β-KETOTHIOAMIDES: VERSATILE PRECURSORS TOWARDS IMPORTANT HETEROCYCLIC FRAMEWORKS

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Abstract. *β-Ketothioamides (KTAs) have proved to be important precursors to furnish diverse heterocyclic moieties over the last couple of decades. The convergence of reactive sites and bench stable nature created keen interest among the chemists towards their synthetic utility and applicability. In fact, KTAs are excellent candidates for numerous organic transformations like cyclizations, cycloadditions and domino reactions, leading to important heterocycles having great material and biological relevance. KTAs show variable reactivity depending upon the substrates and reaction conditions, adding extra features to their applicability.*

Contents

1. Introduction
Heterocyclic compounds are deeply involved in every aspect of organic synthesis, including the materials, pharmaceutical and medicinal field. Most of the heterocyclic compounds are of biological relevance. Heterocycles containing O, N, and S atoms are the most common and relevant in the field of chemistry. Also, the heterocycles having four, five, six, and even seven-membered rings are the most common ones amongst the family of heterocycles. Among these, sulfur and nitrogen are extensively present in amino acids and protein moieties with several bioactivities. Histamine, a monosubstituted imidazole, is derived in vivo from the amino acid histidine by decarboxylation *via* histidine decarboxylase enzyme, which is involved in local immune responses and acts as a neurotransmitter. Moreover, it neutralizes allergic reactions, and participates in regulating gastric acid secretion. Similar to this, there are uncountable number of biomolecules, natural and man-made drugs, agricultural chemicals, and fine chemicals containing sulfur. Penicillin, Dalfopristin, and Quinupristin are some of the antibiotic drugs containing sulfur. Other sulfur-containing drugs for instance, ixabepilone and phthalascidin are used for cancer treatments, and rosuvastatin for hyperlipidemia. Also, quinupristin and dalfopristin have anti-bacterial and anti-fungal properties.

The real taste of organic synthesis comes from the construction of complex moieties *via* operationally simple, atom economical, and environmentally suitable reaction conditions. In this regard, β-ketothioamides (KTAs) have emerged as fascinating and versatile synthons for constructing various heterocycles. KTAs have different chemical properties with intriguing number of reactive centers.[1] Possessing both sulfur and nitrogen heteroatoms, KTAs became very effective and valuable precursors for constructing diverse heterocycles. In 2003, Jagodziński reported only three examples involving KTAs in his review.[2] Currently, various laboratories, including ours, reported several articles involving KTAs as one of the reaction partner towards various chemical transformations. Moreover, the past decade has witnessed rapid progress in the KTAs chemistry, especially in synthesizing functionalized heterocyclic compounds *via* two-component tandem and multicomponent reactions. The other analogs of KTAs like β-oxodithioesters (DTEs), *S,S*-ketene acetals, *N,S*-ketene acetals and *N,N*-ketene acetals are well encountered. This short review covers the importance of KTAs for becoming one of the most important synthons for the construction of diverse

heterocycles, and deals with the recent applications and tunability of the reactive centers of the KTAs to furnish new heterocyclic drugs.

2. Synthesis of β-ketothioamides

There are several methods for synthesizing KTAs, among which the most common one is to make the thioamido group from the appropriate β-ketoamides **1** using the Lawesson's reagent (Scheme 1).[3] Although the availability of the starting β-ketoamide limits the practical use of this technique to some extent, Pace *et al.*[4] used the substituted acetophenone **2** with LDA as a base in THF to generate **3** followed by addition of isothiocyanate as the sulfur and nitrogen source to get the desired product **4** in good yield. Moreover, Shi *et al.* modified the procedure by using NaH as a base in 1,4-dioxane at room temperature, which provided the most convenient method for the synthesis of KTAs **4**.[5]
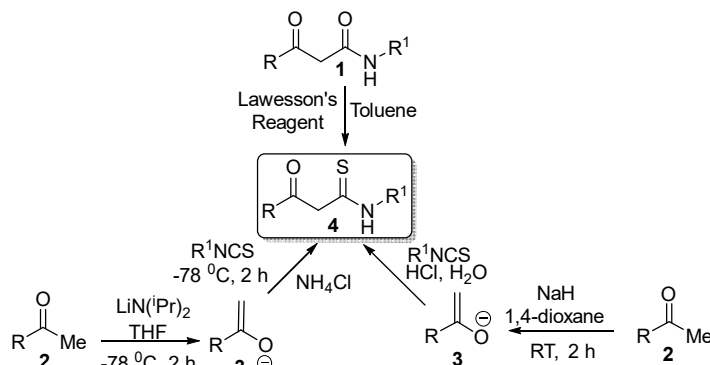
Scheme 1. Preparation of β-ketothioamide.

3. Reactivity profile of β-ketothioamides

Ideal synthons are likely to have multiple functional groups within the moiety, giving the chemists the freedom to direct the building of organic moieties in a controlled fashion. In this regard, KTAs also possess several functional groups, which provide multiple reaction sites, including two electrophilic centers in the form of thiocarbonyl and carbonyl; two nucleophilic centers localized on the heteroatoms (sulfur and nitrogen), and also a potential nucleophilic center, as the α-carbon, can behave as a Michael addition donor. KTAs exist in both the possible tautomeric forms, *i.e.* thioketo and enethiol, under either in both acidic and basic media as depicted in Scheme 2.
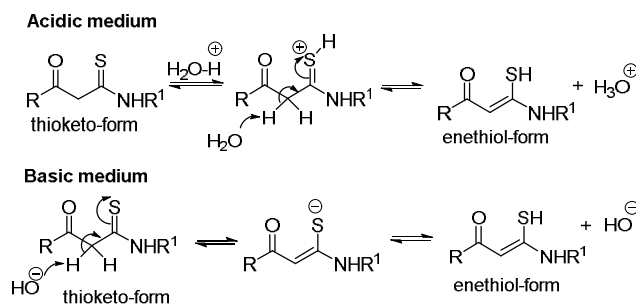

Scheme 2. Acid and base-catalyzed thioketo-enethiol tautomerism of KTAs.

In an acidic medium, the thioketo group is protonated, leading to a positively charged species, followed by the deprotonation from the α-carbon to give the enethiol tautomer. On the other hand, in a basic

medium, deprotonation from the α-carbon takes place first, followed by-protonation to give the enethiol. The latter is also known as *N,S*-ketene acetal, stabilized by hydrogen bonding with carbonyl O atom. KTAs in general exist mostly in the enethiol form in both solid and solution phase, although depends on the reaction conditions which form will dominate over the other (Scheme 2).

Talking about the reactive centers (Scheme 3), there are mainly four of them, in which type-I include the use of di-electrophile to activate the α-carbon and sulfur as nucleophile. Type-II includes sulfur and nitrogen atoms acting as nucleophile to a di-electrophile. In type-III, the thiocarbonyl and carbonyl groups act as electrophiles towards external nucleophiles, and in type-IV, the potential carbon centre and the nitrogen centre act as nucleophiles towards electrophiles. In type-V, the carbonyl and the α-carbon centre could act as electrophile and nucleophile, respectively. Existence of these types of diverse reactive sites allows chemists to tune the KTAs in designing various heterocycles. The crystal structures of the two forms of β-ketothioamide are shown in Figure 1.
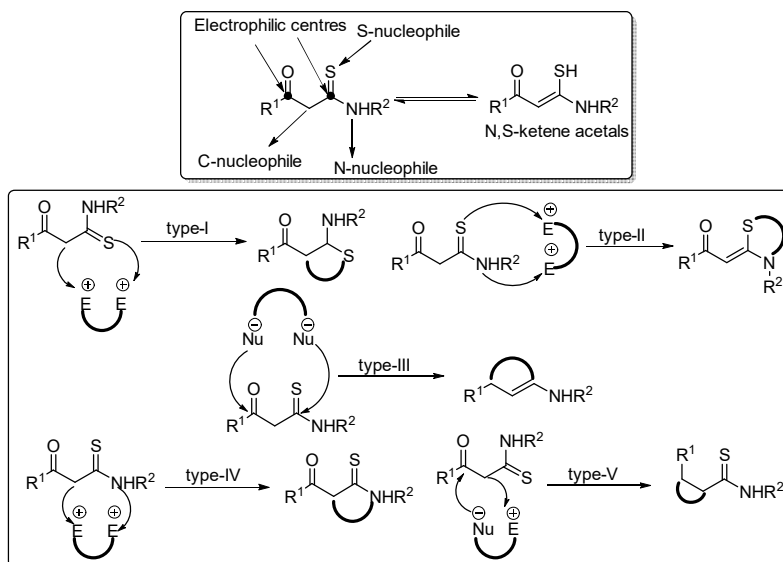
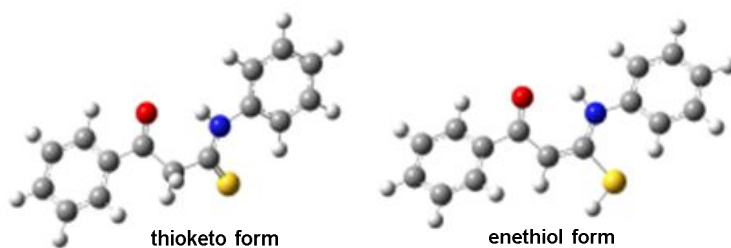**Scheme 3.** Possible reactive centres of β-ketothioamides.

Figure 1. Crystal structure of both forms of β-ketothioamide.

4. Functionalization of β-ketothioamides

Due to the presence of various important functional groups in the β-ketothioamide, its functionalization may lead to the formation of diverse valuable heterocyclic frameworks. β-Ketothioamide can also be converted to its *N,S*-acetal, which can undergo various reactions leading to diverse valuable heterocycles under diverse reaction conditions (Scheme 4).
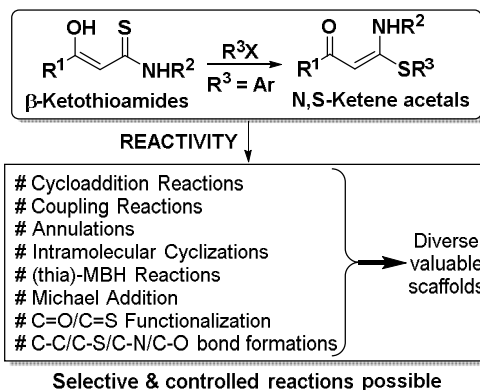
Scheme 4. Functionalization of β-ketothioamide to other useful synthons.

Over the past couple of decades, there has been an ever-increasing number of reports published regarding the functionalization and applicability of the KTAs, showing their importance in the field of organic chemistry enabling different heterocycles. KTAs can undergo versatile reactions including inter-/intramolecular cyclizations, cycloadditions, coupling with suitable partner, and annulation reactions. In addition to this, Michael reactions, Knoevenagel reactions, MBH reactions employing KTAs are well explored for the synthesis of diverse functionalized heterocycles.

5. Synthetic applications of β-ketothioamides

New drug discovery, production of fine chemicals, modified agricultural needs are evntually fulfilled by the synthesis of numerous heterocyclic motifs, and by default is the main door to access the option for development in those areas. The use of simple polyfunctional moieties have always been in the demand as synthons to the synthetic organic chemists for synthesizing a huge library of heterocycles. But, to build new heterocycles from practically simple synthons is still an important synthetic challenge.. To this end, KTAs have emerged significantly in the past decades as an important building block towards the synthesis of various heterocycles. The conjunction of number of different functional groups in the β-ketothioamide (*e.g.* carbonyl, thiocarbonyl, thioamide, enethiol, potential ketene acetals) enables KTAs to show unexpected and unique properties. This is why the β-ketothioamides show number of reactions involving cyclizations, one-pot domino reactions *etc.*, which allows diverse complex structures to be easy-made in a single step. Therefore, the use of KTAs in synthesizing different moieties provides a huge benefit in atom economy, cost effective synthesis, and green synthesis (Figure 2).
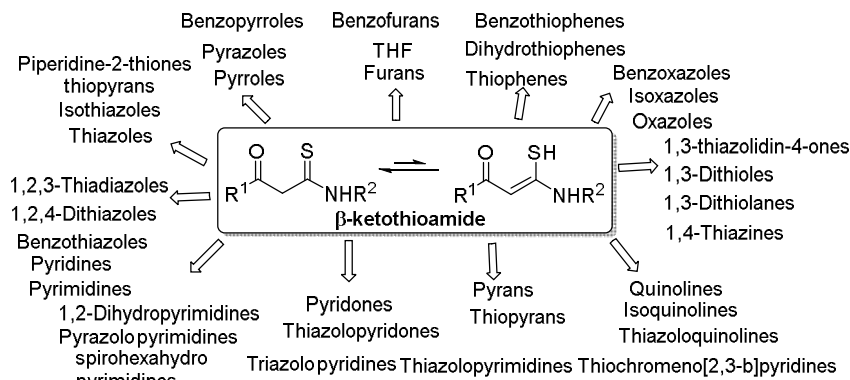

Figure 2. Construction of various cyclic scaffolds from acyclic thioamides.

Thiophene core is an important heterocycle in numerous biologically active pharmacophores and natural products. The reactions between the nucleophilic sites (S and α-C atoms) of KTAs with dielectrophilic reagents could form multisubstituted thiophene derivatives regioselectively. In 2012, Jørgensen and co-workers reported the synthesis of optically active thiophenes **9** from KTAs **5** and α,β-unsaturated aldehydes **6** *via* a highly enantioselective amino-catalyzed epoxidation or aziridination reaction, and an intramolecular *S*-cyclization using **7** in presence of an organocatalyst **8** (Scheme 5).[6]
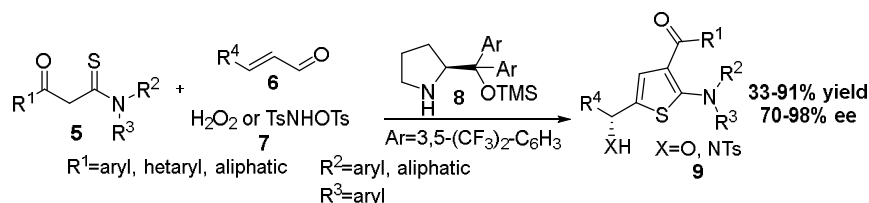
Scheme 5. Synthesis of optically active thiophenes from KTAs and α,β-unsaturated aldehydes.

The possible reaction mechanism is proposed and outlined in Scheme 6 where First, enantioselective aziridine- or epoxyaldehyde **10** is obtained from **6** and **7** with an organocatalyst **8**. Then the α-carbon of KTAs **5** attacks the aldehyde **10** to form intermediate **11**. Finally, *via* intramolecular *S*-cyclization and tautomerization, intermediate **12** is formed which eliminates H_2O to get the desired thiophenes **9** (Scheme 6).
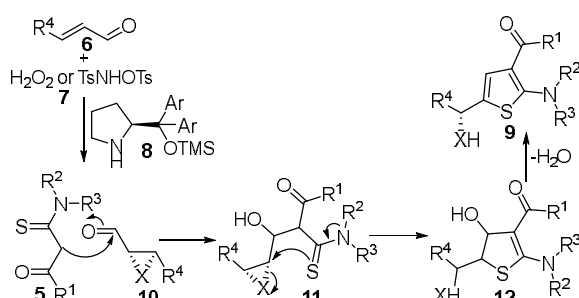

Scheme 6. Synthesis of trisubstituted optically active thiophene derivative.

Recently, Li *et al.*[7] developed an efficient and straightforward three-component synthetic protocol to synthesize tetrasubstituted thiophene derivative **16** from KTAs **15** with arylglyoxals **14** and 5,5-dimethyl-1,3-cyclohexanedione **13** in CF_3CH_2OH within 15 min. This domino process involves the formation of two C−C bonds, one C−N bonds and one new ring with high regioselectivity, high atom economy, transition metal-free, short reaction time, and easy purification. The possible reaction pathway is also depicted below (Scheme 7). In path A, at first, the condensation product **17** from **13** and **14**, undergoes 1,4-addition reaction via S-center to produce **18** which eventually cyclizes to give **19** followed by dehydration, the desired product was obtained. Another possibility can be drawn, which include 1,2 addition of KTAs **15** to **17** which yielded **20**. Then the tautomeric form **21** eliminates H_2O to give **16**.

Our group reported an interesting but simple reaction for the synthesis of fully substituted hydrothiophenes from KTAs **23**.[8] This approach achieves atom, step as well as pot economical and in addition to metal-free pathway. At first, the KTAs **23** got propargylated from **22** to form **24**, then in the next step the propargylated thioamides undergo intramolecular 1,5-cyclization to afford fully substituted (hydro) thiophenes in the presence of base (Scheme 8). Notably, thiazole ring **25** forms as a by-product *via* **30** from the reaction of **23** with *in situ* formed **29** from intermediate **28** (Scheme 9). Various organic and inorganic bases likely Et₃N, K₂CO₃, DABCO, DMAP *etc.* had been screened in result the all the bases promoted the reaction toward exclusive formation of dihydroaminothiophene **26a** along with a trace amount of **26b**.
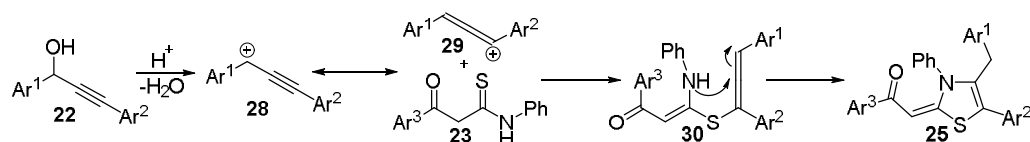
However, Cs_2CO_3 provided only oxidized dihydroiminothiophene **27** exclusively. Et_3N and Cs_2CO_3 furnished **26** and **27**, respectively, in maximum yield.
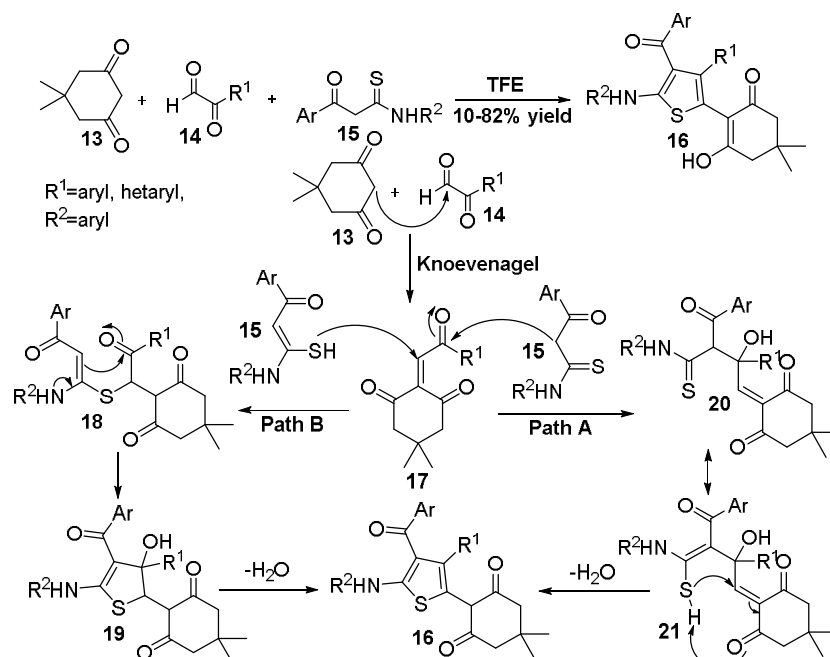
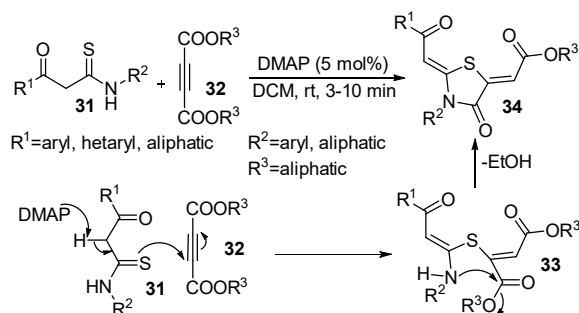**Scheme 7.** Synthesis of thiophenes from KTAs with arylglyoxals and 5,5-dimethyl-1,3-cyclohexanedione.
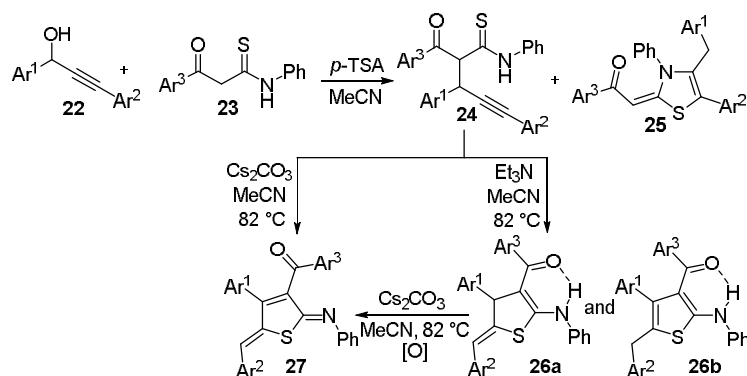
Scheme 8. Regioselective synthesis of highly substituted hydro thiophene from propargylated KTAs.


Scheme 9. Mechanism for the synthesis of thiazole by-product from KTAs.

Thiazolidine, a class of heterocycle having 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. In 2014, Singh et al.[9] reported a DMAP-promoted synthesis of functionalized 1,3-thiazolidin-4-ones **34** by a reaction of KTAs **31** with internal alkynes **32** at room temperature (Scheme 10). The reaction proceeds *via* a nucleophilic attack of thiocarbonyl sulfur of KTAs **31** on internal alkyne **32** to yield **33** followed by a highly regioselective intramolecular *N*-cyclization to afford the corresponding product **34** in good yields.

Scheme 10. Synthesis of 1,3-thiazolidin-4-ones from KTAs with alkynes.

Our group also reported a one-pot synthesis of 1,3-thiazolidin-4-ones **38** starting from KTAs **31** with *in situ*-generated acid anhydride **36** from α-halocarboxylic acid **35** in the presence of DCC at room temperature in the ongoing year.[10] This method involves the formation of C−S and C−N bonds and also one ring in a single synthetic operation, in a milder and metal-free reaction conditions. A plausible mechanism including nucleophilic attacking by thiocarbonyl sulfur of KTAs **31** to **36** yielding **37**, followed by intramolecular *N*-cyclization processes to produce **39** is proposed (Scheme 11).
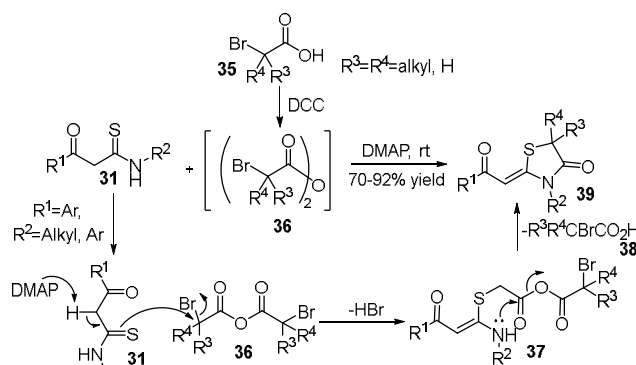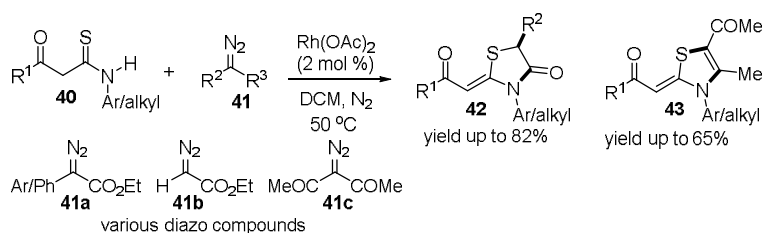

Scheme 11. Synthesis of 1,3-thiazolidin-4-ones from KTAs with *in situ*-generated acid anhydride.

Our group also reported an operationally simple and efficient one-pot protocol for the synthesis of highly functionalized thiazolidin-4-ones **42** and thiazolines **43** *via* Rh(OAc)$_2$-catalyzed annulative coupling of KTAs **40** with diazo compounds **41** (Scheme 12).[11] The reaction proceeds in moderate temperature and under mild conditions. Also, 2,3-dihydrobenzo[*d*]thiazoles can be accessed by this synthetic strategy. Besides this features, atom economy and tolerance of a wide range of functional groups are added characteristics to this strategy.

In the first step, Rh(OAc)$_2$ and the diazo compound **41** react with each other to generate rhodium carbenoid species **44** *via* the extrusion of nitrogen. Next, the rhodium carbenoid species **44** reacts with

thioamide sulfur **40** to form the sulfonium ylide **45**, which in turn follows proton transfer to form *N,S*-acetal intermediate **46** by the regeneration of the rhodium catalyst. Finally, *in situ*-generated *N,S*-acetal intermediate **46** undergoes intramolecular *N*-cyclization by the elimination of ethanol to give the desired thiazolidinones **42** and thiazolines **43** (Scheme 13).


**Scheme 12.** Synthesis of thiazolidin-4-ones and thiazolines from KTAs with diazo compounds.
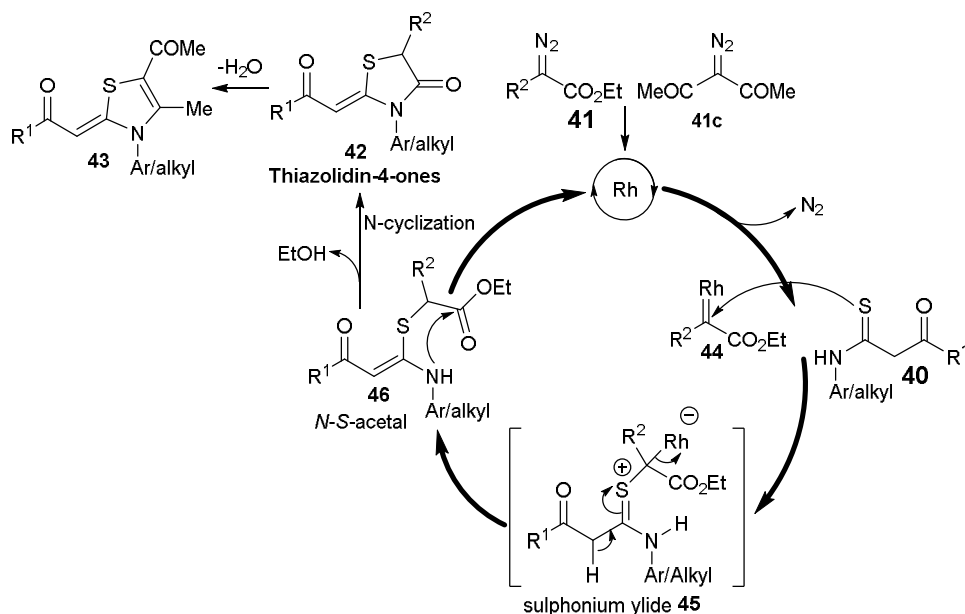
Scheme 13. Mechanism for the synthesis of thiazolidine-4-one *via in situ*-generated Rh-carbenoid system.

An efficient and versatile copper-catalyzed unprecedented intermolecular radical [3+2]-annulation of KTAs **31** with azobisisobutyronitrile (AIBN) **47** was reported by Singh and co-workers recently (Scheme 14).[12] This strategy involves two-component one-pot copper(II)-catalyzed transformation *via* cascade formation of C−S/C−N bonds through the cyclization of *in situ*-generated *N,S*-acetal intermediate from KTAs **31**. This operationally simple method offers direct access to thiazolidin-4-ones **48** in good to excellent yields containing diverse functional groups of different electronic and steric nature. Also it avoids expensive and toxic reagents. AIBN here plays a dual role as radical initiator and unusual source of two carbon coupling partner.

The mechanism is outlined in Scheme 15, where high-valent Cu(III) compound **49** (produced from KTAs **31** and **47**), undergoes reductive elimination to form intermediate **50** generating Cu(I) followed by oxidation by the co-action of O_2 and AcOH to Cu(II) completing the catalytic cycle. Subsequently, intramolecular cyclization of intermediate **50** assisted by Cu(II) delivers intermediate **51**, which upon hydrolysis gives the desired compound 1,3-thazolidinone **48**.
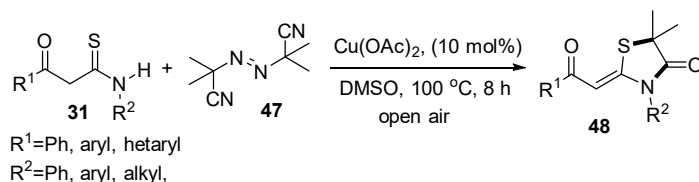
Scheme 14. Synthesis of 1,3-thazolidinone from KTAs and AIBN catalyzed by Cu(OAc)$_2$.
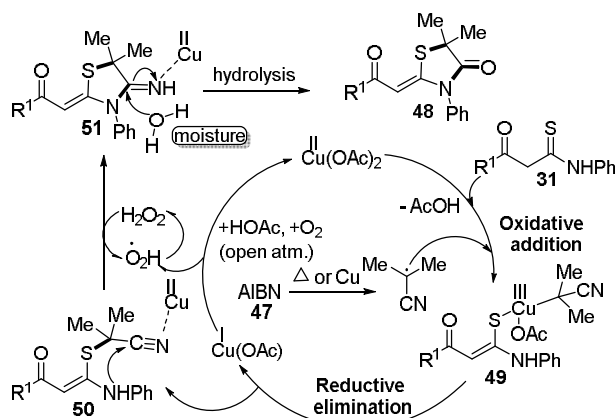
**Scheme 15.** Copper(II) catalyzed [3+2]-annulation of KTAs and AIBN.

Recently, our group reported a simple and sustainable one-pot photo-oxidative formal [3+2]-heterocyclization of KTAs **31** with aryldiazonium salts **52** catalyzed by Ru(bpy)$_3$Cl$_2$ to provide 2,4-disubstituted 5-imino-1,2,3-thiadiazoles **53** (Scheme 16).[13] This strategy provides high to exellent yield of the products and shows great tolerance of functional groups.
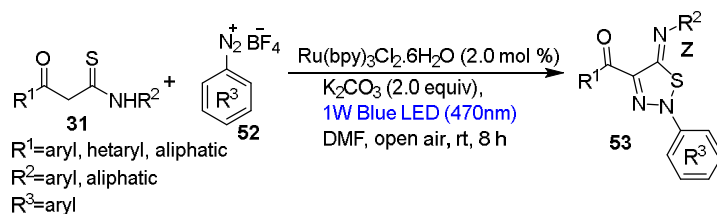

Scheme 16. Synthesis of 1,2,3-thiadiazole from KTAs and aryldiazonium salts under photo-irradiation.

The first step of reaction involved the formation of intermediates **54** and **55** (produced from **31** and **52**) at room temperature, which undergo the oxidation *via* excited photocatalyst (Ru (II)*/Ru(I)) through a reductive quenching process to generate thiyl radical **56**. Simultaneously, the molecular oxygen is reduced to a superoxide ion $O_2^{\bullet-}$ by Ru(I) and the catalyst is regenerated. Thiyl radical **56** undergoes subsequent oxidation *via* superoxide ion $O_2^{\bullet-}$ to generate product **53** and O_2^{2-} eliminate as a byproduct (Scheme 17).

In 2020, Singh *et al.* reported an operationally simple and efficient coupling of KTAs **4** with α-diazo 1,3-diketones **57** under photocatalyst- and additive-free conditions to produce thiazolines **58**.[15] This strategy is far superior to conventional metal-catalyzed carbene-transfer reactions. In addition, this protocol is promising because of its benign and clean conditions, operational simplicity, sustainability, 100% carbon economy, structural diversity, and excellent yields. Being water is the only byproduct gives an additional attribute of this synthetic strategy (Scheme 18).
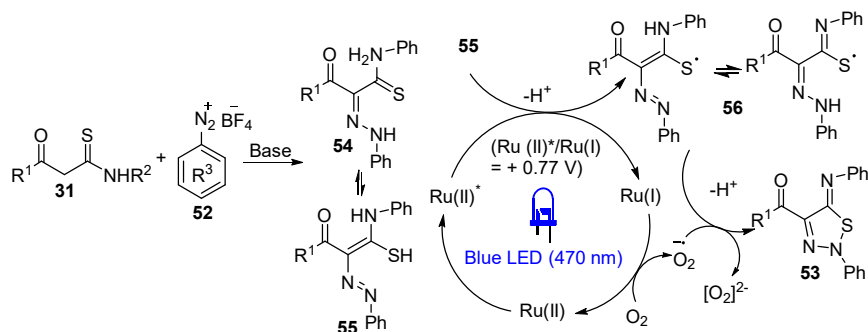
Scheme 17. Synthesis of 1,2,3-thiadiazole *via* [3+2]-heterocyclization from KTAs and aryldiazonium salts.
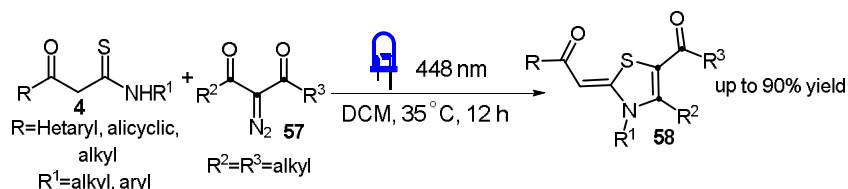
Scheme 18. Synthesis of highly fuctionalized thiazolines.

The proposed reaction mechanism involves blue-light-induced cascade carbene-transfer (*S*-alkylation) and *N*-cyclization reactions. The photolysis of α-diazo-1,3-diketones generates **57** electrophilic singlet carbene intermediate **59** through denitrification. This carbene intermediate **59** reacts with the KTAs **4** at its more nucleophilic S center to generate open-chain *S*-alkylated *N,S*-acetal intermediate **60**. Finally, intermediate **60** undergoes intramolecular *N*-cyclization and yielded **61**, followed by dehydration to give the desired thiazoline **58** (Scheme 19).
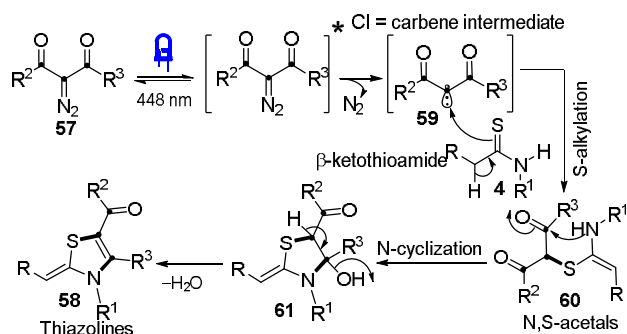

Scheme 19. Highly functionalized thiazolines from coupling of KTAs and α-diazo-1,3-diketones.

Our group also reported the synthesis of a specific class of 1,2,4-dithiazolidines **62** from KTAs **31** in the presence of visible light and eosin Y as a photoinitiator at ambient temperature in an open pot.[16] This strategy is characterized by simple reaction conditions and sustainability, while giving access to a particular class of 1,2,4-dithiazolidines **62**. The developed hydrogen-atom-transfer methodology can be helpful in post-synthetic modification *via* added synthetic handles (Scheme 20).

The mechanistic proposal is outlined in Scheme 21. This reaction involves the generation of a thiyl radical **63** *in situ* from KTAs **31** in the presence of Eosin Y *via* HAT process followed by dimerization to form intermediate **64**. Then the deaminative cyclization cascade occurs which enables the formation of a

dithiazolidine ring **62** through successive building of S–S and N–C bonds under metal- and additive-free conditions. The intermediate **65** then returns to its ground state *via* RHAT process.
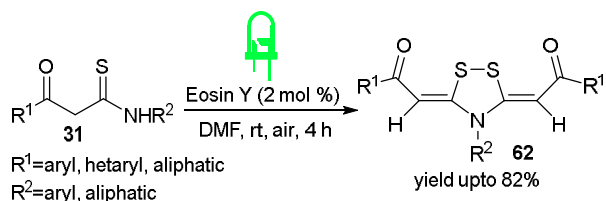

Scheme 20. Visible-light mediated synthesis of 1,2,4-dithiazolidines from KTAs.
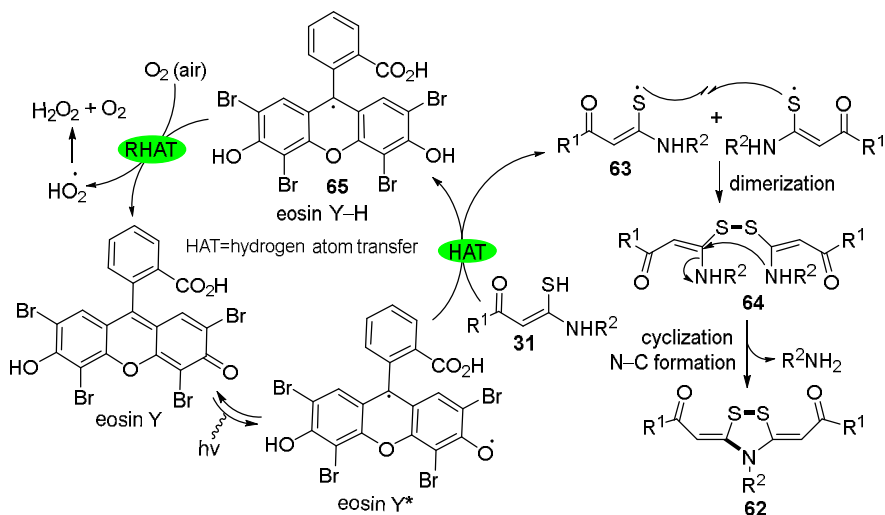
Scheme 21. Plausible mechanism for the visible-light mediated synthesis of 1,2,4-dithiazolidines.

A very interesting and important route for the synthesis of thiazolidine **68** and thiazinanes **69** *via* phosphonium ylide catalysis from KTAs **40** and dihaloalkanes **66** and **67** has been reported by our group.[17] Here phosphonium ylide is utilized as a catalyst to synthesize the desired products thiazolidines **68** and thiazinanes **69** *via* [3+2]- and [3+3]-annulations respectively under metal-free conditions (Scheme 22).
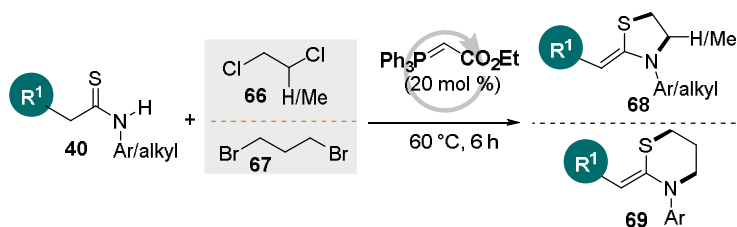
Scheme 22. Synthesize cyclic ketene acetals [thia(zolidines/zinanes)] from KTAs and dihaloalkanes.

Going to the mechanistic insights, the first step is believed to be the reaction between the phosphorus ylide and dichloroethanes **66** and **67** to from a new ylide adduct **70↔71**. In the next step, a nucleophilic attack of the thioamide **40** sulfur atom (soft nucleophile) at the soft electrophilic carbon of the halomethyl group generated intermediate **72** that could not be isolated. Intermediate **72** could probably undergo

intramolecular cyclization *via* its two possible rotamers **72** and **72′** to furnish compounds **68/69** and **73**, respectively. The intermediate **72** undergoes chemoselective *N*-cyclization with the elimination of phosphonium ylide **74** to give the desired products **68** and **69** exclusively. The intermediate **72′** could lead to compound **73** *via* alternative *O*-cyclization, which was not observed even in a trace amount during our investigation (Scheme 23).
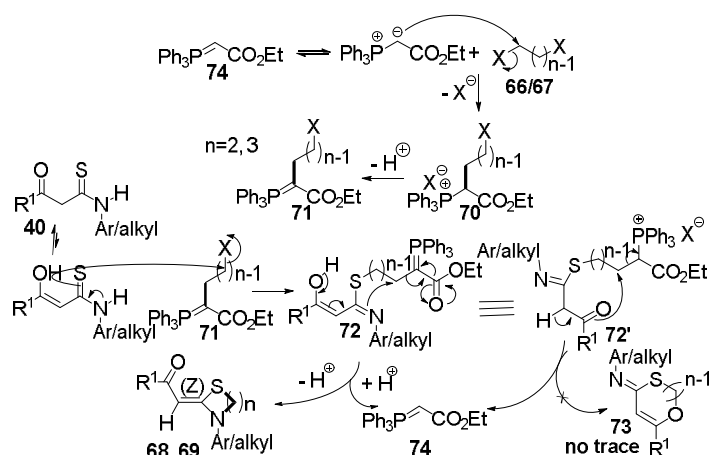

Scheme 23. Possible mechanism for the synthesis of **68** and **69** *via* phosphonium ylide catalysis.

Britsun group synthesized a series of fused heterocycles from KTAs **75** with various amino heterocycles through formal [3+3]-cyclization.[18] Reaction of 5-amino-3,4-disubstituted pyrazoles **76** with KTAs **75**, resulted polysubstituted pyrazolo[1,5-*a*]pyrimidine **77** under solvent-free conditions (Scheme 24).
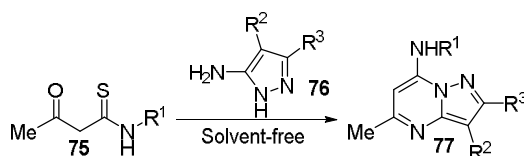

Scheme 24. Synthesis of polysubstituted pyrazolo[1,5-*a*]pyrimidine from KTAs.

Condensation of KTAs **75** with 2-aminoimidazole **78a** or 2-aminobenzimidazole **78b** gave a mixture of 4-(arylamino) imidazo[1,2-*a*]pyrimidine **79** and imidazo[1,2-*a*]pyrimidine-5-thione **80**. The ratio of the two products dependes on the aryl substituents on the KTAs.[19] (Scheme 25).
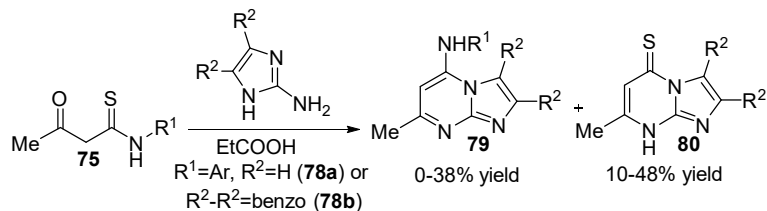

Scheme 25. Condensation reaction of KTAs with 2-aminoimidazole or 2-aminobenzimidazole.

Interestingly, when the KTAs **75** reacted with 2-aminopyridines **81** in acetic acid under a similar procedure, pyrido[1,2-a]pyrimidine-4-thione **82** were obtained regioselectively in good to moderate yield (Scheme 26).[20]
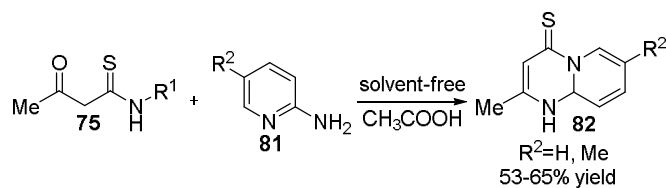

Scheme 26. Reaction of KTAs with 2-aminopyridines.

Li *et al.*[14] developed an efficient self-condensation synthetic protocol to synthesize 1,3-thiazolines **83** and 1,4-dithiines **84** by reactions of KTAs **31** and I_2 at room temperature. Use of 0.5 equivalents I_2 delivers the 1,3-thiazoline derivatives **83**, and KTAs **31** bearing either electron-donating or -withdrawing substituents on the *N*-phenyl ring or phenyl ring linked to the carbonyl group provided the corresponding products in good yields. However, interestingly, when KTAs **31** were used with alkyl amines and in the presence of 1 equivalent of I_2, only the homocoupling product 1,4-dithiines **84** were formed in good yields. This method features high regioselectivity, short reaction times, mild reaction conditions, and easy purification of the products. A plausible mechanism for this reaction is shown in Scheme 27. First, intermediate **31a** is formed by deprotonation of KTAs **31** in the presence of DABCO, then it reacts with I_2 to generate intermediate **85**. When R_2=aryl and the amount of I_2 is 0.5 equivalents, intermediate **86** is obtained by nucleophilic substitution of intermediate **31a** with **85**. Subsequently, **86** undergoes an intramolecular cyclization to give intermediate **87**, which eliminates a molecule of H_2S to form of the 1,3-thiazolines **83**. Whereas R_2=alkyl and the amount of I_2 is 1 equivalent, two molecules of **85** react with each other through a nucleophilic substitution to give intermediate **88**, which generates 1,4-dithiine derivative **84** by tautomerization.
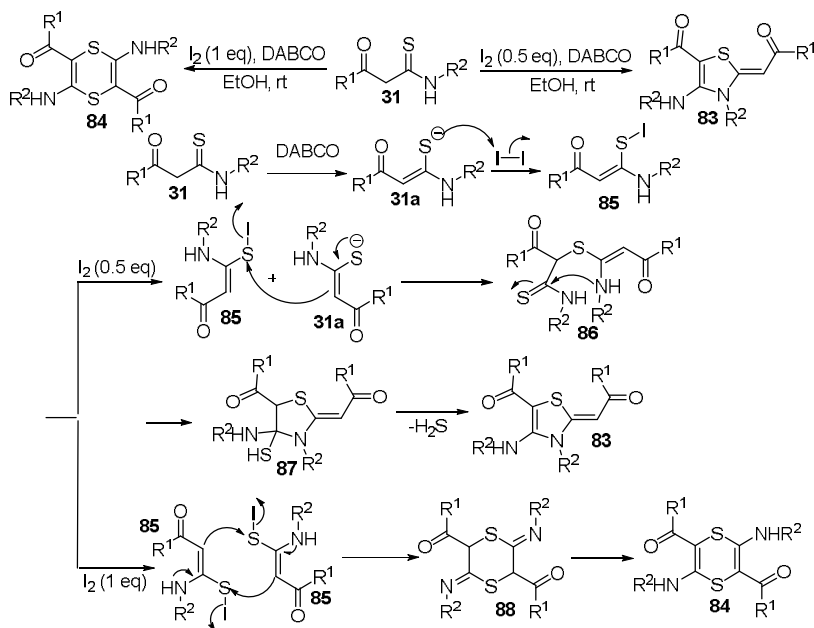

Scheme 27. Synthesis of thiochromeno[2,3-b]pyridines from KTAs self-condensation.

Also, reacting KTAs **75** with 5-amino-1,2,4-triazole **89**, a mixture of 1,2,4-triazolo[1,5-*a*]pyrimidine **90** and 1,2,4-triazolo[1,5-*a*]pyrimidine-7-thione **91** were formed under solvent-free condition. The substituents in the KTAs **75** and the solvent decides the ratio of the two products (Scheme 28).[21]
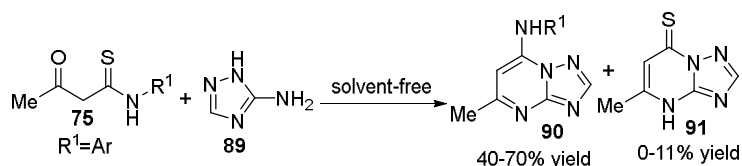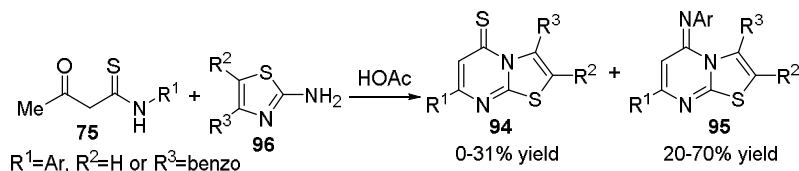

Scheme 28. Synthesis of mixture of 1,2,4-triazolo[1,5-*a*]pyrimidines.

However, when 3-amino-1,2,4-triazole **92** was used as starting material to react with KTAs **75**, only 1,2,4-triazolo[1,5-*a*]pyrimidine **93** were obtained (Scheme 29).[22]
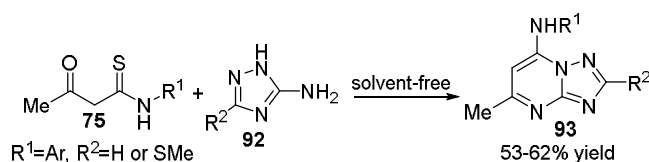

Scheme 29. Selective synthesis of 1,2,4-triazolo[1,5-a]pyrimidines.

Moreover, a mixture of 1,3-thiazolo[3,2-*a*]pyrimidine-5-thione **94** and **95** were obtained by reaction of 2-amino-1,3-thiazole **96** with KTAs **75** in acetic acid.[23] The mixture contains 5-arylimino-1,3-thiazolo[3,2-*a*]pyrimidine **95** as the major product (Scheme 30).


Scheme 30. Synthesis of mixture of 1,3-thiazolo[3,2-*a*]pyrimidine-5-thiones.

Singh *et al.*[24] also reported an one-pot two-steps regioselective protocol for the synthesis of pyrazole derivatives. Here *in situ*-generated β-ketothioamides **99** using β-oxodithioesters **100** and amines **101** were reacted with hydrazines to obtain the products. A variety of functionalized pyrazole **97** (Scheme 31) and fused pyrazole **98** (Scheme 32) derivatives were synthesized through this reaction.
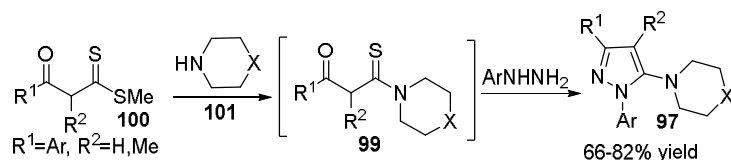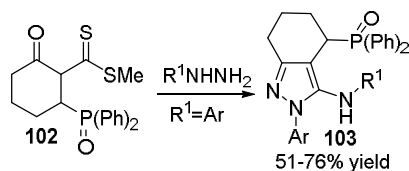

Scheme 31. Synthesis of pyrazoles.

Fort and co-workers[25] reported a similar protocol to generate the fused pyrazole **103** through phosphonate-containing cyclic KTAs **102** with hydrazines (Scheme 33). Except for the reaction using methylhydrazine and KTAs (R[1]=Ph), where a mixture of isomers was formed, all of the products were obtained regioselectively in good yield.
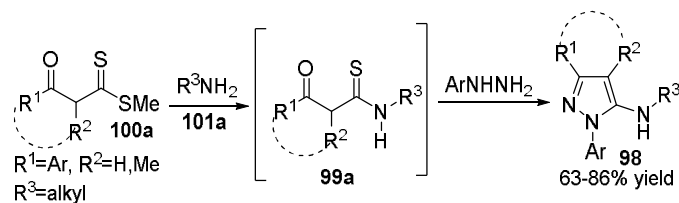
Scheme 32. Synthesis of fused pyrazoles.

Scheme 33. Synthesis of fused pyrazoles through phosphonate-containing cyclic KTAs.

Singh and co-workers[26] also reported a domino Knoevenagel condensation/cyclization cascade to synthesize functionalized pyrrol-2-thione derivative **104** from KTAs **31** and phenylglyoxal **105** catalyzed by indium triflate (Scheme 34). In this process two new bonds (C–C and C–N), one quaternary carbon center and one five-membered ring were created and it proceeds *via* intermediate **106**. All the substrates either electron-donating or electron-withdrawing groups on the aroyl group of the KTAs gave good to excellent yields.
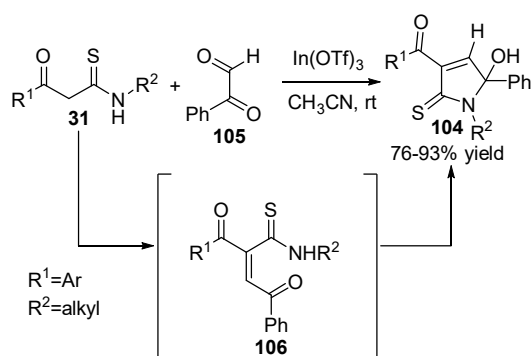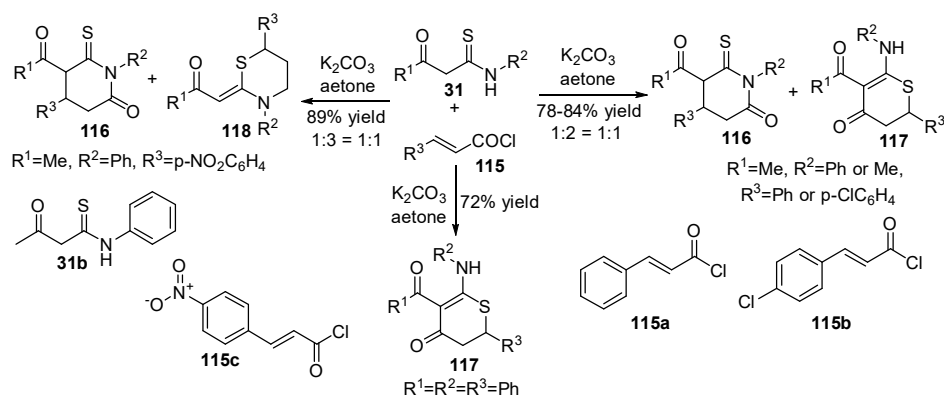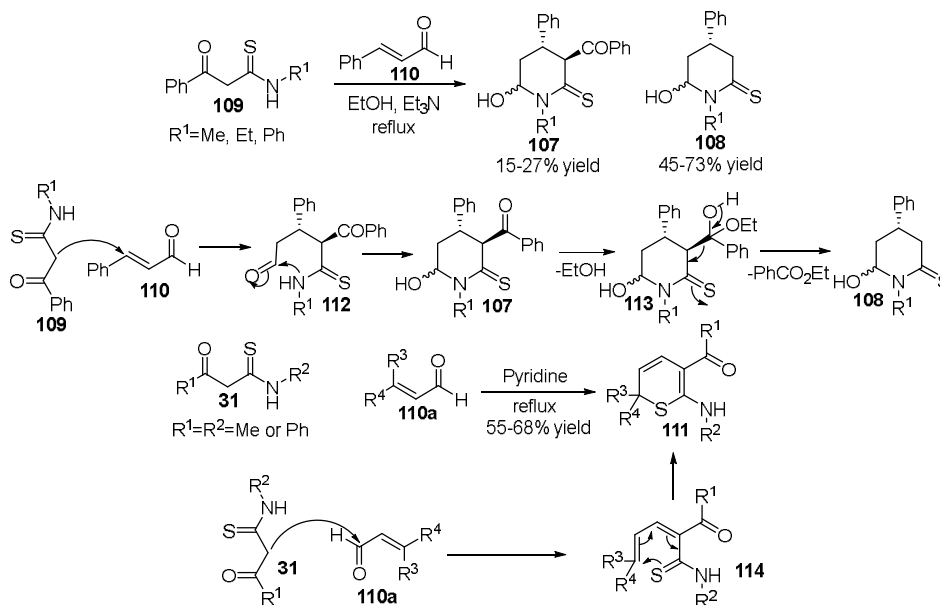

Scheme 34. Synthesis of pyrroles from KTAs.

Jagodziński and co-workers[27] synthesized a mixtures of diastereoisomeric 3-benzoylated **107** and 3-unsubstituted 6-hydroxypiperidine-2-thione derivatives **108** from the reactions between KTAs **109** and α,β-unsaturated aldehydes **110** in refluxing ethanol in the presence of catalytic amounts of triethylamine (Scheme 35). A plausible reaction mechanism involves stereoselective 1,4-addition of KTAs **109** to α,β-unsaturated aldehydes **110**, followed by intramolecular cyclization of the thioamide nitrogen to the aldehyde group in intermediate **112**. Interestingly, the major product here is the debenzoylated product **108**, which could also be obtained by a retro-Claisen-type reaction from **113**. Furthermore, both the structure of the unsaturated aldehyde and the solvent had influence on the reaction. When methylcrotonaldehyde **110a** was used and ethanol was replaced with pyridine, the thiopyran derivatives **111** were obtained through Claisen-type condensation followed by 6π-electrocyclization from intermediate **114**.

Having multiple reaction centers, KTAs sometimes may give mixture of products. Britsun and co-workers[28] used KTAs **31** and 3-aryl-2-propenoyl chlorides **115** as starting materials (Scheme 36). While changing the substituents of the starting materials the product ratios also differs. Using

3-oxo-*N*-phenylbutanethioamide **31b** and 3-phenyl-2-propenoyl chloride **115a** or 3-(4-chlorophenyl)-2-propenoyl chloride **115b** as starting materials in acetone in the presence of K₂CO₃, 6-thioxopiperidin-2-ones **116** and 4*H*-thiopyran-4-ones **117** were formed in 1:1 ratio. However, when condensation of KTAs with 3-(4-nitrophenyl)-2-propenoyl chloride **115c**, 6-thioxopiperidin-2-one **116** and 4*H*-1,3-thiazin-4-one **118** were obtained in 1:1 ratio. Only 4*H*-thiopyran-4-one **117** was obtained when KTAs **31b** reacted with 3-oxo-3*N*-diphenylpropanethioamide.

Scheme 35. Synthesis of piperidine-2-thiones and thiopyrans from KTAs.

Scheme 36. Synthesis of different heterocycles from KTAs with 3-aryl-2-propenoyl chlorides.

There is an important reaction procedure termed as multicomponent reactions (MCRs) which generates high levels of diversity within the molecule as there is involvement of at least three building blocks to be combined.[29] In a MCRs usually all the components are mxed in one pot, thus it can also be called as a subclass of domino reaction. The molecular complexity in this reactions are of high intensity which gives aceess to various heterocycles. Therefore, MCRs became an essential tool to envision the synthesis of

multiple heterocycles as well as natural products. Likely, MCRs utilizing functionalized KTAs are not left behind by the scientists, and are widely used to achieve a wide array of structural diversity in the complex heterocycles.

Recently, Li *et al.*[30] developed many multicomponent reactions based on KTAs, to synthesize functionalized 1,4-dihydropyridines, thiochromeno[2,3-*b*]pyridines, chromeno[2,3-*b*]quinolines *etc.* Hexasubstituted 1,4-dihydropyridine was synthesized by Li *et al. via* the reactions of KTAs **23** with aldehydes **120** and ethyl cyanoacetate **121** followed by *in situ* S-alkylation. This reaction was microwave assisted and very convenient to prepare the hexa-substituted 1,4-dihydropyridines **119** although the reaction is influenced by the substituents on the aromatic aldehydes (Scheme 37). Also it is a complementary protocol to the classical Hantzsch dihydropyridine synthesis.
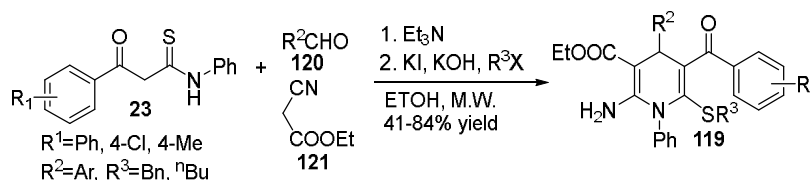

Scheme 37. Synthesis of 1,4-dihydropyridines.

A plausible mechanism is outlined which involves tandem Knoevenagel condensation of ethyl cyanoacetate **121** with the aldehyde **120** to produce **124**. Then Michael addition occurred by the KTAs **23** to the condensation product forming **122** which further undergo *N*-cyclization to generate **123**, followed by tautomerization and S_N2 reaction to the alkyl halide to yield hexasubstituted 1,4-dihydropyridine **119** (Scheme 38).
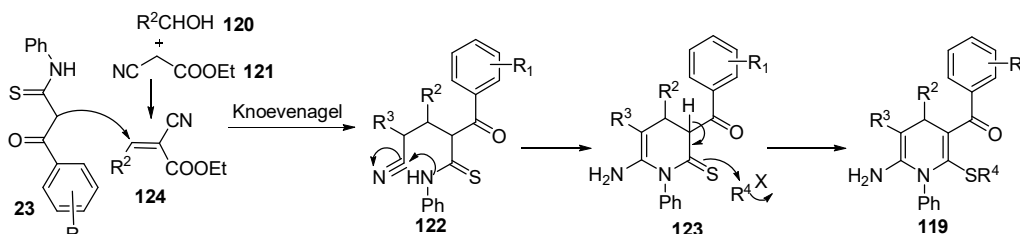
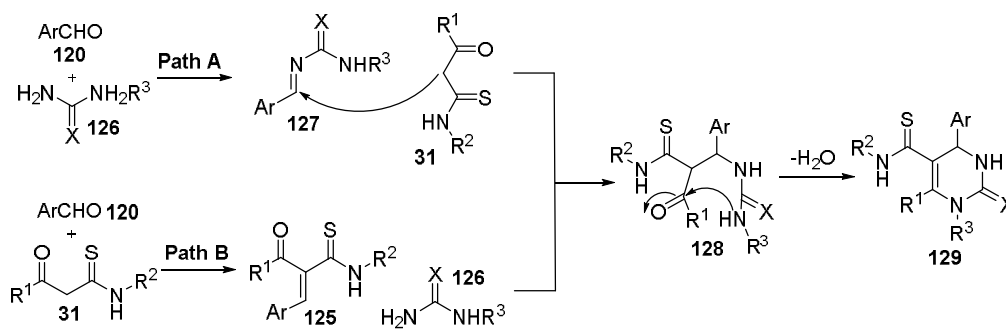**Scheme 38.** Plausible mechanism for the synthesis of 1,4-dihydropyridines.

Britsun and co-workers[31] developed a Biginelli-type reaction to synthesize tetrahydropyrimidine-5-carbothioamides **127** from KTAs **31**, aryl aldehyde **120** and ureas or thioureas **126** (Scheme 39). This reaction is highly regioselective and greatly substrate specific.
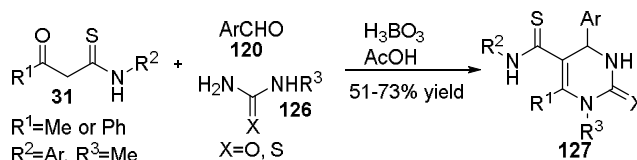
**Scheme 39.** Synthesis of pyrimidine-5-carbothioamides from KTAs.

There are two types of possible mechanism, one is similar to the Biginelli reaction where KTAs **31** reacts with the condensation product **127** from aldehyde **120** and urea **126** to produce intermediate **128** which subsiquently converted to the desired product **129** (Path A). Another approach includes Knoevenagel

condensation from KTAs **31** and aldehydes **120** to afford **125** which reacts with **126** to form the tetrahydropyrimidine-5-carbothioamides **129** *via* intermediate **128** (Path B) (Scheme 40).


Scheme 40. Plausible mechanism for the synthesis of tetrahydropyrimidine-5-carbothioamides.

A one-pot three-component Mannich-type reaction was described by Jagodziński and co-workers to synthesize functional spirohexahydropyrimidine derivatives **130**. This reaction is catalyzed by alcoholic hydrogen chloride using tetralone-derived thioamides **131**, formaldehyde **132** and amines **101a** as starting materials.[32] A possible mechanism is shown in Scheme 41. The α-carbon of the KTAs **23a** attacks the electrophilic imine **133** to obtain amino thioamide **134**, followed by the condensation with another molecule of formaldehyde to yield the desired product. The drawback of the reaction is that it proceeds only with primary aliphatic amines as substrates where secondary amines could not form the spiro heterocycle from formaldehyde due to no hydrogen on the amine group of **134**, rather it produces **135** (Scheme 42).
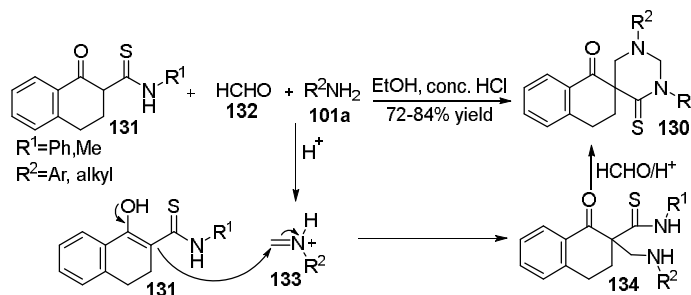

Scheme 41. Synthesis of spirohexahydropyrimidines.
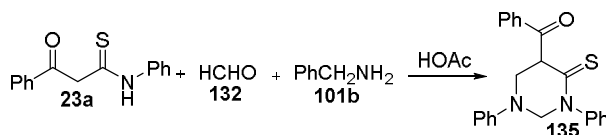
Scheme 42. Reaction of KTAs with formaldehyde and secondary amine.

Li and co-workers developed a new synthon β-(2-chloroaryl)ketothioamides **136**, which have five reactive centers, including a potential leaving halogen group on the aromatic ring. Due to the presence of an electron withdrawing *o*-carbonyl group, the halogen group on the aromatic ring is more likely to be attacked by sulfur or nitrogen atom on KTAs through intramolecular nucleophilic aryl substitution reaction. In 2009, Li *et al.*[33] reported the synthesis of thiochromeno[2,3-*b*]pyridine derivatives **137** under microwave irradiation using KF/neutral Al₂O₃ with PEG-6000 as an environmentally friendly catalyst (Scheme 43). The reaction mechanism begins wth a Knoevenagel reaction to form arylidine malononitrile **139** (derived from

120 and **138**) which is attacked by the α-carbon of KTAs to form the intermediate **140** followed by the *N*-cyclization to get intermediate **141**. After that, intermediate **141** undergoes *S*-cyclization to obtain the desired thiochromeno[2,3-*b*]pyridine **137**.
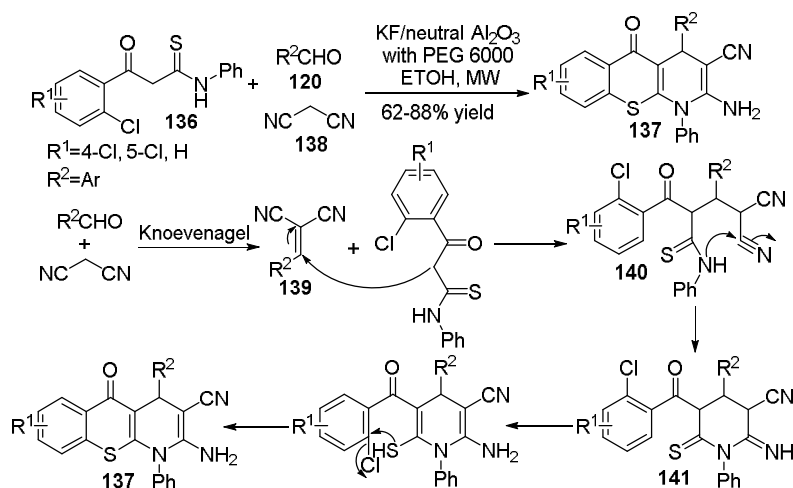
Scheme 43. Synthesis of thiochromeno[2,3-*b*]pyridines from KTAs with aldehydes and malononitrile.

Another multicomponent reaction was reported for the synthesis of thiochromeno[2,3-*b*]pyridine derivatives **142** by Li and co-workers[34] from the reaction of KTAs **136** with aldehydes **120** and Meldrum's acid **143** in the presence of Et₃N. The aliphatic aldehydes only gave mixture of products which limits the method to some extent (Scheme 44).
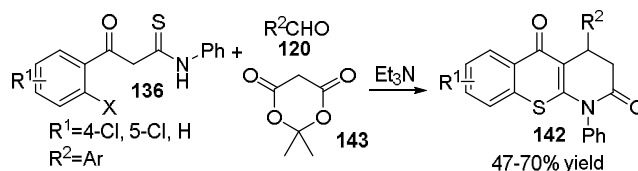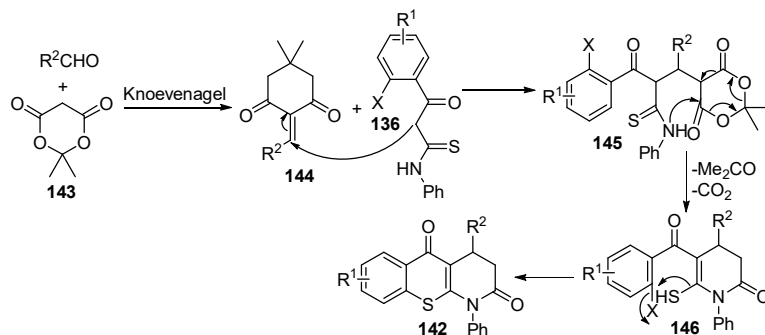

Scheme 44. Synthesis of thiochromeno[2,3-*b*]pyridines from KTAs.

A possible mechanism of the cascade reaction is shown in Scheme 45, which includes a Knoevenagel condensation of aldehydes with Meldrum's acid **143** to form the intermediate **144**. Then, Michael addition took place between **144** and α-carbon of KTAs **136** giving intermediate **145** which subsequently undergoes a regioselective *N*-cyclization intramolecularly. Next, there is an unusual collapse of the Meldrum's acid ring which eliminates acetone and CO_2 to generate the pyridine derivative **146**. Finally, an intramolecular *S*-cyclization with the o-halo group in phenyl ring yielded the desired product **142**.

1,2,3,4-Tetrahydropyridine derivatives **147** and thiochromeno[2,3-*b*]pyridine derivatives **148** were synthesized from KTAs **136**, aldehydes **120**, and aroyl acetonitriles **138a** *via* a highly efficient three-component cascade reaction by Li *et al.*[35] This reaction proceeds *via* DABCO-catalyzed tandem annulation and S_NAr reaction (Scheme 46). In this protocol, two C−C bonds, one C−N bond, one C−S bond, and two new rings were generated involving seven reactive sites. All substrates gave good to excellent yield, however, KTAs bearing either electron-donating or electron-withdrawing substituents on the N-aryl group at *para*-position the reaction does not proceed well.

An operationally simple method was established by Li *et al.*[36] to obtain functionalized tetrahydrobenzo[*b*]pyrans **149** regioselectively using Et₃N as catalyst from KTAs or 2-haloaryl KTAs **136**,

aromatic aldehydes **120** and 5,5-dimethyl-1,3-cyclohexanedione **151** *via* a 3-MCR. Treating the tetrahydrobenzo[*b*]pyrans **149** with K$_2$CO$_3$, gave a novel chromeno[2,3-*b*]quinoline framework **150** *via* an intramolecular S$_N$Ar reaction. The mechanism first includes a Knoevenagel condensation of 5,5-dimethyl-1,3-cyclohexanedione with aldehydes to afford the intermediate **152**. The latter reacts with the KTAs *via* Michael addition to form the intermediate **153**. A rapid keto-enol tautomerization followed by the intramolecular regiospecific *O*-cyclization yielded intermediate **154**. Then *via* the elimination of H$_2$S, tetrahydrobenzo[*b*]pyrans **149** are afforded followed by the attack of the NH group to the *ortho*-halo of aryl group *via* an intramolecular S$_N$Ar to obtain the highly functionalized chromeno[2,3-*b*]quinoline derivatives **150** (Scheme 47).

**Scheme 45.** Possible mechanism for the synthesis of thiochromeno[2,3-*b*]pyridines.
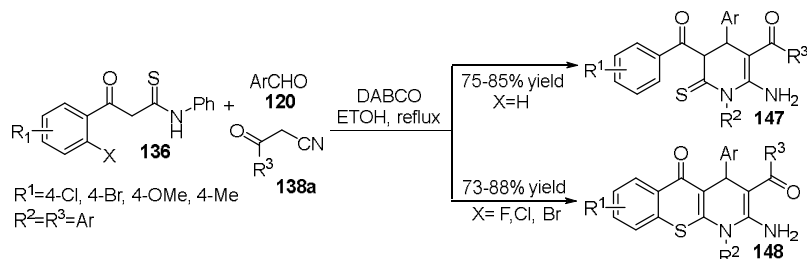
Scheme 46. Synthesis of 1,2,3,4-tetrahydropyridine and thiochromeno[2,3-*b*]pyridines from KTAs.
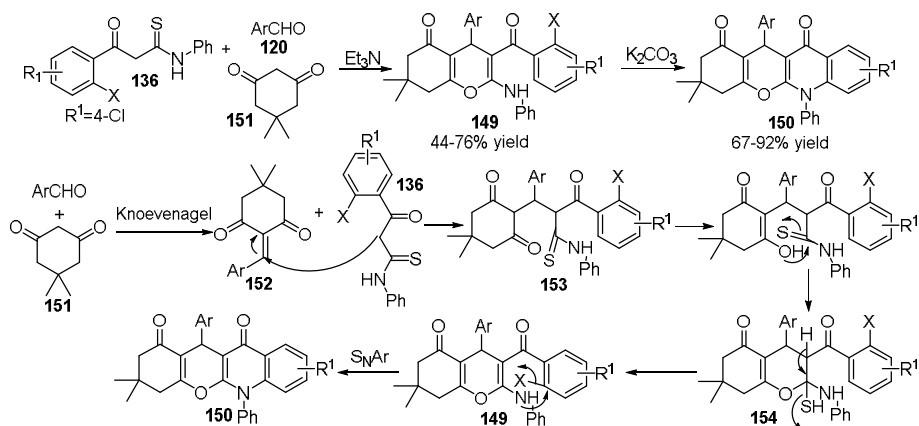

Scheme 47. Synthesis of chromeno[2,3-*b*]quinolines from KTAs.

There are other exciting class of novel KTAs like ethyl 2-(3-oxo-3-arylpropanethioamido)acetates **155** (Scheme 48) and ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido)acetates **156** (Scheme 50) which show intriguing and fascinating structural features. Asokan and co-workers[37] reported a simple method for the synthesis of tetra-substituted pyrrole derivatives **157** from readily available ethyl 2-(3-oxo-3-arylpropanethioamido)acetates **155**. The reaction proceeds *via* S-alkylation to produce **158**, followed by intramolecular cyclization catalyzed by POCl₃, and Vilsmeier-Haack process.
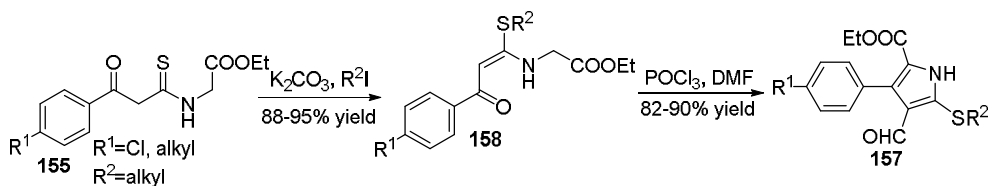
Scheme 48. Synthesis of pyrrole derivatives from KTAs.

Mathew and co-workers[38] synthesized pyrrolo[2,1-*b*]thiazol-6-ones **159** from ethyl 2-(3-oxo-3-arylpropanethioamido)acetates **155** and phenacyl bromides **160** under microwave irradiation (Scheme 49). This method is a two-step regioselective tandem cyclization reaction in one pot which results in functionalized pyrrolothiazoles in good yields. A possible reaction mechanism involves *S*-alkylation with phenacyl bromides to produce **161** followed by intramolecular *N*-cyclization and aza-ene type cyclization.
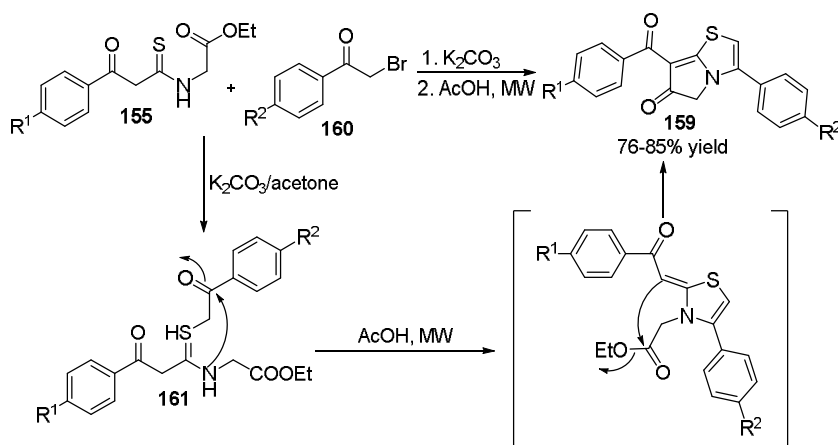

**Scheme 49.** Synthesis of pyrrolo[2,1-*b*]thiazol-6-ones from KTAs.

Li *et al.*[39] reported the synthesis of imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridines **162** from ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido)acetates **156**, aromatic aldehydes **120**, and malononitrile **138** or ethyl 2-cyanoacetate **138b** *via* a simple three-component synthetic protocol using cascade reactions. Here, in this domino process, ten reactive sites participated, which subsequently formed three C−C bonds, two C−N bonds, one C−S bond, and three new rings. Moreover, this method proceeded well with most of the substituents and gave good to excellent yield. Also, the purification is much easier as only washing with ethanol is required (Scheme 50). At first, the α-carbon of KTAs attacks the condensation product **163** to produce **164** followed by *N*-cyclization to yield **165**. Then *via* ketamine-enamine tautomerism and *N*-cyclization **166** was produced which subsequently liberates HCl *via* S-cyclization to obtain the desired product **162**.

The same group also reported a similar one-pot process to synthesize imidazo[1,2-*a*]pyridines **167** from ethyl 2-(3-oxo-3-arylpropanethioamido)acetates **155**, aromatic aldehydes **120**, and malononitrile **138** under microwave irradiation and DABCO as the catalyst.[40] This protocol also follows a similar mechanism

as above, as depicted in Scheme 51 *i.e.* at first, the α-carbon of KTAs attacks the condensation product **139** to produce **164a** followed by *N*-cyclization to yield **165a**. Then *via* ketamine-enamine tautomerism and *N*-cyclization **167** was obtained.
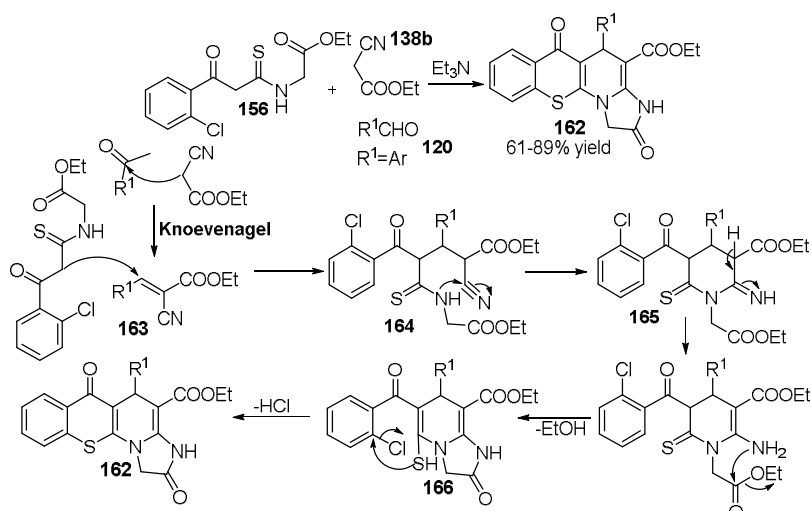
Scheme 50. Synthesis of imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridines from KTAs.
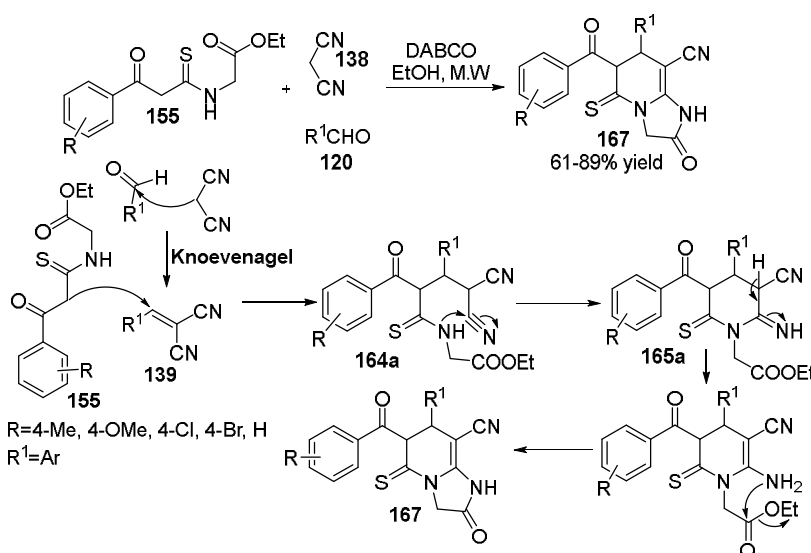
Scheme 51. Synthesis of imidazo[1,2-*a*]pyridines from KTAs.

6. Conclusion and outlook

The use of KTAs in modern organic synthesis has proved to be a booming choice for chemists to build diverse heterocyclic building blocks. Because of the delicate balance between their reactive centers, KTAs have broad applicability in metal-catalyzed, tandem cyclizations, one-pot reactions, *etc.* In this review, we have discussed the use and importance of KTAs throughout the past couple of decades. We also mentioned the recent studies and methodologies using KTAs as a valuable precursor to yield valuable frameworks. In

addition to the reactions with the nucleophilic sites (S and α-C atoms, N and S atoms, or N and α-C atoms) of KTAs, the reactions of the dinucleophilic reagents with the electrophilic sites (carbonyl and thiocarbonyl group) of KTAs are also reported.

Due to the presence of multiple reactive centers, associated with simple reaction conditions, easy purification, and convenient reaction methodologies, reactions involving KTAs will be very important in the future. KTAs can also be used to build various drug moieties containing sulfur, nitrogen, *etc.* The polymeric form of the KTAs might form a suitable cavity for capturing different environmental toxic materials, which could be an exciting topic for further studies. Moreover, there are very few reports of the formation of enantio-enriched compounds from KTAs using chiral studies. This leads to a very hot spot in the field of asymmetric synthesis and would grow a keen interest to the chemists to explore more about the KTAs. The use of bifunctional aminothiourea-based chiral catalysts might work well for the asymmetric reactions from KTAs. In contrast, the use of basic conditions, in the KTAs reactions might limit the use of any chiral Brønsted acid catalysts to some extent.

Acknowledgements

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