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β-Ketothioamides: efficient reagents in synthesis of heterocycles

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β-ketothioamides (KTAs) are versatile building blocks for the rapid construction of various heterocyclic compounds. In the past decade, a number of successful reactions based on KTAs have been developed for the construction of heterocyclic skeletons under mild conditions. This minireview focuses on the annulation reactions of KTAs with dielectrophilic or dinucleophilic reagents. Multicomponent reactions using KTAs to construct various heterocycles are also the major contents in this review.

1. Introduction

β-ketothioamides (KTAs), also referred to as ketene *N*,*S*-acetals, have proven to be fascinating and versatile synthons in construction of heterocycles. Reactions of KTAs with a variety of dielectrophilic or dinucleophilic reagents have been applied to construct various heterocycles. As shown in **Figure 1**, β-ketothioamides have been shown various chemical properties with intriguing five reactive centers. Two nucleophilic centers localize on the heteroatoms (sulfur and nitrogen). A potential nucleophilic center of the α-carbon behaves as a Michael addition donor. The carbonyl and thiocarbonyl groups are two electrophilic centers.

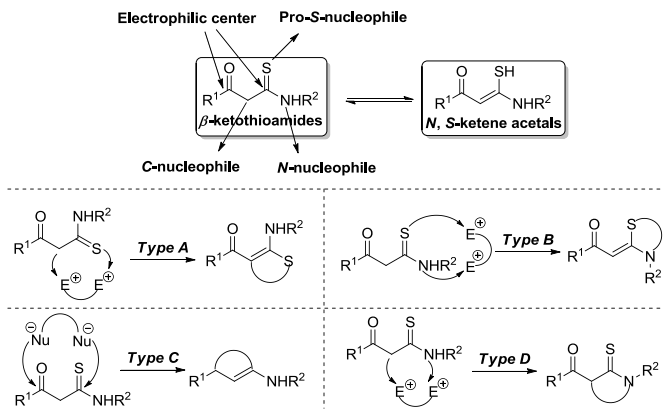


Fig. 1 Structural features and reaction types of β-ketothioamides

Base on the reports in the literatures, the reactions of β-ketothioamides with dielectrophilic or dinucleophilic reagents may divide into four different types (A−D), depending on the nature of the substrates and the reaction conditions. The sulfur atom and nucleophilic α-carbon of KTAs could react with dielectrophilic reagents to obtain substituted thiophene derivatives (**Type A**). Thiazolidines could be formed when sulfur and nitrogen atom of KTAs react with dielectrophilic reagents (**Type B**). When dinucleophilic reagents react with the carbonyl and thiocarbonyl groups of KTAs, fused heterocycles could be formed regioselectively (**Type C**). The amino group and the α-carbon of KTAs react with dielectrophilic reagents could generate pyrroles or pyridines (**Type D**).

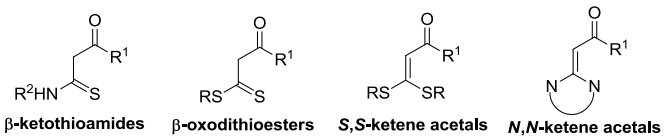
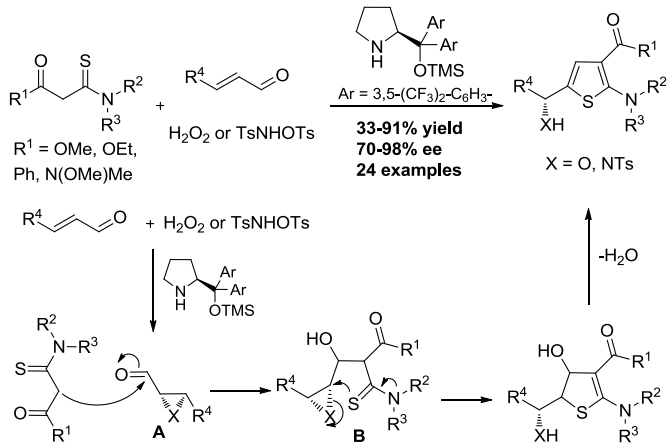


Fig. 2 Structures of several synthons

In 2003, Jagodziński reported a review regarding the chemistry of thioamides, in which only three examples involving β-ketothioamides were reported.[1] Recently, functionalized β-ketothioamides, β-oxodithioesters,[2] *S*,*S*-ketene acetals,[3] and *N*,*N*-ketene acetals[4] have received much attention as versatile building blocks in organic synthesis (**Figure 2**). Among them, the latter three synthons have been reviewed. However, to the best of our knowledge, β-ketothioamides have never been reviewed systematically up to now. The past decade has witnessed a rapid progress in the KTAs chemistry, especially in the synthesis of functionalized heterocyclic compounds via two-component tandem reactions and multicomponent reactions. This minireview mainly summarizes the progress of KTAs in the last decade involving both the research work of our group and other laboratories. The aim was to give an overview of the versatile reactivity of KTAs, and it is divided into six sections according to the reaction types.

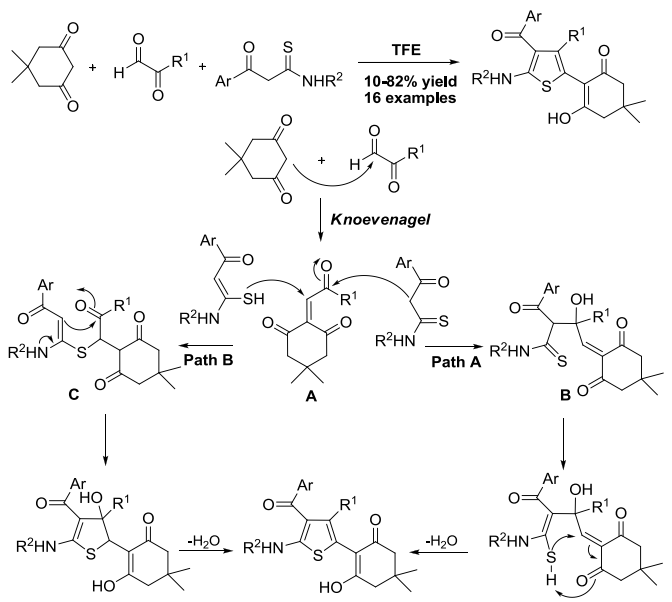
2. Synthesis of thiophene derivatives (Type A)

The thiophene core is an important privileged heterocycle in numerous biologically active pharmacophores and natural products.[5] The reactions of the nucleophilic sites (S and α-C atoms) of KTAs with dielectrophilic reagents could form miltisubstituted thiophene derivatives regioselectively.



Scheme 1 Synthesis of optically active thiophenes from KTAs and α,β-unsaturated aldehydes

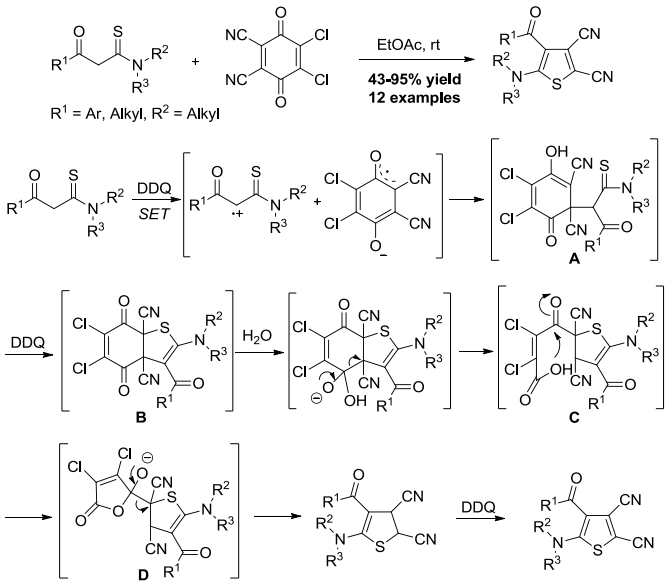
In 2012, Jørgensen and coworkers developed a general methodology for the synthesis of optically active thiophenes from KTAs and α,β-unsaturated aldehydes via an organocatalytic one-pot cascade reaction.[6] This protocol involved a highly enantioselective amino-catalyzed epoxidation or aziridination reaction, and an intramolecular *S*-cyclization. A possible mechanism of the reaction is shown in **Scheme 1**. First, enantioselective aziridine- or epoxy-aldehyde **A** is obtained with an organocatalyst. Then the α-carbon of β-ketothioamide attacks the aldehyde to form intermediate **B**. Finally, the desired thiophenes are obtained by intramolecular *S*-cyclization, tautomerization and H_2O elimination.



Scheme 2 Synthesis of thiophenes from KTAs with arylglyoxals and 5,5-dimethyl-1,3-cyclohexanedione

Recently, we developed an efficient and straightforward three-component synthetic protocol to synthesize tetrasubstituted thiophene derivatives from KTAs with arylglyoxals and 5,5-dimethyl-1,3-cyclohexanedione in CF_3CH_2OH within 15 min.[7] In this domino process, two C−C bonds, one C−N bonds and one new ring were concomitantly formed. The protocol has several features, such as high regioselectivity, high atom economy, transition-metal-free, short reaction time, and easy purification. No recrystallization or column chromatography were required, all the pure compounds were easily afforded by washing with EtOH/H_2O (1:1).

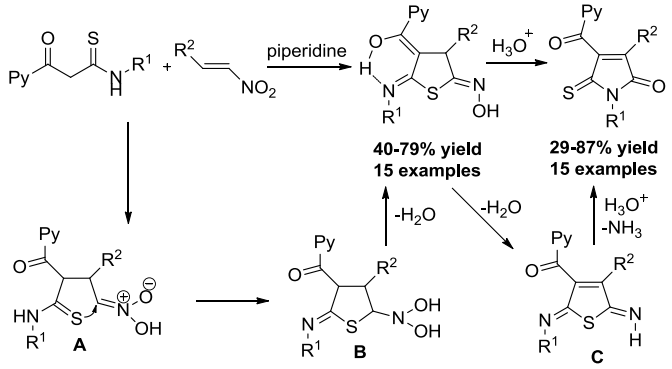
The results showed that most of reactions proceeded well and gave the corresponding thiophenes in moderate to good yields. The KTAs with either electron-donating or electron-withdrawing groups on the aroyl group showed similar reactivity. However, the reactions with KTAs bearing various substituents (R^2) on the *N*-aryl group afforded lower yields. Two plausible mechanisms for this reaction are proposed (**Scheme 2**). TFE played an important role in increasing the electrophilicity of the carbonyl group. First, intermediate **A** is formed through Knoevenagel-type reaction of arylglyoxals with 5,5-dimethyl-1,3-cyclohexane-dione. Then the α-carbon of β-ketothioamides attacks the carbonyl group of intermediate **A** to generate intermediate **B**, which undergoes intramolecular *S*-cyclization to give the desired compounds with elimination of H_2O (Path A). Alternatively, after tautomerization, the mercapto group of KTAs attacks the Knoevenagel adduct **A** through Michael addition to obtain intermediate **C**. The thiophene products are formed through intramolecular cyclization, followed by water elimination (Path B).



Scheme 3 Synthesis of thiophenes from KTAs with DDQ

A concise route for the synthesis of fully substituted thiophenes by a reaction of β-ketothioamides and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in EtOAc at room temperature was developed by Luo and coworkers.[8] For KTAs with various substituents (R^1 = alkyl, aryl or alkoxy group), the reactions proceeded smoothly and gave the desired products in moderate to good yields. A possible mechanism via a radical process is depicted in **Scheme 3**. Initially, the cross coupling intermediate **A** is

generated by a single electron transfer (SET) from carbonyl compound to DDQ. Then, due to the stronger nucleophilicity of the thiocarbonyl than the carbonyl group, the thiophene intermediate **B** is formed by a DDQ-mediated hydride abstraction and subsequent cyclization. Subsequently, ring-opening intermediate **C** is generated through water attacking. The furan-thiophene intermediate **D** is then formed by recyclization. Finally, the desired product is obtained by C−C bond cleavage to release 2,3-dichloromaleic anhydride and aromatization by a third equivalent of DDQ.

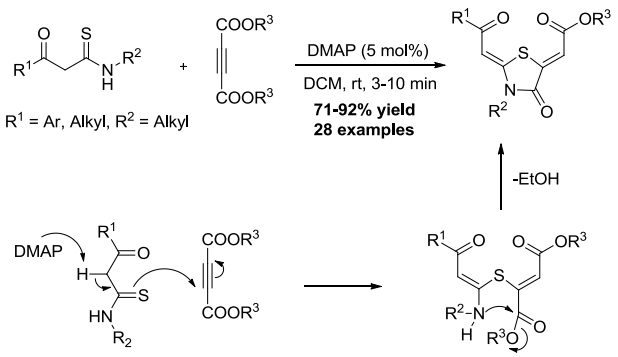


Scheme 4 Synthesis of thiophenes and pyrroles from KTAs with nitrostyrenes

In 2006, Bogdanowicz-Szwed and coworkers reported a protocol to synthesis tetrahydrothiophenes using pyridine substituent β-ketothioamides with nitrostyrenes under the catalysis of piperidine.[9] The KTAs substituted by 3-pyridyl group were more reactive (70-79% yields) than those containing 2- and 4-pyridyl groups (40-70% yields). As shown in **Scheme 4**, a plausible reaction mechanism involving Michael addition, intramolecular *S*-cyclization, and water elimination is proposed. Interestingly, the tetrahydrothiophenes could transform to the pyrrole derivatives when conc. HCl was added. A possible mechanism containing water elimination, imine group hydrolyzation, and Dimroth rearrangement is rationalized.

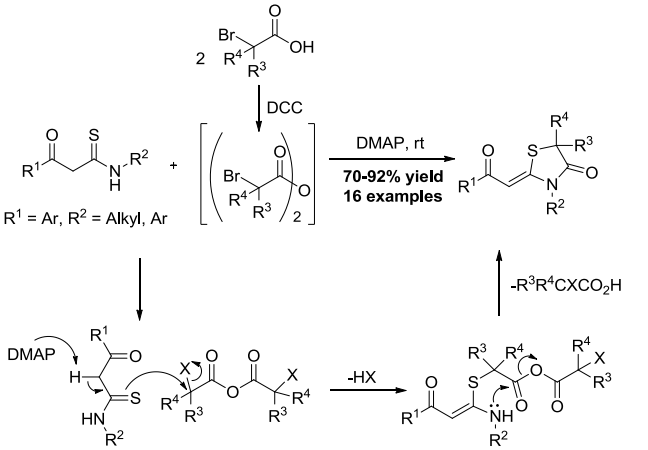
3. Synthesis of thiazolidine derivatives (Type B)

Thiazolidine is a prominent structural motif existed in numerous natural products and synthetic compounds, which possesses a wide range of biological activities, such as anti-inflammatory, antimicrobial and anti-HIV.[10]



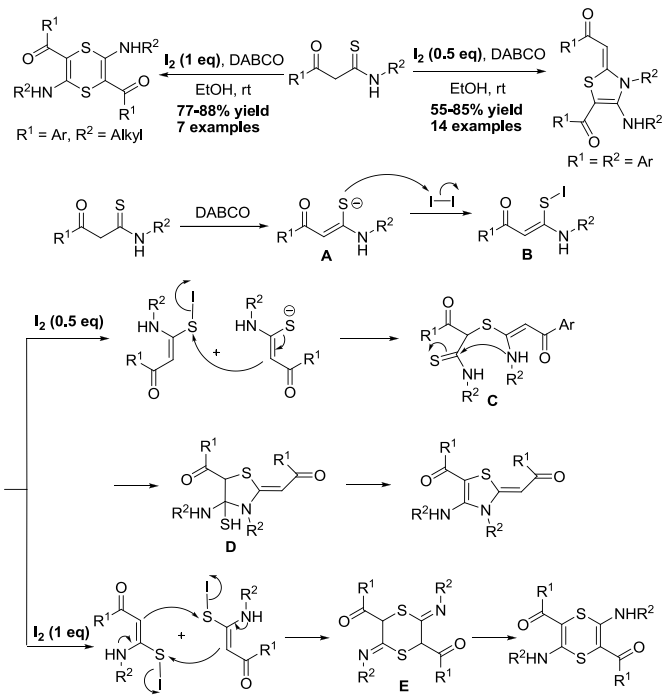
Scheme 5 Synthesis of 1,3-thiazolidin-4-ones from KTAs with alkynes

In 2014, Singh and coworkers reported a DMAP-promoted synthesis of functionalized 1,3-thiazolidin-4-ones by a reaction of β-ketothioamides with internal alkynes at room temperature (**Scheme 5)**.[11] The reaction may be proceeded via a nucleophilic attack of thiocarbonyl sulfur of KTAs on internal alkyne followed by a highly regioselective intramolecular *N*-cyclization procedure. The results demonstrated that the substituents of the KTAs had slight influence on the reactivity, and the reactions proceeded smoothly to afford the corresponding products in good yields.

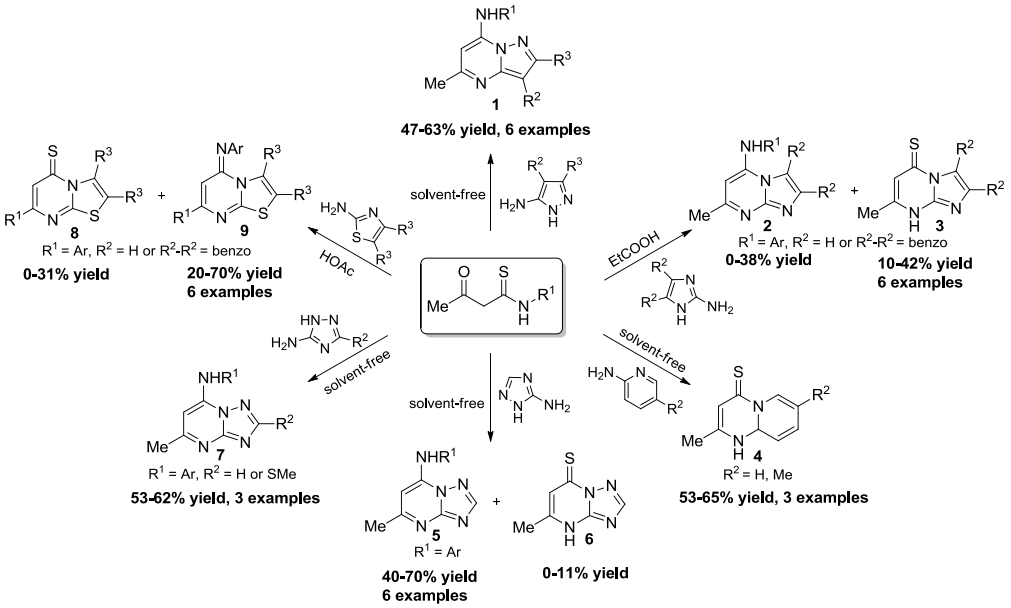


Scheme 6 Synthesis of 1,3-thiazolidin-4-ones from KTAs with *in situ* generated acid anhydride

As shown in **Scheme 6**, Singh and coworkers reported an one-pot synthesis of 1,3-thiazolidin-4-ones starting from β-ketothioamides with *in situ* generated acid anhydride from α-halocarboxylic acid in the presence of DCC at room temperature.[12] The features of this method involves forming C−S and C−N bonds and one ring in a single synthetic operation, mild reaction conditions and metal-free. A possible mechanism including nucleophilic attacking by thiocarbonyl sulfur of KTAs, followed by intramolecular *N*-cyclization processes is proposed.



Scheme 7 Synthesis of thiochromeno[2,3-*b*]pyridines from KTAs self-condensation



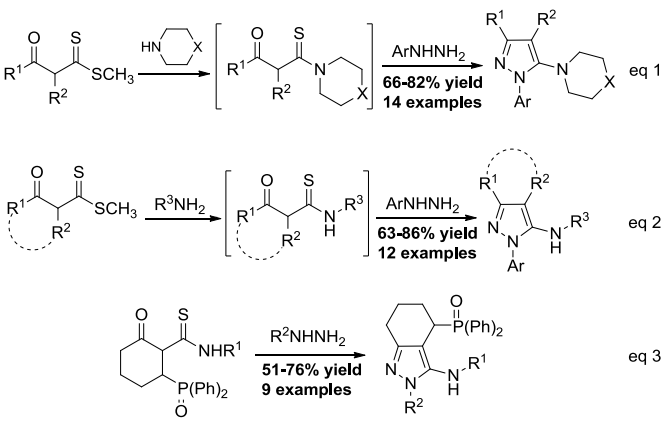
Scheme 8 Synthesis of fused heterocyclic compounds

Recently, we developed an efficient synthetic protocol to synthesize 1,3-thiazolines and 1,4-dithiines by self-condensation reactions of KTAs controlled by I_2 at room temperature.[13] In the presence of 0.5 equivalents I_2 the 1,3-thiazoline derivatives were obtained, and KTAs bearing either electron-donating or electron-withdrawing substituents on the N-phenyl ring or phenyl ring linked to the carbonyl group provided the corresponding products in good yields. However, when KTAs with alkyl amines were used and in the presence of 1 equivalents I_2, only the homocoupling product 1,4-dithiines were formed in good yields. The present synthesis shows fascinating properties such as high regioselectivity, short reaction times, mild reaction conditions, and easy purification.

A plausible mechanism for this reaction is proposed (**Scheme 7**). First, intermediate **A** is formed by deprotonation of KTAs in the presence of DABCO, which reacts with I_2 to generate intermediate **B**. When R^2 = aryl and the amount of I_2 is 0.5 equivalents, intermediate **C** is obtained by nucleophilic substitution of intermediate **A** with **B**. Subsequently, **C** undergoes an intramolecular cyclization to give intermediate **D**, which eliminates a molecule of H_2S to form of the 1,3-thiazolines. Whereas R^2 = alkyl and the amount of I_2 is 1 equivalent, two molecules of **B** react with each other through a nucleophilic substitution to give intermediate **E**, which generates 1,4-dithiine derivatives by tautomerization.

4. Synthesis of fused heterocycles (Type C)

As shown in **Scheme 8**, Britsun group reported a series of protocols to synthesize fused heterocycles from β-ketothioamides with various amino heterocycles through formal [3+3] cyclization. The reactions proceeded in type C pattern. When 5-amino-3,4-disubstituted pyrazoles reacted with KTAs, polysubstituted pyrazolo[1,5-*a*]pyrimidines **1** was obtained under solvent-free conditions.[14] Condensation of KTAs with 2-aminoimidazole or 2-aminobenzimidazole gave a mixture of 4-(arylamino) imidazo[1,2-*a*]pyrimidine **2** and imidazo[1,2-*a*]pyrimidine-5-thiones **3**. The ratio of the two products depended on the aryl substituents on the KTAs.[15] The imidazo[1,2-*a*]pyrimidine-5-thiones **3** were formed by nucleophilic attacking of the exocyclic amino group of 2-aminopyridines on the carbonyl group of KTAs, followed by intramolecular cyclization with elimination of aryl amine. However, the pyrido[1,2-*a*]pyrimidine-4-thiones **4** were obtained regioselectively through KTAs and 2-aminopyridines in acetic acid under a similar procedure.[16] When 5-amino-1,2,4-triazole was used to reacted with KTAs, a mixture of 1,2,4-triazolo[1,5-*a*]pyrimidines **5** and 1,2,4-triazolo[1,5-*a*]pyrimidine-7-thiones **6** were formed under solvent-free condition.[17] The ratio of the two products depended on the substituents in the KTAs and the solvent. Interestingly, only 1,2,4-triazolo[1,5-*a*]pyrimidines **7** were obtained when 3-amino-1,2,4-triazole was used as starting material to react with KTAs.[18] When 2-amino-1,3-thiazole reacted with KTAs in acetic acid, a mixture of 1,3-thiazolo[3,2-*a*]pyrimidine-5-thiones **8** and 5-arylimino-1,3-thiazolo[3,2-*a*]pyrimidines **9** were obtained.[19] The major product was the latter one.

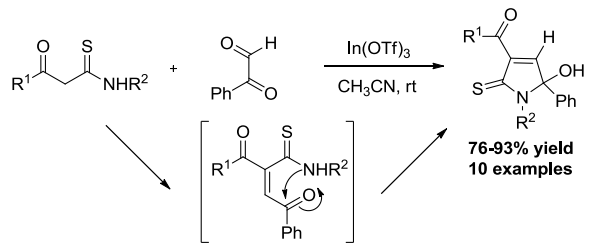


Scheme 9 Synthesis of pyrazoles and fused pyrazoles

Recently, a one-pot two-steps regioselective protocol for the synthesis of pyrazole derivatives was developed by Singh and coworkers.[20] The products were obtained from hydrazines with *in situ* generated β-Ketothioamides using β-oxodithioesters and amines. A variety of functionalized pyrazole (eq 1) and fused pyrazole (eq 2) derivatives were synthesized through this reaction. Fort and coworkers reported a similar protocol to generate the fused pyrazoles through phosphonate-containing cyclic KTAs with hydrazines (eq 3).[21] All of the products were obtained regioselectively in good yield, except for the reaction using methylhydrazine and KTAs (R^1 = Ph), which a mixture of isomers was formed.

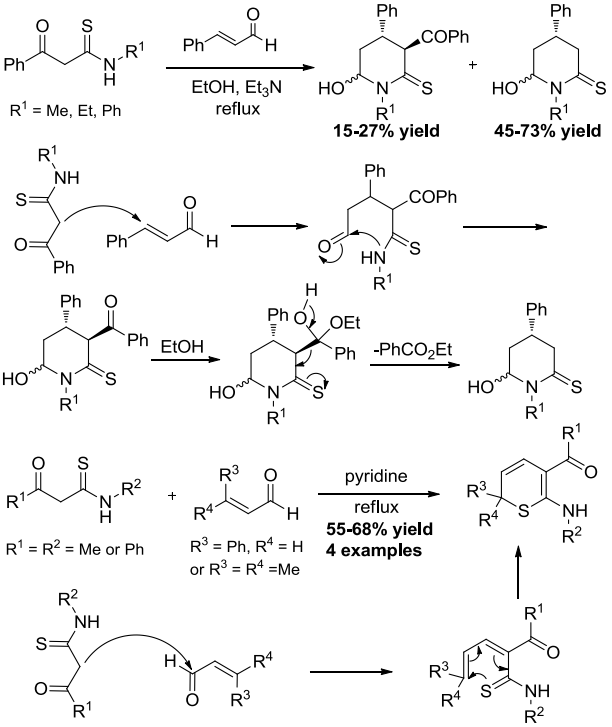
5. Synthesis of pyrroles or pyridines (Type D)

Recently, Singh and coworkers reported a method to synthesize functionalized pyrrol-2-thione derivatives by using KTAs and phenylglyoxal catalyzed by indium triflate through domino Knoevenagel condensation/cyclization cascade (**Scheme 10**).[22] Two new bonds (C–C and C–N), one quaternary carbon center and one five-membered ring were created by the two-component process. It was found that β-ketothioamides with either electron-donating or electron-withdrawing groups on the aroyl group were all good substrates for the reaction and gave the products in good to excellent yields.



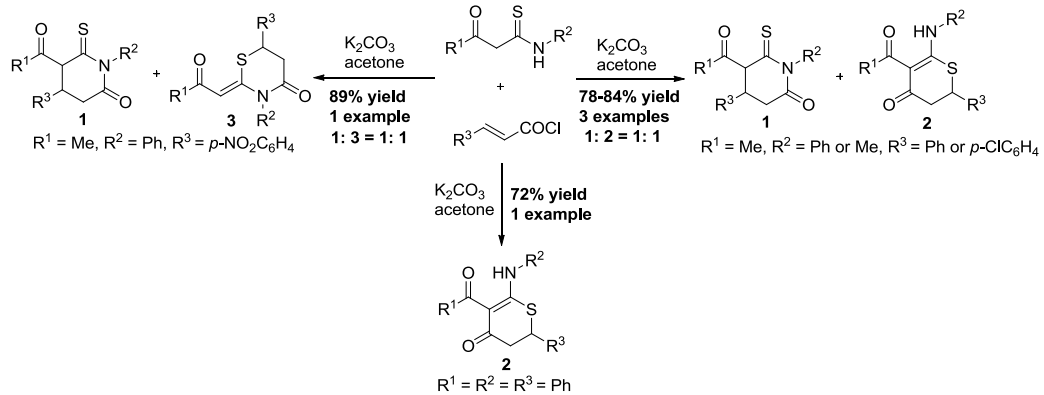
Scheme 10 Synthesis of pyrroles

As shown in **Scheme 11**, Jagodziński and coworkers reported the reactions of KTAs and α,β-unsaturated aldehydes in refluxing ethanol in the presence of catalytic amounts of triethylamine to obtain mixtures of diastereoisomeric 3-benzoylated and 3-unsubstituted 6-hydroxypiperidine-2-thione derivatives.[23] A plausible reaction mechanism involves stereoselective 1,4-addition of KTAs to α,β-unsaturated aldehydes, followed by intramolecular cyclization of the thioamide nitrogen to the aldehyde group. Interestingly, the major product is the debenzoylate product, which could be obtained by a retro-Claisen-type reaction. Furthermore, both the structure of the unsaturated aldehyde and the solvent affected the reaction. When methylcrotonaldehyde was used and ethanol was replaced with pyridine, the thiopyran derivatives were obtained through Claisen-type condensation, followed by 6π-electrocyclization.



Scheme 11 Synthesis of piperidine-2-thiones and thiopyrans

Since β-ketothioamides have several reaction centers, sometimes the products were mixtures. In 2006, Britsun and coworkers developed a reaction using KTAs and 3-aryl-2-propenoyl chlorides as starting materials (**Scheme 12**).[24] The products and ratios were different when changing the substituents of the starting materials. 6-Thioxopiperidin-2-ones **1** and 4*H*-thiopyran-4-ones **2** were formed in1:1 ratio when using 3-oxo-*N*-phenylbutanethioamide and 3-phenyl-2-propenoyl chloride or 3-(4-chlorophenyl)-2-propenoyl



Scheme 12 Synthesis of heterocycles from KTAs with 3-aryl-2-propenoyl chlorides

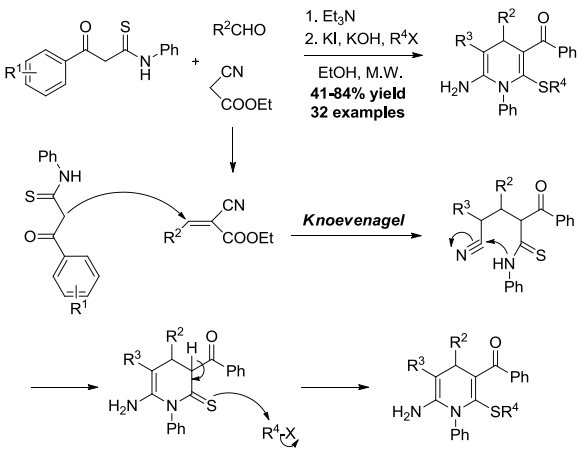
chloride as materials in acetone in the presence of K_2CO_3. However, when condensation of KTAs with 3-(4-nitrophenyl)-2-propenoyl chloride, 6-thioxopiperidin-2-one **1** and 4*H*-1,3-thiazin-4-one **3** were obtained in 1:1 ratio. Only 4*H*-thiopyran-4-one **2** was obtained when KTAs reacted with 3-oxo-3-*N*-diphenylpropanethioamide.

6. Synthesis of heterocyclic compounds via multi-component reactions

Multicomponent reactions (MCRs) are important procedures for generating high levels of diversity because they utilize at least three building blocks to be combined.[25] They can be considered as a subclass of domino reactions as they are usually mixed all starting materials in one pot under the reaction conditions. Since several substrates are put together in one-pot, the molecular complexity is built up very rapidly, and there is also the possibility of generating manifold heterocycles. MCRs are an important strategy in the synthesis of heterocyclic scaffolds as well as in the total synthesis of natural products. The diversity and easy accessibility to a large number of compounds means that MCRs represent a very important tool in modern drug discovery.

MCRs utilizing functionalized KTAs as building blocks are getting more attentions due to their versatile reactivity to achieve a wide array of structural diversity. Recently, our group developed many multicomponent reactions based on KTAs, which allowed the synthesis of functionalized 1,4-dihydropyridines, thiochromeno[2,3-*b*]pyridines, chromeno[2,3-*b*]quinolines, and so on.

6.1 1,4-Dihydropyridines

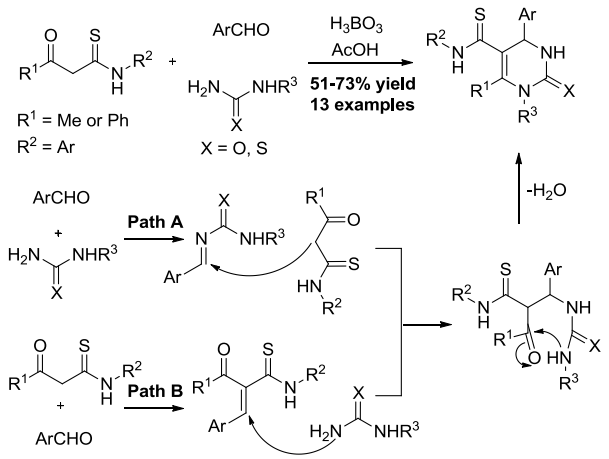


Scheme 13 Synthesis of 1,4-dihydropyridines

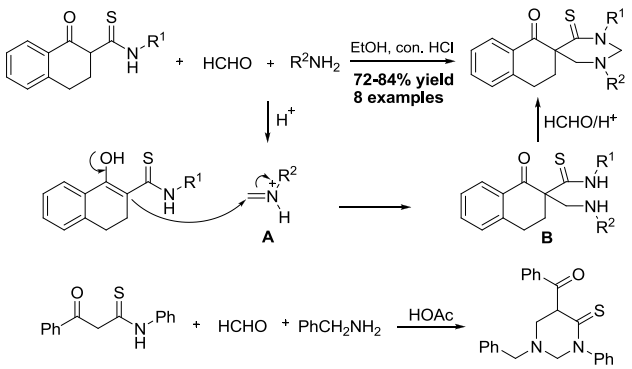
As shown in **Scheme 13**, we described an one-pot two-step protocol for microwave-assisted synthesis of Hantzsch-type hexa-substituted 1,4-dihydropyridines via reactions of KTAs with aldehydes and ethyl cyanoacetate followed by in situ *S*-alkylation.[26] The results showed that the substituents on the aromatic aldehydes had slight influence on the reactivity, and all substrates gave good yields. However, when aliphatic aldehydes were used instead of aryl aldehydes, the products were obtained in lower yields. A plausible mechanism involving tandem Knoevenagel condensation of ethyl cyanoacetate with aldehyde, Michael addition, *N*-cyclization, followed by tautomerization and S_N2 reaction was proposed. This protocol is complementary to the classical Hantzsch dihydropyridine synthesis, and it is convenient to prepare the hexa-substituted 1,4-dihydropyridines.

6.2 Pyrimidine derivatives

The Biginelli reaction is a multicomponent reaction using aryl aldehyde, ethyl acetoacetate and urea as materials to synthesize 3,4-dihydropyrimidin-2(1*H*)-ones. Recently, a Biginelli-type reaction was developed by Britsun and coworkers to synthesize tetrahydropyrimidine-5-carbothioamides through β-ketothioamide, aryl aldehyde and ureas or thioureas (**Scheme 14**).[27] Interestingly, the reactions did not proceed in the absence of boric acid. The aldehydes with electron-donating groups on the aryl ring gave higher yields (70-72%) than those with electron-withdrawing groups (51-58%). The cyclization reaction occurred regioselectively at the carbonyl group of KTAs, not the thiocarbonyl group. A plausible mechanism similar to the Biginelli reaction is proposed by the authors (Path A). However, another approach beginning with Knoevenagel condensation from KTAs and aldehydes could not be excluded (Path B).



Scheme 14 Synthesis of pyrimidine-5-carbothioamides



Scheme 15 Synthesis of spirohexahydropyrimidines

In 2013, Jagodziński and coworkers described a one-pot three-component Mannich-type reaction for the construction of functional spirohexahydropyrimidine derivatives catalyzed by alcoholic hydrogen chloride using tetralone-derived thioamides, formaldehyde and amines as starting materials.[28] A possible mechanism is outlined in **Scheme 15**. The α-carbon of the thioamide attacks the electrophilic imine **A** to obtain amino

thioamide **B**, which subsequently condenses with another molecule of formaldehyde to yield the target product. However, the reactions successfully proceeded only using primary aliphatic amines as substrates. Secondary amines could not react with formaldehydes to form the spiro heterocycle due to no hydrogen on the amine group of intermediate **B**, not steric hindrance proposed by the authors. When linear β-ketothioamide was used to react with benzylamine and formaldehyde, the hexahydropyrimidine was formed in high yield (88%).

6.3 Thiochromeno[2,3-*b*]pyridines

β-(2-Chloroaryl)ketothioamides (**Figure 3**), as new synthons developed by our group, show promising structural features. Besides the five reactive centers, there is a potential leaving halogen group on the aromatic ring. Owing to the presence of an electron-withdrawing *o*-carbonyl group, the halogen group on the aromatic ring was subjected to attack by sulfur or nitrogen atom on KTAs through intramolecular nucleophilic aryl substitution reaction (S_NAr), which is a new methodology to form thiopyran or pyridine rings.

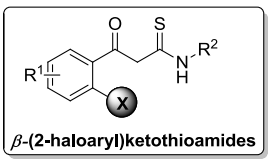
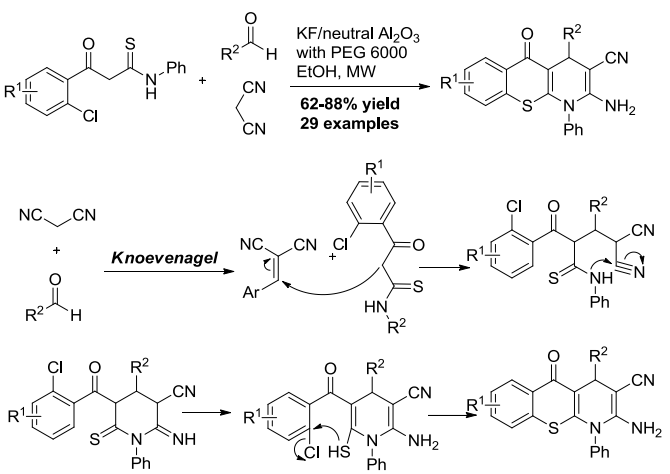


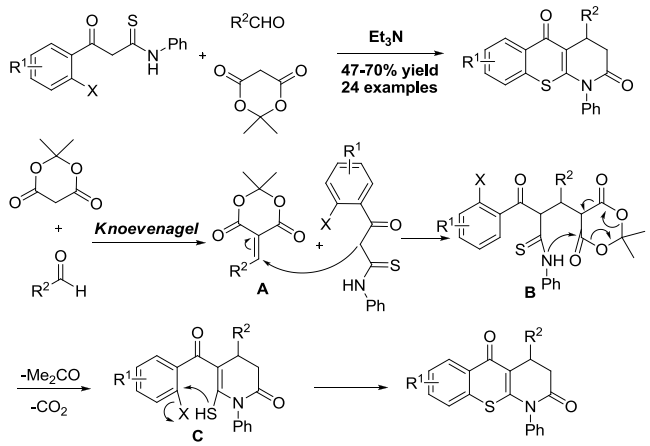
Fig. 3 Structure of β-(2-chloroaryl)ketothioamides

In 2009, we developed an efficient protocol to synthesize the thiochromeno[2,3-*b*]pyridine derivatives by using KF/neutral Al_2O_3 cooperated with PEG 6000 as an environmental friendly catalyst under microwave irradiation (**Scheme 16**).[29] Based on the experimental results, two C–C bonds, one C–S bond, one C–N bond, and two new rings were constructed with all reactants efficiently utilized in the chemical transformation. The reaction was very clean under microwave irradiation, and the products were obtained by simple recrystallization.



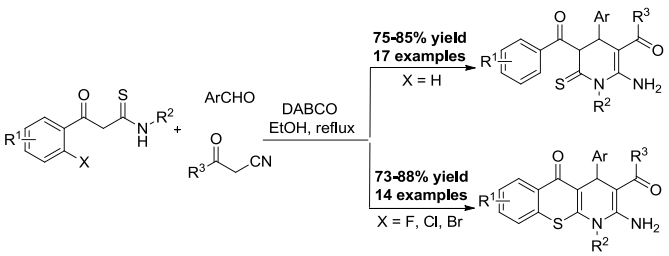
Scheme 16 Synthesis of thiochromeno[2,3-*b*]pyridines from KTAs with aldehydes and malononitrile

In the same year, a multicomponent reaction for the synthesis of thiochromeno[2,3-*b*]pyridine derivatives from the reaction of KTAs with aldehydes and Meldrum's acid in the presence of Et_3N was developed by our group.[30] The results showed that aromatic aldehydes carrying electron-withdrawing groups resulted in better yields than the substrates with electron-rich groups. Unfortunately, when aliphatic aldehydes were used, the reactions were sluggish and resulted in a mixture of products. A possible mechanism of the cascade reaction is depicted in **Scheme 17**. First, Knoevenagel condensation of aldehydes with Meldrum's acid forms the intermediate **A**. Then, Michael addition between **A** and KTAs gives intermediate **B**. Subsequently, intramolecular regioselective *N*-cyclization followed by unusual collapse of the Meldrum's acid ring with elimination of acetone and CO_2 generates the pyridine derivative **C**. Finally, intramolecular *S*-cyclization with the o-halo group in phenyl ring provides the product.

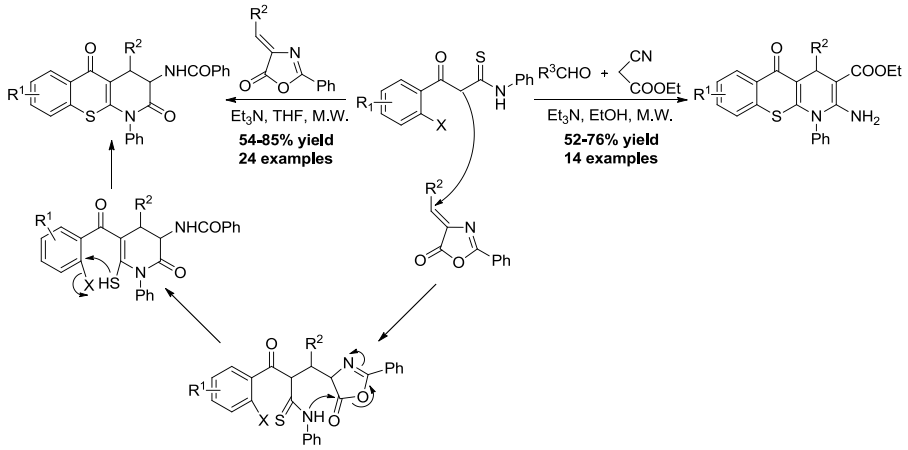


Scheme 17 Synthesis of thiochromeno[2,3-*b*]pyridines from KTAs with aldehydes and Meldrum's acid

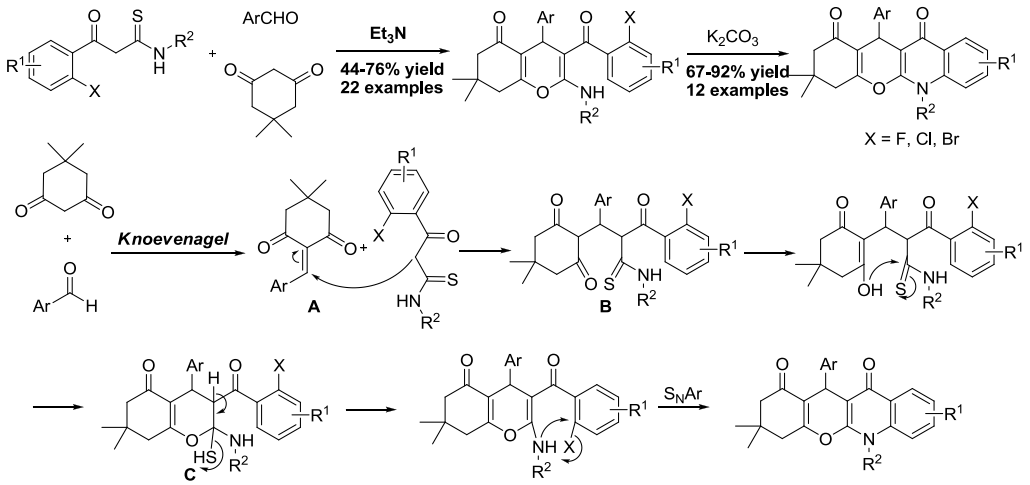
In 2012, we developed a highly efficient three-component cascade reaction to synthesize 1,2,3,4-tetrahydropyridine derivatives or thiochromeno[2,3-*b*]pyridine derivatives from KTAs, aldehydes, and aroyl acetonitriles, via DABCO-catalyzed tandem annulation and S_NAr reaction (**Scheme 18**).[31] In this processes, seven reactive sites were involved, two C−C bonds, one C−N bond, one C−S bond and two new rings were generated. The results showed that the corresponding thiochromeno[2,3-*b*]pyridines was afforded in good to excellent yields, whether electron-donating or electron-withdrawing substituents were performed on the aromatic ring of aldehyde. However, the results were unsatisfactory when the KTAs bearing either electron-donating or electron-withdrawing substituents on the N-aryl group at para-position, such as CH_3, OEt, and CF_3. The reaction mechanism is similar to **Scheme 16**.



Scheme 18 Synthesis of thiochromeno[2,3-*b*]pyridines from KTAs with aldehydes and aroyl acetonitriles



Scheme 19 Synthesis of thiochromeno[2,3-*b*]pyridines form KTAs with aldehydes and ethyl 2-cyanoacetate or oxazol-5(4*H*)-ones



Scheme 20 Synthesis of chromeno[2,3-*b*]quinolines from KTAs with aldehydes and 5,5-dimethyl-1,3-cyclohexanedione

As shown in **Scheme 19**, a series of fused tricyclic thiochromeno[2,3-*b*]pyridines were described by our group via the reaction of KTAs with 4-arylidene-2-phenyloxazol-5(4*H*)-ones or aromatic aldehydes and ethyl 2-cyanoacetate under microwave irradiation, respectively.[32] The results demonstrated that the substituents on aldehydes had slight influence on the reaction, and all substrates showed good yields. Interestingly, for KTAs bearing electron-withdrawing substituents on the aromatic ring, the yields were higher. A similar possible mechanism including Michael addition, intramolecular *N*-cyclization and intramolecular S_NAr reaction is proposed.

6.4 Chromeno[2,3-*b*]quinolines

Recently, we developed a 3-MCR of KTAs or 2-haloaryl KTAs, aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione to obtain functionalized tetrahydrobenzo[b]pyrans regioselectively using Et_3N as catalyst.[33] A novel chromeno[2,3-*b*]quinoline framework was generated via an intramolecular S_NAr reaction in the presence of K_2CO_3. In this process, two C−C bonds, one C−O bonds, one C−N bonds, and two new rings are formed with all reactants efficiently utilized. Additionally, the products only need to be recrystallized or washed with ethanol, which avoided the extensive purification procedures such as chromatography. It was demonstrated that both electron-withdrawing and electron-donating aromatic aldehydes and KTAs gave the target tetrahydrobenzo[*b*]pyrans in moderate yields.

A plausible mechanism is outlined in **Scheme 20**. First, Knoevenagel condensation of 5,5-dimethyl-1,3-cyclohexanedione with aldehydes affords the intermediate **A**. Then, the adduct reacts with the KTA to form the intermediate **B** via Michael addition. Intermediate **C** could be obtained by a rapid keto−enol tautomerization, followed by the intramolecular regiospecific *O*-cyclization. Tetrahydrobenzo[b]pyrans are afforded by eliminating one molecule of H_2S. Finally, the NH group attacks the *o*-halo of aryl group via an intramolecular S_NAr to form the highly functionalized chromeno[2,3-*b*]quinoline derivatives.

7. Application of ethyl 2-(3-oxopropanethio amido)acetates

Ethyl 2-(3-oxo-3-arylpropanethioamido)acetates and ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido)acetates, as novel KTAs with six and seven chemically distinct reactive sites respectively, show

intriguing and fascinating structural features and have a different reactivity profile from KTAs A and B (**Figure 4**).

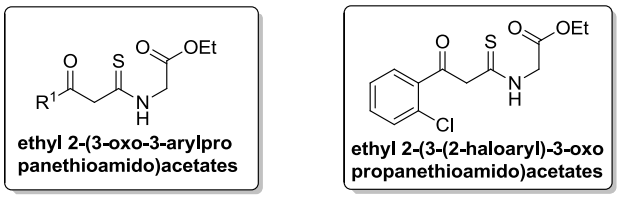
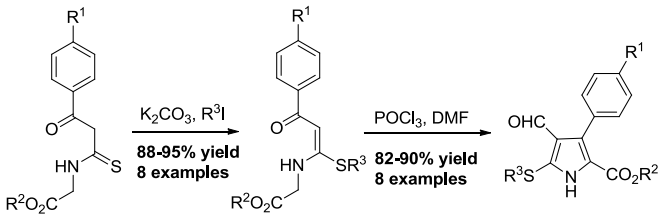


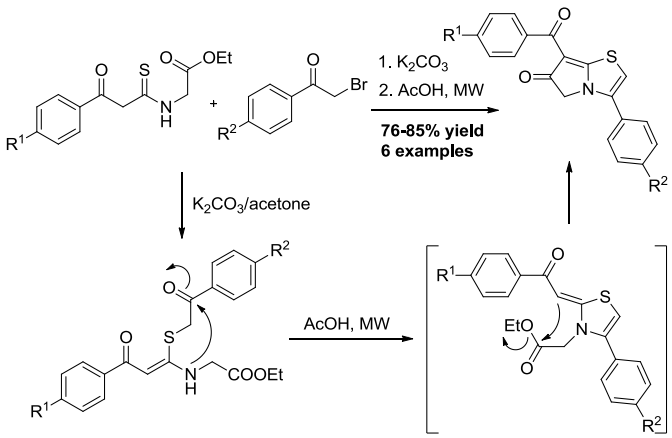
Fig. 4 Structures of ethyl 2-(3-oxopropanethioamido)acetates

In 2006, a simple method for the synthesis of tetra-substituted pyrrole derivatives was developed by Asokan and coworkers from readily available ethyl 2-(3-oxo-3-arylpropanethioamido) acetates.[34] The reaction involves a sequence of transformations, including *S*-alkylation, intramolecular cyclization catalyzed by $POCl_3$, and Vilsmeier–Haack process (**Scheme 21**). The chloromethyleneiminium salt derived from the Vilsmeier reagent played an important role in the reaction.



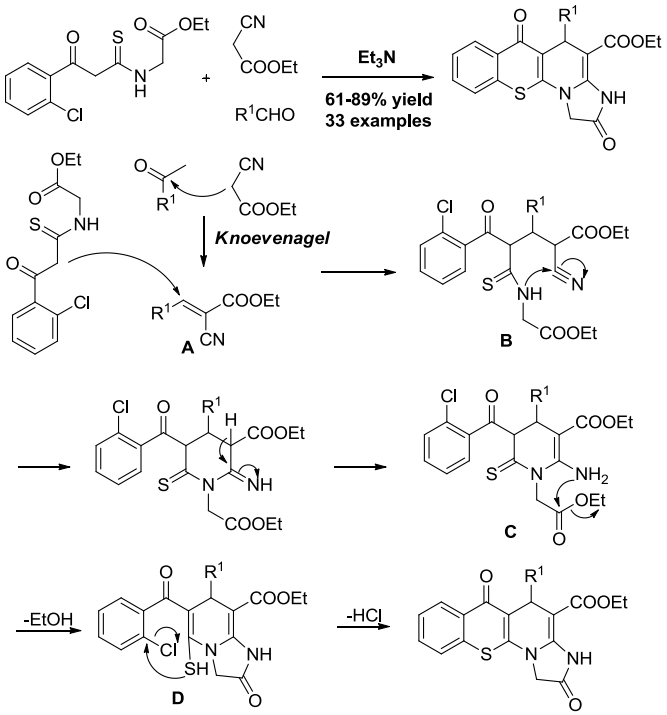
Scheme 21 Synthesis of pyrrole derivatives

In 2010, Mathew and coworkers developed a two-step method for the synthesis of pyrrolo[2,1-*b*]thiazol-6-ones from ethyl 2-(3-oxo-3-arylpropanethioamido)acetates and phenacyl bromides under microwave irradiation (**Scheme 22**).[35] The functionalized pyrrolothiazoles were formed in good yields via a regioselective tandem cyclization in one-pot. A possible reaction mechanism is proposed, which involves *S*-alkylation with phenacyl bromides, intramolecular *N*-cyclization and aza-ene type cyclization.



Scheme 22 Synthesis of pyrrolo[2,1-*b*]thiazol-6-ones

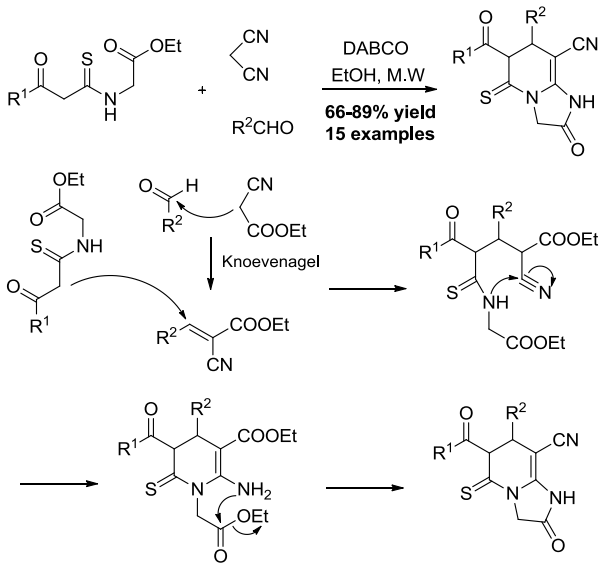
Recently, we developed a straightforward three-component synthetic protocol to synthesize imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridines from ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido) acetates, aromatic aldehydes and malononitrile or ethyl 2-cyanoacetate via cascade reactions.[36] Ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido)acetates are a novel precursor with seven chemically distinct reactive sites, which show intriguing structural features and have a different reactivity profile from KTAs. In this three-component domino process, ten reactive sites participated in the transformation that led to the concomitant creation of three C−C bonds, two C−N bonds, one C−S bond and three new rings. The results showed that most of reactions proceeded well and gave the corresponding products in good yields. The substituents on the aryl ring of KTAs had slight influence on the yields of products. It is noteworthy that all of the isolated products only need washing with ethanol rather than column chromatography or recrystallization.



Scheme 23 Synthesis of imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridines

A plausible mechanism for this reaction is proposed (**Scheme 23**). First, intermediate **A** is generated through Knoevenagel condensation by aldehyde and acetonitrile derivative. Then after deprotonation by Et_3N, KTA reacts with intermediate **A** through Michael addition to generate the intermediate **B**. Subsequently, intermediate **B** undergoes *N*-cyclization, followed by rapid imine-enamine tautomerization to give intermediate **C**. Next, intermediate **D** is obtained by intramolecular *N*-cyclization of **C** and keto-enol tautomerization. Finally, intramolecular aryl nucleophilic substitution leads to the target molecules.

A similar one-pot process to synthesize imidazo[1,2-*a*]pyridines by using ethyl 2-(3-oxo-3-arylpropanethioamido)acetates, aromatic aldehydes and malononitrile through microwave irradiation using DABCO as the catalyst was developed by our group.[37] The imidazo[1,2-*a*]pyridine is an important scaffold in natural and synthetic drugs, and present in many pharmacologically active substances. A similar possible mechanism is depicted in **Scheme 24**. In this domino reaction, eight different active sites are involved, three C−C bonds, two C−N bonds and two new rings are constructed and only one molecule of H_2O and one molecule of C_2H_5OH are lost.



Scheme 24 Synthesis of imidazo[1,2-*a*]pyridines

8. Conclusions and perspectives

As shown in this minireview, we have presented an overview of the use of β-ketothioamides in the synthesis of heterocyclic compounds over the past decade. KTAs are definitely one of the versatile synthetic intermediates which can undergo a variety of transformations. In addition to the reactions of the nucleophilic sites (S and α-C atoms, N and S atoms, or N and α-C atoms) of KTAs with dielectrophilic reagents, the reactions of the electrophilic sites (carbonyl and thiocarbonyl group) of KTAs with dinucleophilic reagents are also reported. Recently, another notable application of KTAs is construction of diversified heterocyclic skeletons through multicomponent reactions.

Because of the versatile reactivity, mild reaction conditions and simplified purification procedures, the reactions initiated by KTAs will be focus of intensive research efforts in the future. However, only one example using KTAs to construct enatiometric heterocyclic skeletons has been reported until now. Since most reactions using KTAs as starting materials provide products with chiral centers, developing methodologies of directly accessing enantiomerically pure compounds is in urgent requirement. Furthermore, the chiral heterocycles constructed with KTAs may be expectable to enhance the chance of discovering more biologically active heterocyclic molecules. Due to most reactions involving KTAs are carried out under basic conditions, chiral Brønsted acid catalysts such as chiral phosphoric acids might be unsuitable for these reactions. Nevertheless, the asymmetric reactions of KTAs might be catalyzed by chiral Brønsted base catalysts, such as chiral bifunctional aminothiourea organocatalysts. We believe that with the rapid development of asymmetric catalysts, asymmetric syntheses based on KTAs will become the hot spot in this field

Acknowledgements

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Notes and references

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