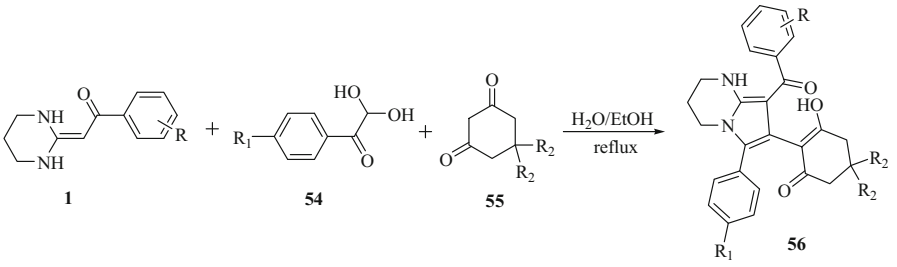
Yan discovered HKAs **1** reacted with acenaphthylene-1,2-dione **61** and ethyl trifluoroacetylacetate to afford polycyclic pyrroles **62** bearing four consecutive quaternary stereocenters (Scheme 34) [47]. Most of the products were generated with diastereoselectivity up to 99:1. An efficient synthesis of oxa-aza[3.3.3]propellanes **63** (Scheme 35) [48] were developed via one-pot four-component reaction involving ninhydrin, malononitrile, diamines and nitroketene dithioacetal. The reaction proceeded by an attack of nitroketene aminals generated in situ from the



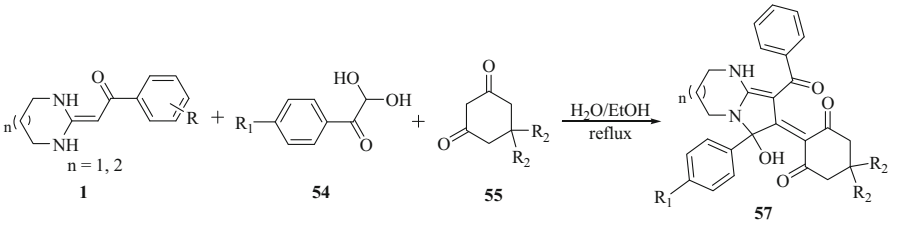
Scheme 28 Synthesis of pyrrolo[3,4-*e*]pyridine derivatives



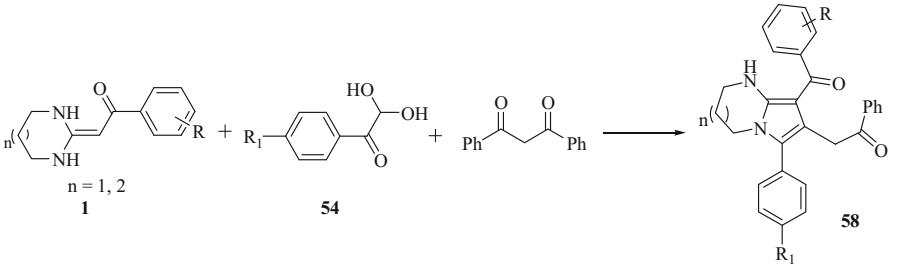
Scheme 29 Synthesis of bicyclic pyrrolidinone



Scheme 30 Synthesis of highly functionalized fused pyrrole derivatives



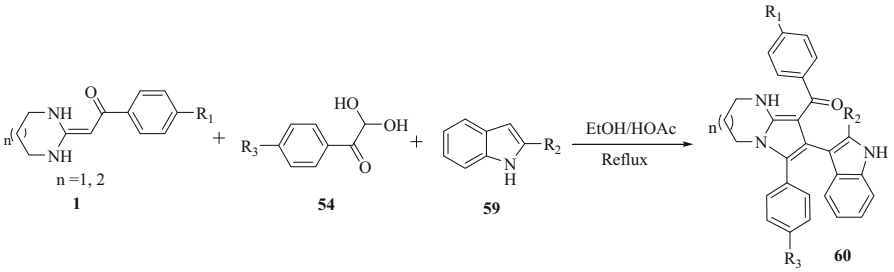
Scheme 31 Synthesis of highly functionalized fused pyrrole derivatives



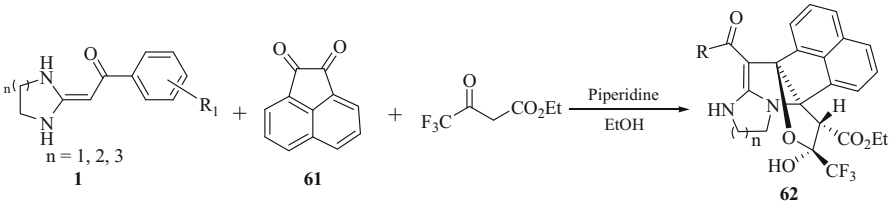
Scheme 32 Synthesis of multi-functional fused pyrroles

addition of various diamines to a Knoevenagel adduct of malononitrile with ninhydrin followed by sequential cyclization.

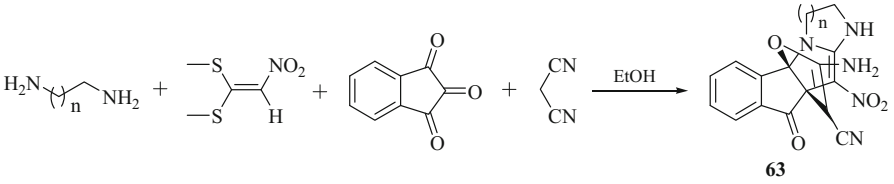
It was found that six- or seven-membered HKAs reacted with ethyl 2,3-diiodoacrylate or diethyl 2,3-diiodofumarate **64** to yield bicyclic pyrroles **65**



Scheme 33 Synthesis of bicyclic pyrrole derivatives

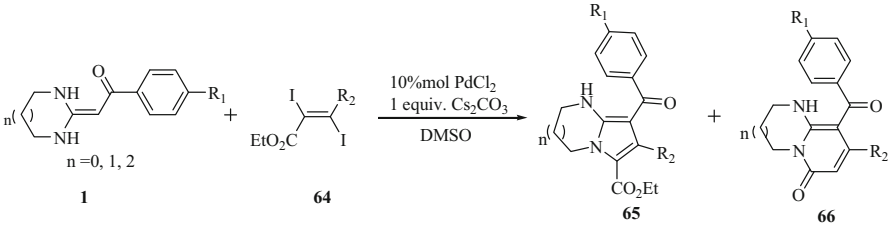


Scheme 34 Synthesis of polycyclic pyrroles



Scheme 35 Synthesis of oxa-aza[3.3.3]propellanes

catalyzed by $PdCl_2$ in the presence of Cs_2CO_3 [49]. However, when five-membered HKAs were used as substrates, a series of bicyclic pyridones **66** were obtained under the same conditions as above in moderate yield (Scheme 36). This may be due to variations in the nucleophilicity of HKAs with different ring sizes. Usually, six-membered HKAs were more reactive than other HKAs.



Scheme 36 Synthesis of bicyclic pyrroles and pyridones

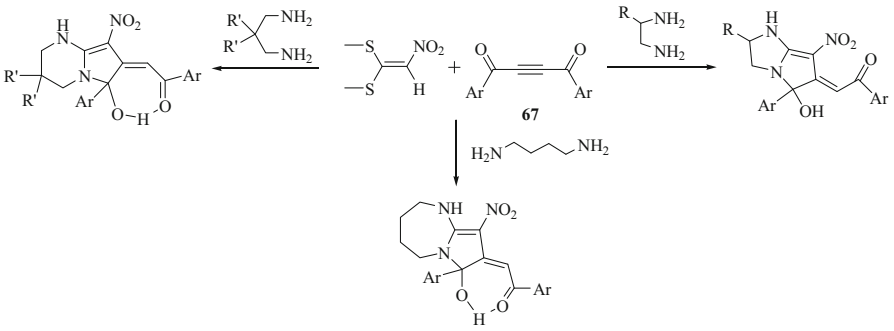
Alizadeh reported three-component reaction of nitroketene dithioacetal with 1,n-diamines in the presence of diaroylacetylene **67** or acetylenedicarboxylate **68** afforded fully substituted 1*H*-pyrrolo[1,2-a]-fused 1,3-diazaheterocycles (Scheme 37) [50] or bicyclic pyrrolidinones **69** (Scheme 38) [51] in good to excellent yields. They also reported [52] three-component reaction of 1,n-diamines, nitroketene dithioacetal and ninhydrin in aqueous media gave indeno[2′,1′:4,5]pyrrolo [1,2-*a*]-fused 1,3-diaza-heterocycles **70** in good yields (Scheme 39).

Synthesis of indole derivatives

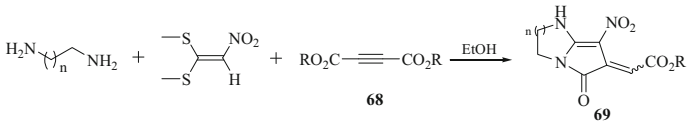
The indole skeleton is one of the most abundant and relevant heterocycles in natural products and drugs. In 2010, Lin's group developed an efficient synthesis of 1,3-diazaheterocycle-fused [1,2-*a*] indoles **72** (Scheme 40) by refluxing a reaction mixture of HKAs **1** and 1,4-benzoquinones **71** in the presence of acetic acid via a Nenitzescu strategy [53]. The reaction started with an attack of HKAs at the α-position of 1,4-benzoquinones **71**, then the adduct underwent imine–enamine tautomerization, subsequent condensation and elimination of H_2O to afford the target compound.

In 2014 it was found when HKAs **1** were treated with quinones **73** in ethanol at room temperature, indolone derivatives **74** were produced in 30 min via an unexpected anti-Nenitzescu strategy (Scheme 41) [54]. The reaction started with aza–ene reaction of HKAs onto carbonyl of 1,4-benzoquinones **73**, then the adduct underwent imine–enamine tautomerization, Michael addition, keto–enol tautomerization and oxidation to afford the target compound. The origin of site selectivity was explained according to the computational results.

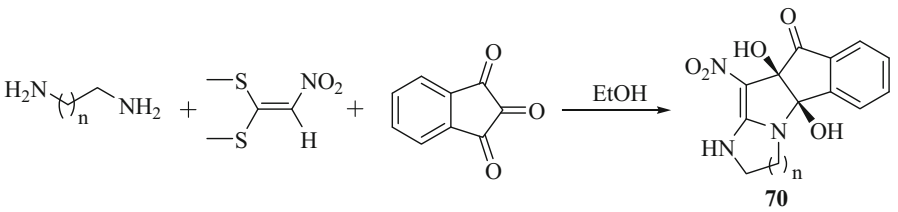
In 2015, they also found HKAs **1** could be treated with halogenated quinones **75** without a catalyst in acetone at room temperature to yield fused [1,2-*a*]indolone derivatives **76** via a Nenitzescu strategy (Scheme 42) [55]. It should be noted ring



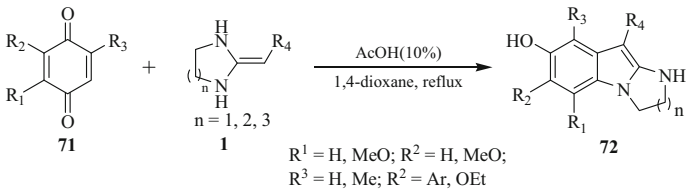
Scheme 37 Synthesis of 1*H*-pyrrolo[1,2-a]-fused 1,3-diazaheterocycles



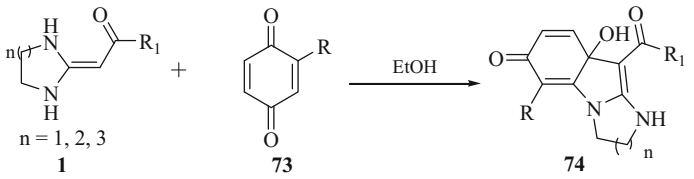
Scheme 38 Synthesis of bicyclic pyrrolidinones



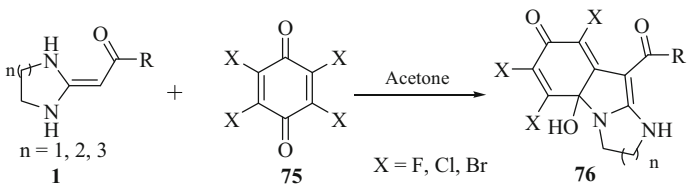
Scheme 39 Synthesis of indeno[2′, 1′:4,5]pyrrolo[1,2-*a*]-fused 1,3-diazaheterocycles



Scheme 40 Synthesis of 1,3-diazaheterocycle-fused [1,2-*a*] indoles



Scheme 41 Synthesis of indolone derivatives



Scheme 42 Synthesis of fused [1,2-*a*]indolone derivatives

sizes and the electron-withdrawing property of the halides had an obvious effect on reaction yield. Six- and seven-membered HKAs were proved to be more reactive than five-membered HKAs. The halides with a stronger electron-withdrawing property usually gave higher yields.

In 2009, Zeng et al. [56] developed a convenient electrochemical approach for the synthesis of fused indole derivatives containing active hydroxyl groups from catechols **78** and HKAs **77** (Scheme 43).

Koca developed a convenient procedure for the preparation of isoindole derivatives **83** (Scheme 44). Heating a mixture of HKAs **81** with 2 equiv. of acetylenic esters **68** in the presence of 4-dimethylaminopyridine (DMAP) for 30 min led to the formation of a fused isoindole derivative **3** [57]. A possible reaction scenario was proposed.

Synthesis of coumarin derivatives

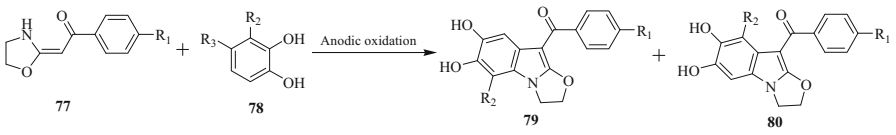
Coumarin derivatives are a structural framework in a large number of bioactive natural products. In 2010, Lin's group reported HKAs **1** reacted with coumarin derivatives **84** catalyzed by potassium hexamethyldisilazane (KHMDS) in dioxane under microwave irradiation to yield a series of polycyclic coumarin derivatives (Scheme 45) [58]. A mechanism involving 1,4-Michael addition, imine–enamine tautomerization, cyclocondensation and aromatization was proposed.

A regioselective method for synthesis of fused coumarin derivatives **86** was developed by reaction of HKAs **1** with 4-chloro-3-formylcoumarin **85** (Scheme 46) [59]. The reaction proceeded smoothly in EtOH catalyzed by Et_3N via aza–ene, imine–enamine tautomerization, cycloaddition and dehydration to afford the product in excellent yields.

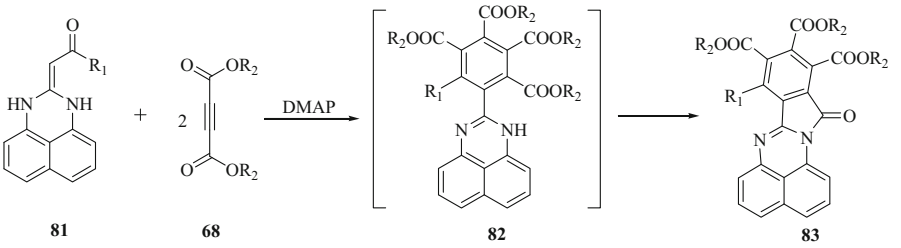
Yan developed a facile approach for the synthesis of tetracycloisocoumarins **88** based on AcOH-catalyzed cyclocondensation and rearrangement of HKAs **1** with 2,2-dihydroxy-2*H*-indene-1,3-dione **87** (Scheme 47) [60].

Synthesis of miscellaneous heterocycles

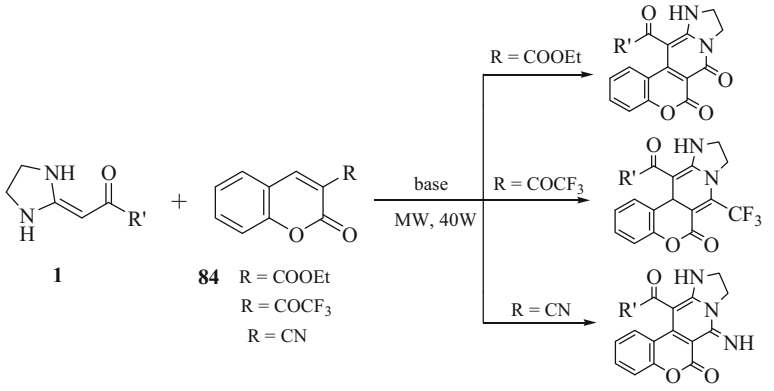
Zhu's group found that fluoroalkanesulfonyl azide **89** reacted readily with HKAs **1** at room temperature, and developed an quantitative synthesis of 1,3-diazaheterocycle-fused 1,2,3-triazoles **90** by 1,3-dipolar cycloaddition of HKAs with fluoroalkanesulfonyl azide **89** (Scheme 48) [61]. This method was applicable to



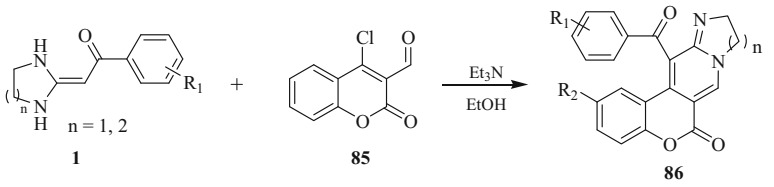
Scheme 43 Synthesis of fused indole derivatives



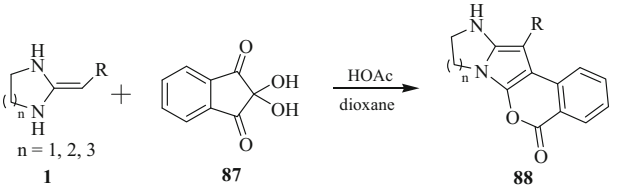
Scheme 44 Synthesis of isoindole derivatives



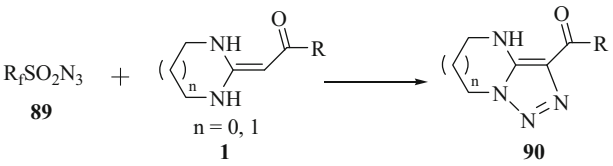
Scheme 45 Synthesis of coumarin derivatives



Scheme 46 Synthesis of fused coumarin derivatives



Scheme 47 Synthesis of tetracycloisocoumarins



Scheme 48 Synthesis of 1,3-diazaheterocycle-fused 1,2,3-triazoles

various HKAs and fluoroalkanesulfonyl azides and is suitable for combinatorial and parallel synthesis in new drug discovery.

Xu reported five-membered HKAs **1** reacted with ethyl 2-(bromomethyl)benzoate **91** in refluxing acetonitrile to afford the *C*-benzylated products **92** which underwent intramolecular cyclization under alkaline conditions to produce fused benzazepinones **93** (Scheme 49) [62].

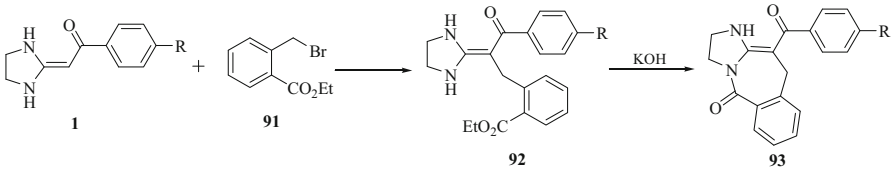
Lin's group developed a concise and efficient route for the synthesis of highly substituted imidazopyrroloquinoline derivatives **96** by simply refluxing a reaction mixture of different types of isatins **94** and HKAs **95** under catalysis of acetic acid (Scheme 50) [63]. A library of highly substituted imidazopyrroloquinoline derivatives was rapidly constructed as a result. A mechanism of the cascade reaction was proposed.

In 2013, Zhang discovered heating a mixture of HKAs **1** with 2-chloroquinoline-3-carbaldehydes **97** under the catalysis of piperidine at 75 °C afforded 1,3-diazaheterocycle-fused[1,2-a] [1, 8] naphthyridine derivatives **98** (Scheme 51) [64]. The reaction was studied via a joint experimental–computational approach.

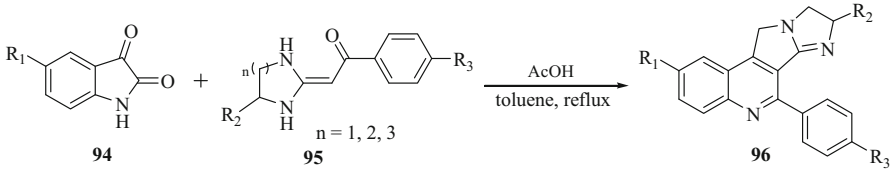
Yan reported HKAs **39** underwent substitution–cyclization reaction with polyhalo isophthalonitrile **99** in the presence of *t*-BuOK to afford 1,3-diazaheterocycle-fused [1,2-*b*]isoquinolin-1(2*H*)-imines **100**, which could be hydrolyzed to give highly functional polyhalo 1,3-diazaheterocycle-fused [1,2-*b*]isoquinolin-1(2*H*)-ones **101** (Scheme 52) [65].

Yaqub [66] developed a novel method for the synthesis of tetracyclic fused-ring heterocycles **103** (Scheme 53), which are closely related to circumdatin alkaloids, via the reaction of substituted 3-formylchromone **102** with HKAs. The solvent polarity was found to play an important role on the yield of tetracyclic fused-ring heterocycles.

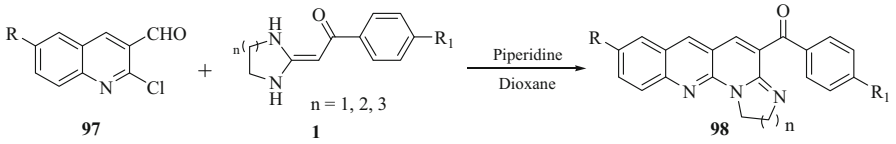
Alizadeh [67] developed a concise and efficient method for the synthesis of pyrimido[1,6-*a*]pyrimidine and imidazo[1,2-*c*]pyrimidine derivatives **105** by simply



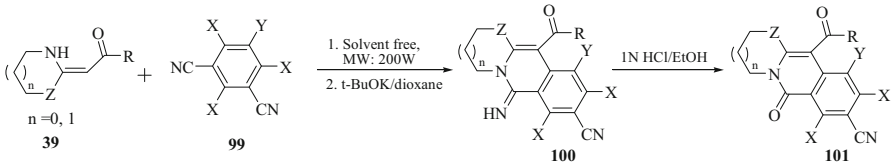
Scheme 49 Synthesis of fused benzazepinones



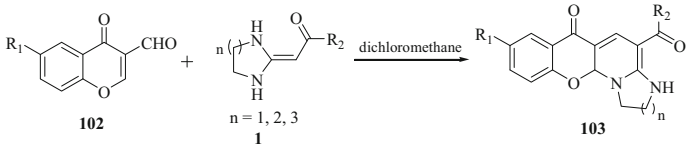
Scheme 50 Synthesis of imidazopyrroloquinoline derivatives



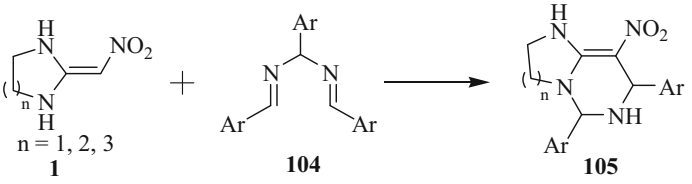
Scheme 51 Synthesis of fused[1,2-*a*] [1, 8] naphthyridine derivatives



Scheme 52 Synthesis of fused [1,2-*b*]isoquinolin-1(2*H*)-imines

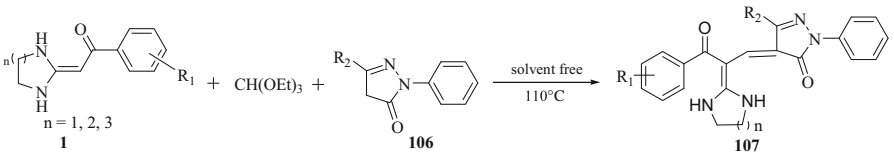


Scheme 53 Synthesis of tetracyclic fused-ring heterocycles

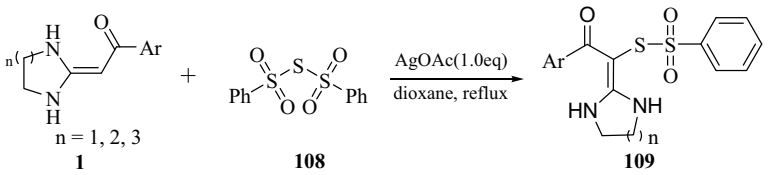


Scheme 54 Synthesis of pyrimido[1,6-*a*]pyrimidine and imidazo[1,2-*c*]pyrimidine

refluxing a reaction mixture of HKAs **1**, or generated HKAs in situ from the addition of various diamines to nitroketene dithioacetal and *N*,*N*′-bis(arylmethylidene)arylmethane **104** (Scheme 54).



Scheme 55 Synthesis of 1*H*-pyrazol-5(4*H*)-one-based heterocyclic ketene aminal



Scheme 56 Synthesis of 2-benzenesulfonothiol-HKAs

Yan developed an efficient one-pot synthesis of novel 1*H*-pyrazol-5(4*H*)-one-based heterocyclic ketene aminal **107** by refluxing a mixture of HKAs **1**, 1-phenyl-1*H*-pyrazol-5(4*H*)-ones **106** and triethoxymethane under solvent-free and catalyst-free conditions (Scheme 55) [68].

A series of 2-benzenesulfonothiol-HKAs **109** (Scheme 56) were prepared via a silver(I)-mediated direct sulfenylation of HKAs with benzenesulfonic thioanhydride **108** [69]. The preparation method was efficient and convenient.

Conclusions

Possessing three reactive sites including α-carbon, nitrogen and oxygen in one molecule, HKAs could react with a variety of biselectrophiles, even 1,3-dipoles, to produce novel heterocyclic compounds hardly accessible by other methods. Recent developments in the preparation of various heterocyclic nuclei by reactions of HKAs were reviewed. From a chemist's point of view, MCRs closely approach the concept of ideal synthesis. Considering the importance of chirality, MCRs and synthesis of chiral HKAs and their asymmetric reactions will draw the attention from more and more chemists; on the other hand, as people are more aware of environmental protection, green HKA chemistry will have a bright future.

Acknowledgments This work was supported by the National Natural Science Foundation of China (no. 21575112) and funding from the Education Department of Shaanxi Province (15JS091).

References

1. Z.T. Huang, M.X. Wang, Prog. Nat. Sci. **12**, 249 (2002)
2. Z.T. Huang, Z.R. Liu, Chem. Ber. **122**, 95 (1989)
3. L.B. Wang, C.Y. Yu, Z.T. Huang, Synthesis **26**, 1441 (1994)
4. Z.T. Huang, L.H. Tzai, Chem. Ber. **119**, 2208 (1986)

5. Z.T. Huang, Z.R. Liu, Heterocycles **24**, 2247 (1986)
6. Z.T. Huang, M.X. Wang, J. Chem. Soc. Perkin Trans. **1**, 1085 (1993)
7. R.C.F. Jones, P. Patel, S.C. Hirst, M.J. Smallridge, Tetrahedron **54**, 6191 (1998)
8. R.C.F. Jones, P. Patel, S.C. Hirst, Tetrahedron Lett. **30**, 5361 (1989)
9. J.H. Zhang, M.X. Wang, Z.T. Huang, Tetrahedron Lett. **39**, 9237 (1998)
10. J.H. Zhang, M.X. Wang, Z.T. Huang, J. Chem. Soc. Perkin Trans. **1**, 2087 (1999)
11. R.C.F. Jones, P. Patel, S.C. Hirst, I. Turne, Tetrahedron **53**, 11781 (1997)
12. J.H. Zhang, M.X. Wang, Z.T. Huang, J. Chem. Soc. Perkin Trans. **1**, 321 (1999)
13. K.M. Wang, S.J. Yan, J. Lin, Eur. J. Org. Chem. **79**, 1129–1145 (2014)
14. J.P. Liao, T. Zhang, C.Y. Yu, Z.T. Huang, Synlett **18**, 761–764 (2007)
15. M. Yaqub, C.Y. Yu, Y.M. Jia, Z.T. Huang, Synlett **19**, 1357–1360 (2008)
16. W.Y. Xu, Y.M. Jia, J.K. Yang, Z.T. Huang, C.Y. Yu, Synlett **21**, 1835–1840 (2010)
17. C.Y. Yu, P.H. Yang, M.X. Zhao, Z.T. Huang, Synlett **17**, 1835–1840 (2006)
18. P.H. Yang, W.Z. Wang, Y.S. Duan, C.T. Qu, Q.Z. Zhang, Heterocycl. Commun. **19**(3), 167–169 (2013)
19. Y.L. Ma, K.M. Wang, X.R. Lin, S.J. Yan, J. Lin, Tetrahedron **70**, 6578–6584 (2014)
20. A. Alizadeh, A. Rezvanian, C. R. Chim. **17**, 103–107 (2014)
21. A. Alizadeh, T. Firuzyar, A. Mikaeili, J. Heterocycl. Chem. **50**, 676–679 (2013)
22. L.R. Wen, Q.C. Sun, H.L. Zhang, M. Li, Org. Biol. Chem. **11**(42), 7276–7288 (2013)
23. F.C. Yu, R. Huang, H.C. Ni, J. Fan, S.J. Yan, J. Lin, Green Chem. **15**, 453–462 (2013)
24. X.B. Chen, X.M. Liu, R. Huang, S.J. Yan, J. Lin, Eur. J. Org. Chem. **78**, 4607–4613 (2013)
25. A. Alizadeh, T. Firuzyar, A. Mikaeili, Synthesis **42**, 3913–3917 (2010)
26. L.R. Wen, C.Y. Jiang, M. Li, L.J. Wang, Tetrahedron **67**, 293–302 (2011)
27. L.R. Wen, C. Liu, M. Li, L.J. Wang, J. Org. Chem. **75**, 7605–7614 (2010)
28. M. Li, Z.M. Zhou, L.R. Wen, Z.X. Qiu, J. Org. Chem. **76**, 3054–3063 (2011)
29. M. Li, P. Shao, S.W. Wang, W. Kong, L.R. Wen, J. Org. Chem. **77**, 8956–8967 (2012)
30. V.J. Ram, N. Agarwal, A. Sharon, P.R. Maulik, Tetrahedron Lett. **43**, 307–310 (2002)
31. A. Sharon, R. Prantap, P.R. Maulik, V.J. Ram, Tetrahedron **61**, 3781–3787 (2005)
32. X.S. Shao, Z.P. Xu, X.F. Zhao, X.Y. Xu, L.M. Tao, Z. Li, X.H. Qian, J. Agric. Food Chem. **58**, 2690–2695 (2010)
33. S. Chakrabarti, K. Panda, N.C. Misra, H. Iia, H. Junjappa, Synlett **16**, 1437–1441 (2005)
34. A. Alizadeh, A. Rezvanian, Helv. Chim. Acta **95**, 152–156 (2012)
35. A. Alizadeh, A. Rezvanian, Synlett **22**, 1105–1108 (2011)
36. A. Alizadeh, A. Mikaeili, T. Firuzyar, M. Ahmadi, Helv. Chim. Acta **94**, 1343–1346 (2011)
37. A. Alizadeh, R. Ghanbaripour, L.G. Zhu, Synth. Commun. **43**, 2575–2582 (2013)
38. S.J. Yan, Y.F. Niu, R. Huang, J. Lin, Synlett **20**, 2821–2824 (2009)
39. S.J. Yan, Y.L. Chen, L. Liu, N.Q. He, J. Lin, Green Chem. **12**, 2043–2052 (2010)
40. F.C. Yu, S.J. Yan, R. Huang, Y.J. Tang, J. Lin, RSC Adv. **1**, 596–601 (2011)
41. X.B. Chen, D.D. Zhu, X.Y. Wang, S.Y. Yan, J. Lin, Tetrahedron **69**, 9224–9236 (2013)
42. X.B. Chen, L. Zhu, L. Fang, S.J. Yan, J. Lin, RSC Adv. **4**, 9926–9934 (2014)
43. J. Liu, H.R. Zhang, X.R. Lin, S.J. Yan, J. Lin, RSC Adv. **4**, 27582–27590 (2014)
44. X.B. Chen, Z.C. Liu, L.F. Yang, S.J. Yan, J. Lin, ACS Sustain. Chem. Eng **2**, 1155–1163 (2014)
45. X.B. Chen, S.J. Yan, A. Su, W. Liu, J. Lin, Tetrahedron **71**, 4745–4751 (2015)
46. X.B. Chen, X.Y. Wang, D.D. Zhu, S.J. Yan, J. Lin, Tetrahedron **70**, 1047–1054 (2014)
47. X.B. Chen, Z.C. Liu, X.R. Lin, R. Huang, S.J. Yan, J. Lin, ACS Sustain. Chem. Eng. **2**, 2391–2398 (2014)
48. A. Rezvanian, A. Alizadeh, Tetrahedron **68**, 10164–10168 (2012)
49. L. Hu, K.M. Wang, M. Zhao, X.R. Lin, H.Y. Zhu, S.J. Yan, J. Lin, Tetrahedron **70**, 4478–4484 (2014)
50. A. Alizadeh, A. Rezvanian, Y. Deng, Tetrahedron **66**, 9933–9937 (2010)
51. A. Alizadeh, A. Mikaeili, J. Heterocycl. Chem. **51**, 527–531 (2014)
52. A. Alizadeh, A. Zarei, A. Rezvanian, Synthesis **43**, 497–501 (2011)
53. L.J. Yang, S.J. Yan, W. Chen, J. Lin, Synthesis **42**, 3536–3544 (2010)
54. B. Zhou, Z.C. Liu, W.W. Qu, R. Yang, X.R. Lin, S.J. Yan, J. Lin, Green Chem. **16**, 4359–4370 (2014)
55. F.C. Yu, X.P. Hao, X.R. Lin, S.J. Yan, J. Lin, Tetrahedron **71**, 4084–4089 (2015)
56. C.C. Zeng, F.J. Liu, D.W. Ping, L.M. Hu, Y.L. Cai, R.G. Zhong, J. Org. Chem. **74**, 6386–6389 (2009)

57. S.H. Űngoren, İ. Koca, F. Yilmaz, Tetrahedron **67**, 5409–5414 (2011)
58. S.J. Yan, J. Lin, Chin. J. Org. Chem. **30**(3), 465–468 (2010)
59. F.C. Yu, Z.Q. Chen, X.P. Hao, S.J. Yan, R. Huang, J. Lin, RSC Adv. **4**, 6110–6115 (2014)
60. S.J. Yan, Y.L. Chen, L. Liu, Y.J. Tang, J. Lin, Tetrahedron Lett. **52**, 465–467 (2011)
61. J.W. Gu, W.T. Xiong, Z.H. Zhang, S.Z. Zhu, Synthesis **43**, 1717–1722 (2011)
62. Z.H. Xu, Y.F. Jie, M.X. Wang, Z.T. Huang, Synthesis **34**, 523–527 (2002)
63. F.C. Yu, S.Y. Yan, L. Hu, Y.C. Wang, J. Lin, Org. Lett. **13**(18), 4782–4785 (2011)
64. Y.C. Zhang, Z.C. Liu, R. Yang, J.H. Zhang, S.J. Yan, J. Lin, Org. Biomol. Chem. **11**, 7276–7288 (2013)
65. S.Y. Yan, C. Huang, C.X. Su, Y.F. Ni, J. Lin, J. Comb. Chem. **12**, 91–94 (2010)
66. M. Yaqub, R. Perveen, Z. Shafiq, H. Pervez, M.N. Tahirb, Synlett **23**, 1357–1360 (2012)
67. A. Alizadeh, J. Mokhtari, M. Ahmadi, Tetrahedron **68**, 319–322 (2012)
68. F.C. Yu, Z.Q. Chen, X.P. Hao, X.Y. Jiang, S.Y. Yan, J. Lin, RSC Adv. **3**, 13183–13192 (2013)
69. T.T. Liu, X.R. Lin, R. Huang, L.F. Yang, S.J. Yan, J. Lin, Tetrahedron **70**, 8858–8862 (2014)