α-ENOLIC DITHIOESTERS: AN ATTRACTIVE PLATFORM FOR THE SYNTHESIS OF FUNCTIONALIZED HETEROCYCLES

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Abstract. *α-Enolic dithioesters have emerged as outstanding intermediates and continue to intrigue chemists with its electrophilic and nucleophilic sites, displaying an exceptionally fine balance between stability and reactivity. They also offer unique and multiple opportunities for the inclusion of sulfur-based functionalities into organic molecules, and are emerging as especially useful and versatile building blocks for various organic transformations. Recent breakthroughs in the utilization of these substrates have revitalized interest in diverse skeletally different heterocycles, and the recent past decade has witnessed one of the most exploited substrates for various transformations. An ever-increasing number of significant publications reporting the development of new reactions or synthetic sequences starting from α-enolic dithioesters are visible. This mini review highlights major developments in this area and updates the major progress in the field of domino reactions employing α-enolic dithioesters as one of the synthon covering the recent literatures. It illustrates how α-enolic dithioesters have emerged as outstanding building blocks for the development of a wide variety of fascinating one-pot domino reactions, leading to diverse monocyclic and polycyclic heterocyclic scaffolds.*

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1. Introduction

The art of designing and creating organic molecules in a highly efficient, economical and eco-compatible manner has always been fascinating, and a big challenge to synthetic chemists. Organic chemistry is the largest area of specialization among the various fields of chemistry. The underlying theory of heterocycles pervades the entire science. Among various heterocyclic systems, the six- and five-membered O-, N-, S- and P-heterocycles are probably one of the most common structural motifs spread across natural/man-made products, and from simple to structurally complex metabolites present in the structure of several biologically interesting compounds. Sulfur heterocyclic compounds have retained the interest of organic and inorganic researchers over the decades of historical development of chemistry. Apart from the common organic compounds, there are thousands of drugs, agricultural chemicals, fine chemicals and reagents, which contain sulfur. The element is extensively present in cysteine, methionine, and ferredoxin (the sulfur containing amino acids and proteins) as well as in pentathiepin molecules having antifungal, antitumor, and antimicrobial properties. Parallel to that, sulfur is also considered as a very important element in biomolecular systems. Further, the molecules with sulfur containing groups are widely applied as functional materials in rubber industry, polymer chemistry, pharmaceutical industry, as anti-oxidant, anti-radiation agents etc. Common sulfur-containing groups present in the molecules include thiols, sulfides, disulfides, sulfoxides, sulfones, sulfates, sulfonamides, thioketones, thiocyanates and isothiocyanates.

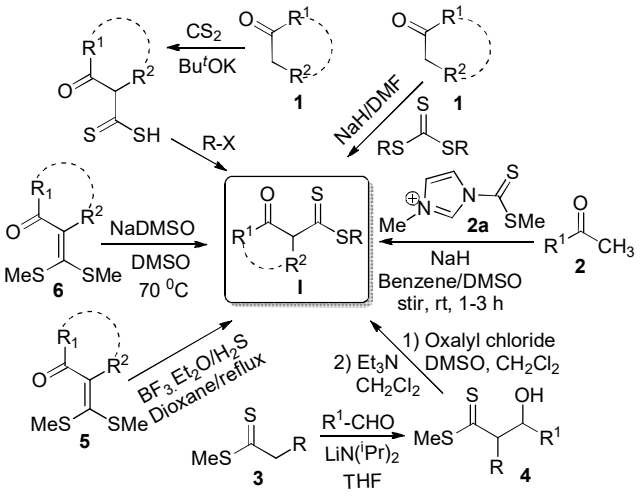
The essence of organic synthesis lies in its ability to construct structurally/skeletally diverse simple/complex molecules in excellent yield within short reaction time from cheap and viable starting

materials in a pot-, step-, atom-, and cost-economic manner under operationally simple and eco-friendly conditions. In this regard, β-keto/α-enolic dithioester (DTE) a simple polyfunctional molecule bearing adequate stability and reactivity, has been transformed to numerous interesting bioactive scaffolds. β-Ketodithioesters were first envisaged in 1968 by Beer and co-workers. Now, it has developed as a mature reactive intermediate in organic synthesis and opened up a new dynamic field in organic chemistry.[1] The number of applications of DTEs in organic synthesis, material chemistry, fine chemicals, and pharmaceuticals is increasing rapidly. Due to the presence of a number of tunable functionality in the molecule, it has a tremendous synthetic scope to be utilized as the versatile building block in the synthesis of various sulfur heterocycles. The β-keto/α-enolic dithioester scaffold has proven to be a versatile substrate toward the construction of carbon-carbon and carbon-heteroatom bonds enabling to a variety of valuable products. A major challenge of modern synthesis is to design not only efficient and selective cascades, but also eco-compatible that provides maximum structural diversity and complexity with a minimum number of synthetic steps. Therefore, new protocols in terms of efficiency, minimal environmental hazards, operational simplicity, and high selectivity are still demanding and would be of great relevance to synthetic, material, and medicinal chemists.

This report summarizes the key concepts behind β-keto/α-enolic dithioesters (DTEs) and provides an overview of current applications in organic synthesis. It illustrates how β-keto/α-enolic dithioesters have emerged as outstanding building blocks for the development of one-pot domino reactions, leading to diverse fascinating heterocyclic frameworks. The aim of this report is to point out the most recent advances in this field and to encourage the use of this intermediate to complex molecules and useful natural products. All works discussed in this report aim at demonstrating that β-keto/α-enolic dithioesters not only allow the design of operationally simple eco-efficient processes, but also open a straightforward access to new chemicals and materials.

2. Synthesis of β-keto/α-enolic dithioesters

Dithiocarboxylic acid esters are valuable synthons in synthetic organic chemistry. β-Ketodithioesters with general formula **I** have been prepared from substituted acetophenones **1** by the addition of carbon disulfide in the presence of potassium *t*-butoxide followed by alkylation.[2a] Alternatively, Junjappa *et al.*[2b] showed the utilization of 3-methylimidazolium-1-carbodithioic acid methyl ester **2a** instead of dimethyltrithiocarbonate along with active methylene compounds **2** for the synthesis of β-keto/α-enolic dithioesters **I** (Scheme 1).

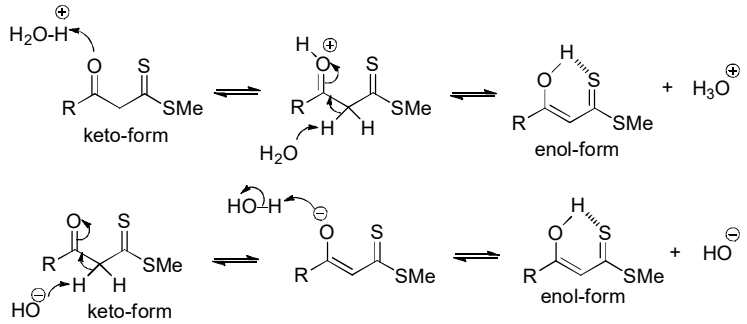


Scheme 1. Synthesis of β-keto/α-enolic dithioesters.

Beslin and Houtteville utilized dithioester **3** in the synthesis of β-keto/α-enolic dithioesters **I** by regiocontrolled condensation of dithioester **3** and aldehyde followed by oxidation of the β-hydroxydithioester **4** so formed.[3] The most convenient synthesis of β-keto/α-enolic dithioesters can be achieved by thiocarbonylation reaction of active methylene ketone with dimethyl trithiocarbonates and chlorodithioformates.[4] $BF_3.Et_2O$ mediated hydrolysis of α-oxoketene dithioacetals **5** by hydrogen sulphide constitutes another method for β-keto/α-enolic dithioester synthesis.[5] β-Keto/α-enolic dithioesters can also be prepared from the selective demethylation of *α*-oxoketene dithioacetal by dimsyl sodium (Scheme 1).[6]

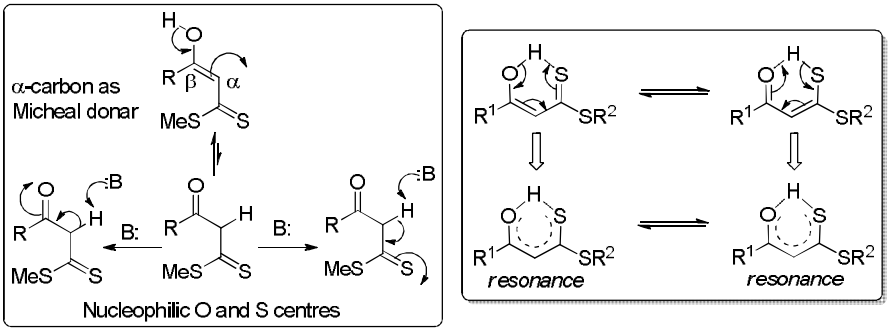
3. Reactivity profile of β-keto/α-enolic dithioesters

Simple polyfunctional molecules are ideal starting materials in diversity-oriented synthesis (DOS), which aims at providing quick access to libraries of molecules. Synthons containing both electrophilic and nucleophilic sites have great potential in developing new reaction pathways. One such simple synthon is β-keto/α-enolic dithioester, a thio-analogue of the normal β-ketoester (Scheme 2). Remarkably, its reactivity is far different from β-ketoester due to its distinguishing arrangement and close proximity of three nucleophilic (O, C and S) and two electrophilic (C=O and C=S) sites. The presence of such a large number of reactive centres makes this molecule highly useful for organic transformations. Oxygen and sulfur atoms along with α-carbon, which acts as Michael donors are nucleophilic, while β-carbonyl carbon and thiocarbonyl carbon are electrophilic in nature. The electron-withdrawing character of the β-keto functionality increases the acidity of the α-protons. This increased acidity of the α-proton in turn promotes a shift of the keto-enol tautomerism toward the enol form that is further stabilized by intramolecular hydrogen bonding and conjugation of the carbon-carbon double bond with the carbonyl group.



Scheme 2. Acid (Top) and base (Bottom) catalyzed keto-enol tautomerism of β-ketodithioester.

Enols are nucleophiles with reactivity in between that of alkenes and enolates, thus making them ideally suited for carbon-carbon bond formation under mild conditions. Although the keto-enol interconversion is normally represented as simple tautomerism (as in Scheme 2), it is important to recognize that this process may be catalyzed through both acids and bases (*i.e.*, conditions readily attainable in aqueous or other mild environments). As will be outlined in the remainder of this report, formation of simple and complex molecules from β-keto/α-enolic dithioesters under acid/base catalysis is a keystone principle for organic transformations under various catalytic conditions. For example, a base may be used to increase nucleophilicity of the α-carbon in the β-ketodithioester by promoting enol formation or stabilize an enolate intermediate as depicted in Scheme 3, while a hydrogen bonding catalyst may activate the electrophile toward nucleophilic attack by the enol or other nucleophiles, as outlined in Scheme 3. As it is obvious from spectral and crystallographic analyses that it solely exists in α-enolic form in both the solid as well as in solution phase, often it is treated as α-enolic dithioester rather than β-ketodithioester (Figure 1). However, the equilibrium between keto-enol tautomerism depends upon reaction conditions.



Scheme 3. Possible reactive centres of α-enolic dithioester and resonance-assisted hydrogen bonding.

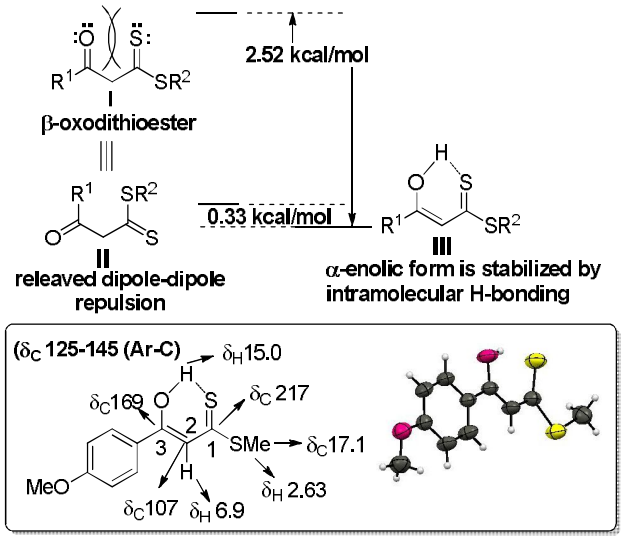


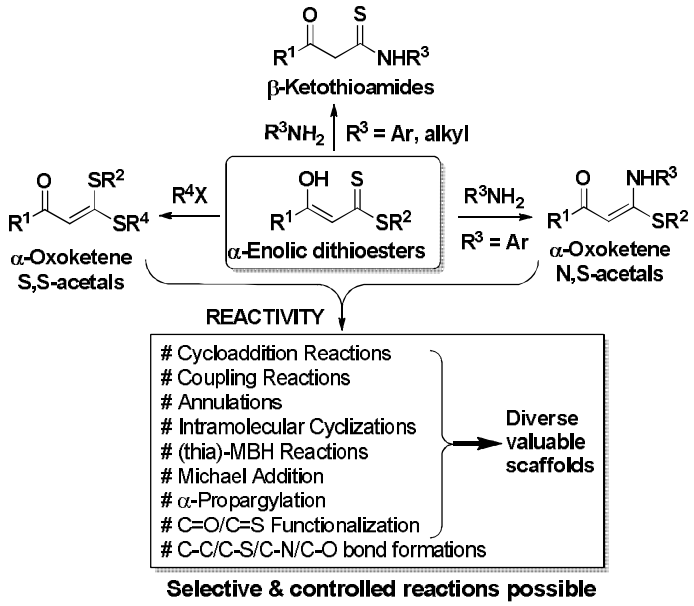
Figure 1. Structure of α-enolic dithioester.

4. Functionalization of β-keto-/α-enolic dithioester

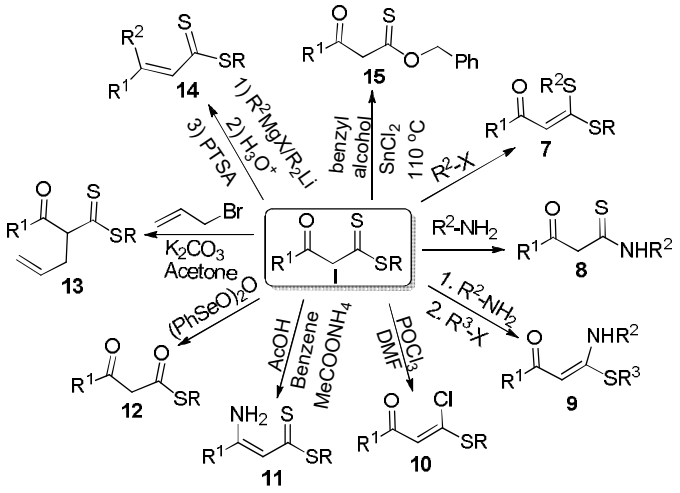
The versatility of this class of compounds is due to its unique structure comprised of a carbonyl group at β-position to a dithioester moiety. Besides the self-participation of α-enolic dithioester in different synthetic methodologies, it can also be converted to pioneer different daughter precursors like α-oxoketene *S,S*-acetal, α-oxoketene *N,S*-acetal, β-ketothioamide etc. simply by treating α-enolic dithioester with different counterparts[7] like alkyl halides, aromatic and aliphatic amines, respectively (Scheme 4). An ever-increasing number of significant publications reporting the development of new reactions or synthetic sequences starting from β-oxodithioesters and their derivatives are visible. Proper tuning of these functional groups makes the dithioester a versatile precursor for the synthesis of various useful molecules of biological importance.

Previously some research groups have practiced functionalization of β-ketodithioester for the use in different synthetic contexts for various purposes. β-ketodithioester **I** has been easily and efficiently converted to α-oxoketene-*S,S*-acetal **7**, β-ketothioamide **8** and α-oxoketene-*N,S*-acetal **9**, which could be further utilised as valuable building blocks in various organic synthesis. Suma and Asokan[8a] prepared the chlorinated product **10** by treating β-ketodithioester **I** with Vielsmayer-Hack reagent. Vigante *et al*.[8b]

transformed β-ketodithioester into alkyl β-aminodithiocrotonate **11**. Labiad and Villemin[8c] reported the process of selective transformation of the thiocarbonyl group to carbonyl **12** group using seleninic anhydride (Scheme 5).



Scheme 4. Functionalization of α-enolic dithioester to other useful synthons.



Scheme 5. Transformation of β-oxodithioesters to other useful synthons.

Some of these compounds have been used for the synthesis of sulfur containing heterocyclic systems.[8d] α-Allyl substituted 1,3-diketone compounds are known as useful intermediates in organic synthesis. Junjappa *et al*.[8e] synthesized and utilized structurally similar α-allyl-β-ketodithioester **13**. They achieved this conversion *via* S-alkylation of *α*-enolic dithioester **1** with allyl bromide in the presence of K_2CO_3 in acetone

followed by [3+3]-thio-Claisen rearrangement. Masson and Thuillier[8f] reported an interesting chemoselective addition of organometallic reagents to β-ketodithioester **I** for the synthesis of β-hydroxydithioester, which then transform to α,β-unsaturated dithioester **14** and described some potential synthetic uses of these synthons. Recently, Singh and co-workers[8g] disclosed transesterification of β-ketodithioester catalyzed by stannous chloride under solvent-free conditions to afford thioester **15** (Scheme 5).

5. Synthetic applications of β-keto/α-enolic dithioesters

Synthetic organic chemistry (SOC) occupying a central role in every area of our increasingly technological society, retained its importance as it is an integral part of new drug discovery, and is the basis of bulk of chemical industry. Synthesis of heterocycles is a key to organic synthesis, since heterocycles are indispensable materials in the functioning of any developed society. Simple polyfunctional molecules are ideal starting materials in diversity-oriented synthesis (DOS), which aims at providing quick access to libraries of molecules. Although particularly attractive, direct annulation reactions to the heterocyclic framework from acyclic precursors still constitute an important synthetic challenge. During the past decade, methods available for the synthesis of β-ketodithioester and its derivatives have significantly expanded, making it one of the most exploited substrates for various transformations. If two or three functional groups in a molecule are situated far away, they exhibit their own specific properties. However, if they are in close proximity, in addition to their own specific properties they could also display quite unique unexpected properties resulting from the identity and interconnectedness (interact with one another) of the multiple functional groups. It would illustrate how β-oxodithioesters have emerged as outstanding intermediates for the development of a wide variety of fascinating one-pot domino reactions, allowing complex and diverse structures to be easily generated from simple materials forming multiple bonds in a single step. This concept cuts several purification steps, minimizes chemical waste generation, as well as increases yield and saves time. Thus, a one-pot reaction is not only operationally simple, economically advantageous and chemically efficient, but also eco-friendly and green. Figure 2 shows the general and wide applicability of acyclic dithioester to various significant cyclic frameworks.

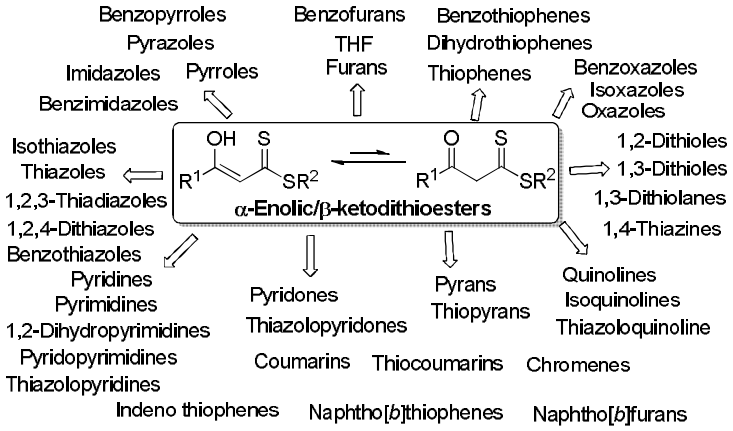
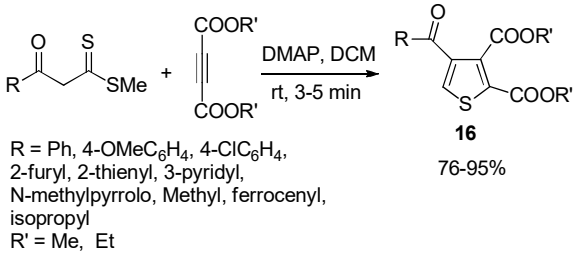


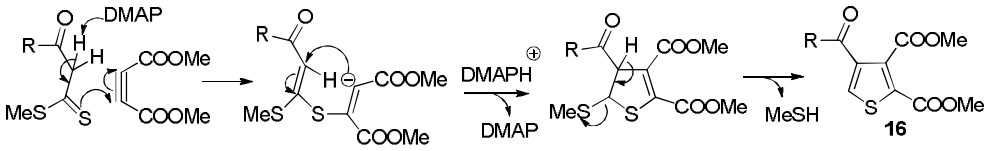
Figure 2. Construction of various cyclic scaffolds from acyclic dithioesters.

An efficient and experimentally rapid protocol for the synthesis of 2,3-dicarboalkoxy-4-aroyl/heteroaroyl/alkanoyl thiophenes **16** has been developed *via* 1-2 (C–S) and 3-4 (C–C) bond connections catalyzed by 4-dimethylaminopyridine (DMAP) in solvent dichloromethane (DCM) (Scheme 6).[9a]



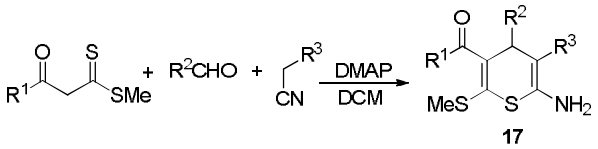
Scheme 6. Synthesis of trisubstituted thiophenes.

The plausible reaction scenario for this one-pot two-component heteroannulation has been proposed and outlined in Scheme 7. The first step in the mechanism is believed to be the abstraction of acidic proton of β-ketodithioester by DMAP followed by nucleophilic attack on the sp-hybridized carbon of the dialkyl acetylenedicarboxylate to generate an open-chain adducts α-oxoketene dithioacetals that undergo intramolecular cyclocondensation *via* C–C bond formation with the extrusion of MeSH to give the thiophene derivatives. The intermediacy of α-oxoketene dithioacetal has been confirmed by its isolation and characterization when TEA was utilized as base.



Scheme 7. Thiophene formation *via* α-oxoketene dithioacetal.

A convergent and regioselective heteroannulation protocol for the synthesis of fully substituted 2-amino-4-(aryl/alkyl)-5-(aroyl/heteroaroyl)-3-(cyano/carboalkoxy)-6-methylthio-4*H*-thiopyran derivatives **17** has been devised *via* one-pot three-component domino coupling of β-oxodithioesters, aldehydes, and malononitrile/ethyl or methyl cyanoacetate, promoted by 4-dimethylamino pyridine (DMAP) in solvent dichloromethane (DCM) as well as under solvent-free conditions in excellent yields (Scheme 8).[9b]

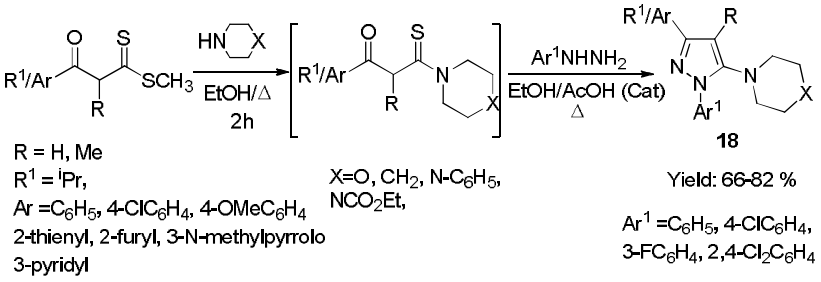


Scheme 8. Synthesis of substituted 4*H*-thiopyrans.

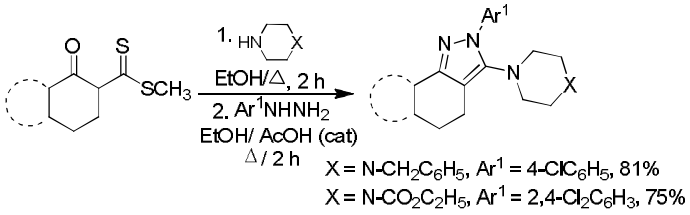
Singh *et al.*[9c] developed an efficient and highly regioselective protocol for the synthesis of 5-amino substituted pyrazoles **18** *via* one-pot three component cyclocondensation of β-oxodithioester, amine, and hydrazine in refluxing ethanol in the presence of catalytic amount of AcOH (Scheme 9). The reported densely functionalized pyrazoles have been constructed through the cyclization of *in situ* generated thioamide intermediate from β-oxodithioester. Several β-oxodithioester obtained from cyclic ketones such as cyclohexanone and α-tetralone also provided amino substituted fused pyrazole in good yield with variety of cyclic amines and substituted hydrazines (Scheme 10). Use of primary amine in the reaction also afforded good yield and the results are shown in Scheme 11.

Singh and co-workers[10a] utilized β-oxodithioester in the multicomponent reaction for the first time. They employed this molecule as an alternative to the 1,3-dicarbonyl compound in the Biginelli reaction. A

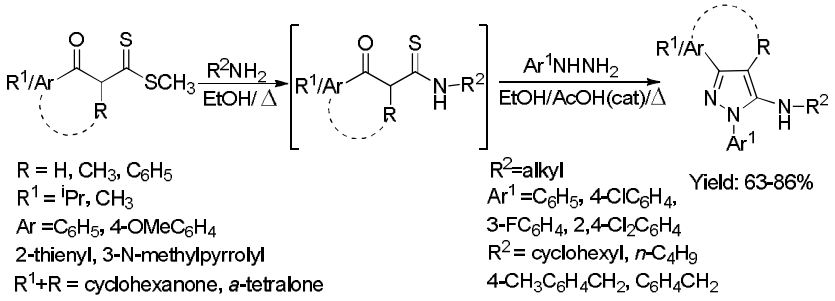
series of dihydropyrimidinones **19** were synthesized through the Biginelli reaction of β-oxodithioester, aromatic aldehyde and the urea at 100 °C in the presence of catalyst $SnCl_2.2H_2O$ under solvent-free conditions (Scheme 12). It takes almost 3-4 h to complete the reaction and provided the corresponding Biginelli products in 70-82% yield. Our group[10b] also reported the same reaction with improvement in the reaction efficiency. We employed silica-sulfuric acid as a recyclable heterogeneous catalyst. The use of urea in this reaction increases the yield of the product; in absence of urea decrement of yield was observed (Scheme 12).



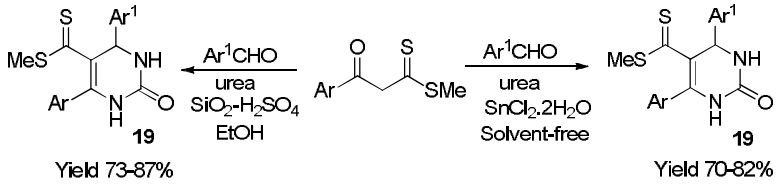
Scheme 9. Synthesis of amino substituted pyrazoles.



Scheme 10. Synthesis of fused pyrazoles.

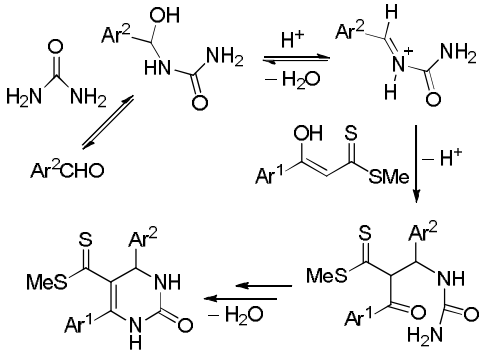


Scheme 11. Synthesis of 5-alkylaminopyrazoles.



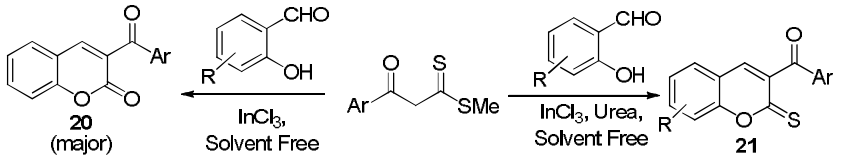
Scheme 12. Synthesis of dihydropyrimidones.

The plausible mechanism of this Biginelli reaction has been drawn in Scheme 13. The first step is believed to be the condensation between the aldehyde and urea to generate iminium intermediate, with some similarities to the Mannich condensation. The iminium intermediate thus formed acts as an electrophile for the nucleophilic addition of the α-carbon of dithioester. The ketone carbonyl of the resulting open-chain ureide adduct undergoes cyclocondensation with the urea NH_2 followed by dehydration (facilitated by SiO_2-H_2SO_4) to give the cyclised product (Scheme 13).



Scheme 13. Mechanism for Biginelli reaction.

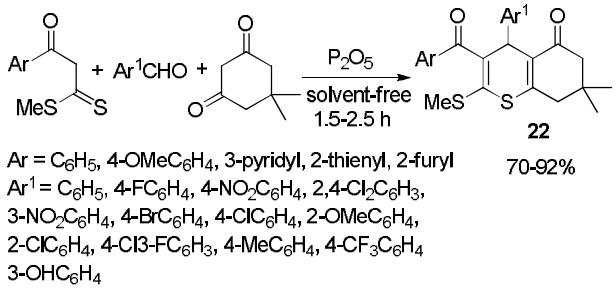
$InCl_3$ mediated solvent-free synthesis of aroyl or alkanoyl substituted chromene-2-thiones **21** as well as coumarin derivatives **20** have been reported,[10c] and antileishmanial activity of the chromene-2-thione analogues were evaluated.[10d] One of the most interesting feature of the above synthesis is the selectivity dependency of the product formation with promoter urea *i.e.*, in presence of urea chromene-2-thione derivatives **21** are the exclusive product but in absence of urea coumarin derivatives **20** are the major one (Scheme 14).



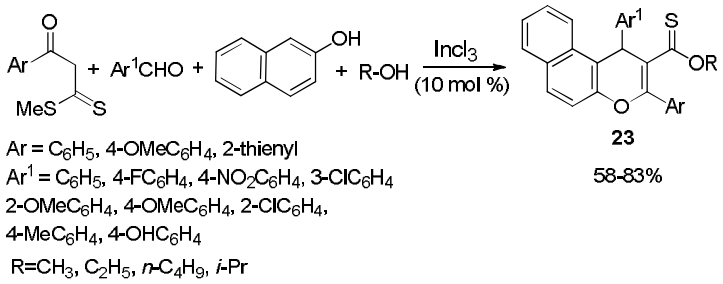
Scheme 14. Selective synthesis of chromene-2-ones and chromene-2-thiones.

Thiochromone derivatives are known to exhibit versatile pharmacological activity. Singh *et al.*[11] developed a operationally simple, mild and efficient annulation protocol for the synthesis of highly functionalized thiochromene derivatives **22** *via* one-pot reaction of β-ketodithioester, aldehyde and cyclic-1,3-diketone under solvent-free condition at 100 °C within 1.5-2.5 h catalyzed by P_2O_5 (Scheme 15). This is the first report for the synthesis of thiochromones **22** *via* multicomponent ring annulation of β-oxodithioester utilizing easily available and inexpensive Phosphorus pentoxide (P_2O_5), which acts both as catalyst as well as dehydrating agent.

Singh and co-workers[12] developed a general protocol for the synthesis of 4*H*-benzo[*f*]chromenes **23** *via* a four component reaction of β-oxodithioester, aromatic aldehyde, β-naphthol and primary alcohols in the presence of catalyst $InCl_3$ (Scheme 16). This transformation presumably proceeds *via* domino Knoevenagel condensation/Michael addition/intramolecular cyclodehydration/transesterification sequence creating four new bonds and one stereocenter in a single operation. Interestingly, alcohol plays dual role as a reactant as well as a reaction medium.

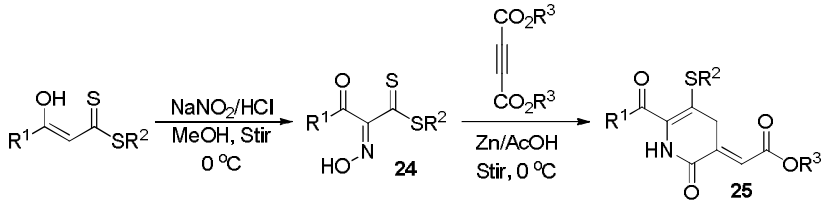


Scheme 15. Synthesis of thiochromones.



Scheme 16. Synthesis of benzochromenes.

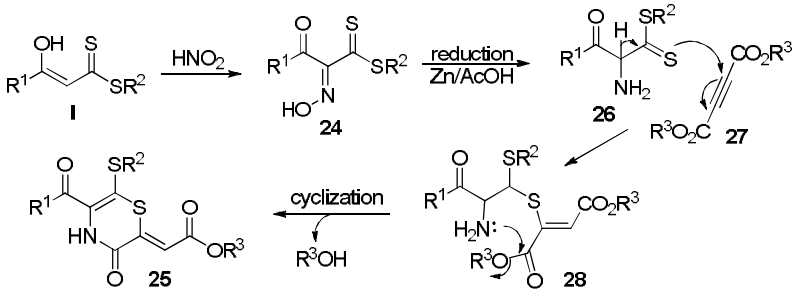
An operationally simple and facile synthesis of α-hydroxyimino-β-oxodithioesters **24** by nitrosation of α-enolic dithioesters have been reported.[13] Further the treatment of compound **24** with internal alkynes afforded diverse 1,4-thiazin-3-ones **25** *via* domino reduction/annulation strategy under mild reaction conditions (Scheme 17).



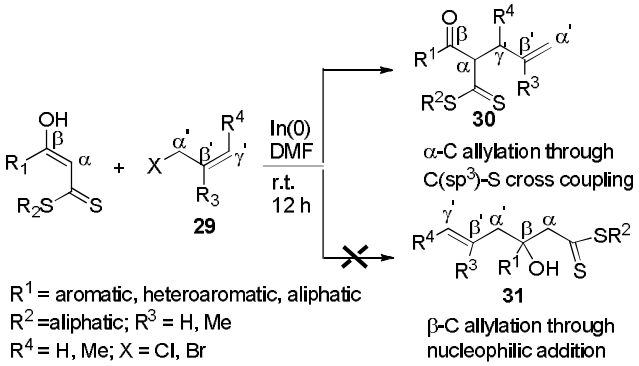
Scheme 17. Synthesis of α-hydroxyimino-β-oxodithioester and further functionalization.

In this transformation, the key steps involved are first α-enolic dithioester **I** upon nitrosation forms oxime intermediate **24**, which was isolated and again subjected to Zn/AcOH reduction to give amine intermediate **26**, which could not be isolated. Subsequently, the reactive amine intermediate **26** undergoes a conjugate addition with activated alkyne **27** to give an acyclic adduct intermediate **28**. Intermediate **28** undergoes nucleophilic attack of amine nitrogen to the ester carbonyl carbon followed by elimination of R^3OH to give the desired 1,4- thiazine-3-ones **25** (Scheme 18).

Singh and co-workers[14] have developed a facile indium(0)-mediated regioselective alkylation protocol for α-enolic ester/dithioester systems that proceeds through a Csp^3–S/O cross-coupling reaction of alkylindium reagents and α-enolic esters/dithioesters. A reasonable mechanism that describes the overall reaction pathway has also been documented (Scheme 19).

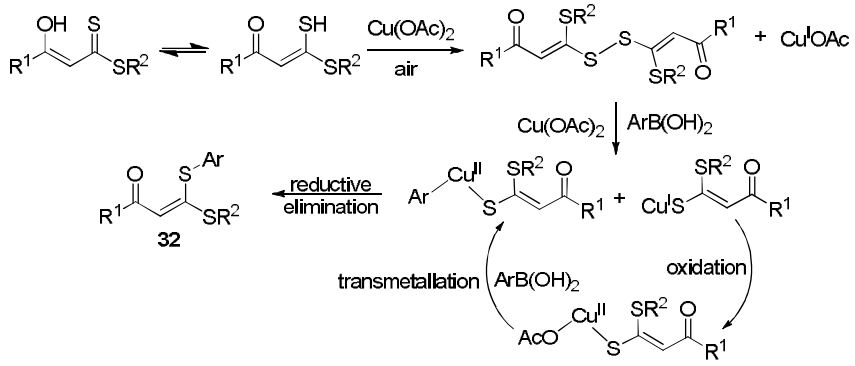


Scheme 18. Synthesis of 1,4-thiazin-3-ones **25** *via* domino reduction/annulation strategy.



Scheme 19. Indium(0)-mediated regioselective alkylation of α-enolic dithioester.

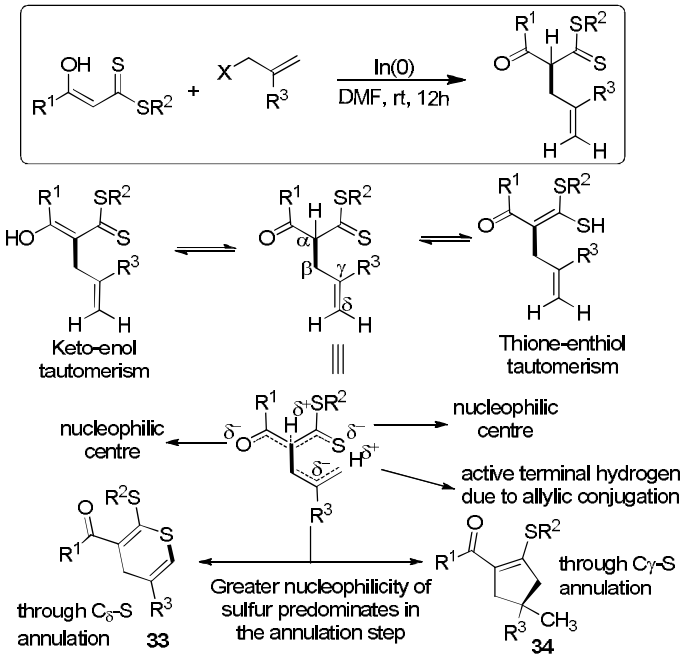
A highly efficient one-pot regioselective protocol for *S*-arylation leading to unsymmetrical α-oxoketene *S*-aryl, *S*-alkyl acetals **32** through the cross-coupling of arylboronic acids with α-enolic dithioesters at room temperature under ligand-free and base-free mild conditions has been developed.[15] In this reaction, $Cu(OAc)_2$ acts as an effective promoter for this transformation (Scheme 20).



Scheme 20. Regioselective S-arylation of *α*-enolic dithioesters.

Singh *et al.*[16] introduced a highly efficient and atom-economic dual reaction manifold to synthesize 4*H*-thiopyran and 4,5-dihydrothiophene frameworks *via* regioselective intramolecular C–S fusion of

α-allyl-β′-oxodithioesters. The selective formation of the sulfur-heterocycles has been efficiently tuned by the use of two different catalytic systems. Palladium activates the C_δ–H of the allyl termini and facilitates the intramolecular C_δ–S coupling to furnish six-membered thiopyran skeletons **33** exclusively. Conversely, the allylic double bond of the same substrate has been activated by $BF_3{\cdot}Et_2O$ to promote the C_γ–S cyclization leading to the formation of a five-membered dihydrothiophene nucleus **34** (Scheme 21).

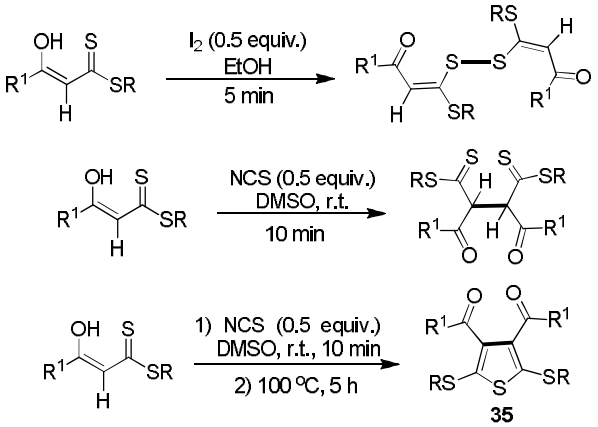


Scheme 21. α-Functionalization and further transformation to cyclic systems.

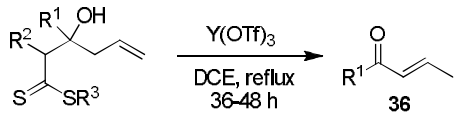
Singh *et al.*[17] developed a method where an α-enolic dithioester undergoes oxidative homodimerization in the presence of molecular iodine and facilitates the formation of S–S coupling leading to *S,S′*-bis(dithioacetals), while *N*-chlorosuccinimide (NCS) facilitates C–C coupling to give α,α′-bis(β-oxo dithioesters), respectively in good yield. Furthermore, the newly generated α,α′-bis(β-oxodithioesters) have been directly employed in the synthesis of fully substituted thiophenes **35** with a unique symmetrical substitution pattern in a one-pot, two-step reaction sequence (Scheme 22).

Chowdhury *et al.* [18] synthesized β-allyl-β-hydroxydithioesters by the regioselective Grignard addition to the β-oxodithioesters. Further, they successfully employed this precursor in selective $C(sp^3)$–$C(sp^3)$ bond cleavage to construct α,β-unsaturated ketone residues **36** by the treatment of an emerging catalyst yttrium(III)triflate $Y(OTf)_3$. On the other hand, heteroaryl substituted β-allyl-β-hydroxydithioesters led to the useful diene precursors through selective dehydration under the similar conditions (Scheme 23).

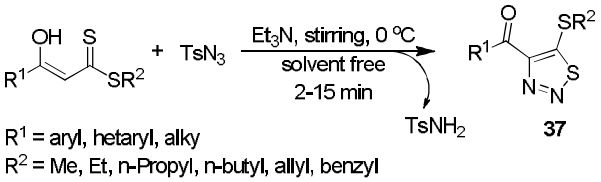
Nagaraju and co-workers[19] devised a method by which an efficient, sustainable, and regioselective one-pot synthesis of hitherto unreported 4-aroyl/hetaroyl/alkanoyl-5-alkyl/allyl/benzylsulfanyl-1,2,3-thiadiazoles **37** has been achieved by [3+2]-cycloaddition of α-enolic dithioesters with tosyl azide through cascade 1-2 (S–N) and 3-4 (C–N) bond connections involving Wolff-type heterocyclization. The eco-compatibility, mild conditions, excellent yields, easy purification, and avoidance of expensive/toxic reagents are additional advantages of this protocol to access this medicinally privileged substructure (Scheme 24).



Scheme 22. Synthesis of fully substituted thiophenes.



Scheme 23. Synthesis of α,β-unsaturated ketones.



Scheme 24. Synthesis of 1,2,3-thiadiazoles.

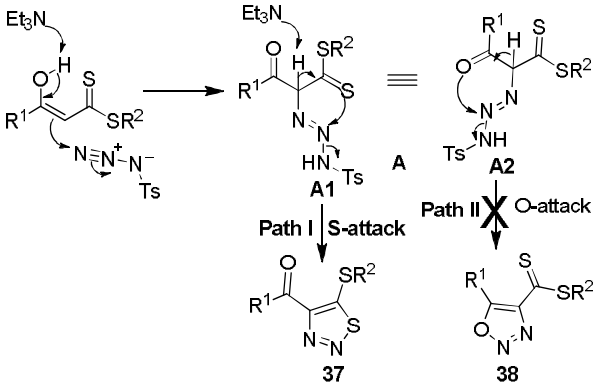
The first step in the mechanism is the abstraction of enolic proton from α-enolic dithioesters by Et_3N followed by nucleophilic attack of α-carbon on the sp-hybridized electrophilic nitrogen of tosylazide, forming C–N bond to generate the intermediate **A**. The intermediate **A** can undergo cyclization *via* its two possible rotamers **A1** and **A2** through pathways I and II to furnish 1,2,3-thiadiazole **37** and 1,2,3-oxadiazole **38**, respectively with the extrusion of *p*-tosyl amide. The intermediate **A1** undergoes intramolecular cyclization by attack through sulfur *via* route I to give the desired 1,2,3-thiadiazole **37**, exclusively. The formation of 1,2,3-oxadiazole **38** was not observed even in trace during the course of the reaction (Scheme 25).

An economical and straightforward synthesis of diverse 4,5-disubstituted 1,2,3-thiadiazoles **37** from α-enolic dithioesters has been achieved *via* nitrosation/reduction/diazotization/cyclization sequence in one-pot through the formation of cascade 1-2 (N–S) and 3-4 (C–N) bonds. Importantly, this is the first straightforward entry to highly functionalized 1,2,3-thiadiazoles from dithioesters.[20] (Scheme 26).

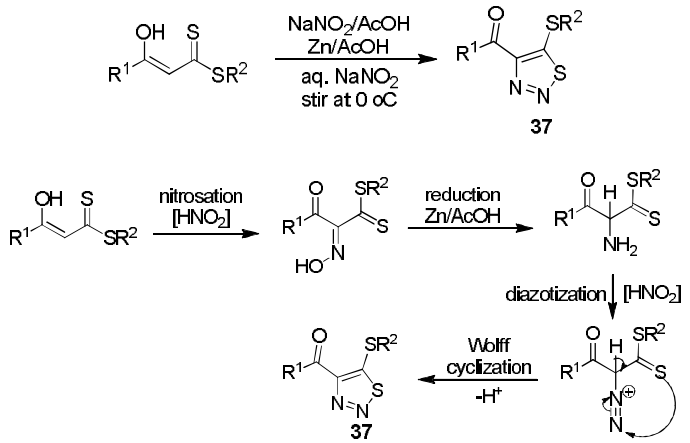
Singh and co-workers[21] introduced a coupling protocol where 3,4,5-trisubstituted 1,2-dithioles **38** has been synthesized *via* palladium catalyzed self-coupling of *α*-enolic dithioesters. Pd(0) efficiently catalyses the activation and cleavage of S–H and C–S bonds to achieve cascade coupling, which results in the concomitant formation of S–S and C–C bonds enabling five-membered 1,2-dithioles (Scheme 27).

Later on Ramulu *et al.*[22] synthesized 1,2-dithiols **38** by copper catalyzed self-coupling of α-enolic dithioesters *via* consecutive formation of S–S and C–C bonds (Scheme 28). Low-cost copper powder

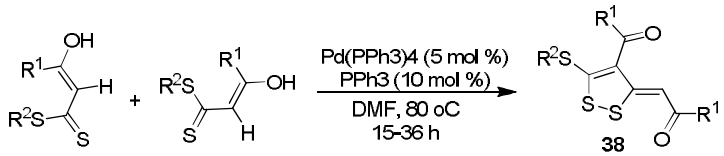
together with Ag_2O as oxidant and promoter can be recycled at least four times with no loss of catalytic activity, making this strategy an ideal alternative to existing methods. Notably, *in situ* formation of *S,S'*-bis(dithioacetal) as a reactive intermediate has been proven, and the corresponding mechanistic insights are experimentally established.



Scheme 25. Plausible Mechanism for the formation of 1,2,3-thiadiazoles.

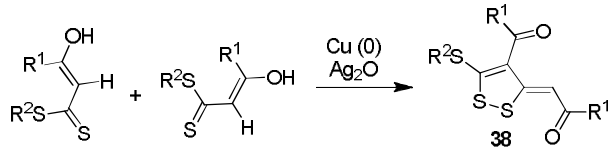


Scheme 26. Synthesis of 1,2,3-thiadiazoles.

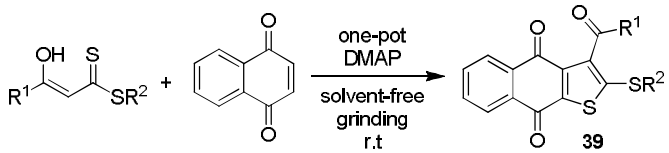


Scheme 27. Synthesis of 3,4,5-trisubstituted 1,2-dithioles.

Solvent-free mechanochemical route to naphtho[2,3-*b*]thiophenes **39** *via* oxidative [3+2]-heteroannulation of α-enolic dithioesters and β-oxothioamides with 1,4-naphthoquinone has been achieved at room temperature[23] (Scheme 29).

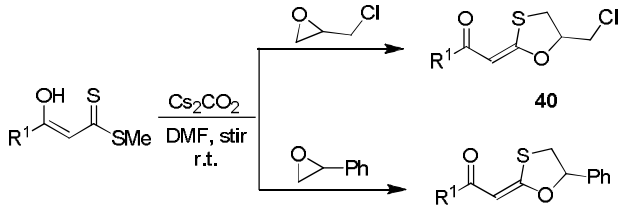


Scheme 28. Synthesis of 1,2-dithioles.



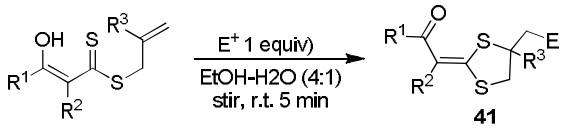
Scheme 29. Synthesis of 2,3-disubstituted naphtho[2,3-*b*]thiophene-4,9-diones.

α-Enolic dithioesters undergo cascade [2+3]-heteroannulation with epoxides promoted by non-nucleophilic moderate base Cs_2CO_3 at room temperature to give 1,3-oxathiolan-2-ylidenes **40** for the first time (Scheme 30). Typical features of this strategy include metal-free mild reaction conditions, atom-economy, high yield and efficacy of forming two consecutive C–S and C–O bond, and one ring in a single stroke. Thiomethanol (MeSH) is the only by-product, and the stereochemistry of the exocyclic α-oxoketene moiety of 1,3-oxathiolane was assigned to have *Z*-configuration.[24]



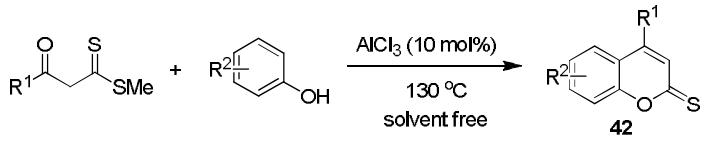
Scheme 30. Synthesis of 1,3-oxothiolan-2-ylidenes.

A new and user-simple domino protocol for the efficient synthesis of 2-alkylidene-1,3-dithiolanes **41** has been developed *via* molecular iodine mediated iodocyclization of S-allylated α-enolic dithioesters at room temperature. The attractive features of this strategy include mild reaction conditions, short reaction time, high atom economy, high selectivity, easy purification, excellent yields and wide substrate scope. Notably, many examples gave the exocyclic double bond of the 1,3-dithiolane with *Z*-configuration, while others gave *E/Z* mixtures; interconversion of the *E*- and *Z*-isomers was observed under acidic and thermal conditions[25] (Scheme 31).



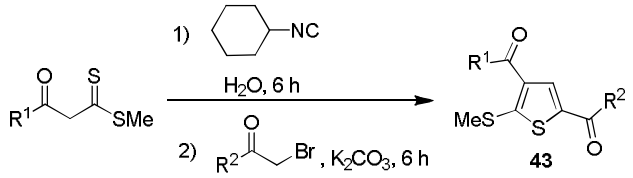
Scheme 31. Synthesis of 2-alkylidene-1,3-dithiolanes.

Singh and co-workers[26] reported a facile synthesis of chromene-2-thiones **42** by the Pechmann condensation of phenols with β-oxodithioesters catalyzed by 10 mol % of $AlCl_3$ at 130 °C under solvent-free conditions (Scheme 32). The better results were obtained in the case of substituted phenols such as resorcinol, substituted resorcinol and pyrogallol.



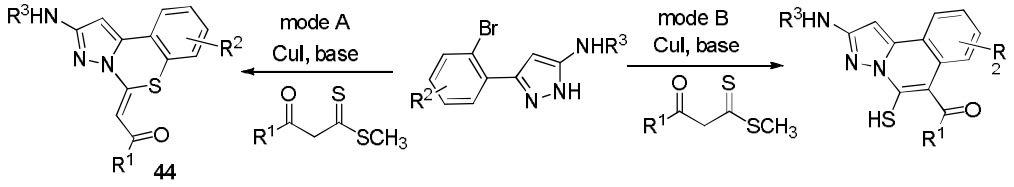
Scheme 32. Synthesis of chromene-2-thiones.

Polysubstituted thiophene derivatives **43** were obtained by multicomponent reaction of β-ketodithioesters, α-haloketones, and cyclohexylisocyanide in aqueous medium[27] (Scheme 33).



Scheme 33. Synthesis of polysubstituted thiophene derivatives.

Li and co-workers[28] developed a method, where a benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives **44** has been developed by tandem Ullmann coupling reactions of β-oxodithioesters with 3-(2-bromoaryl)-1*H*-pyrazoles in C−S bond formation manner, in which β-oxodithioesters play dual roles as a substrate and ligand. A series of benzo[*e*]pyrazolo[1,5-*c*][1,3]thiazine derivatives were obtained in good to excellent yields with CuI as the copper source in the presence of NaOH in CH_3CN at 80 °C under N_2 atmosphere (Scheme 34). A plausible mechanism has been shown in Scheme 35.



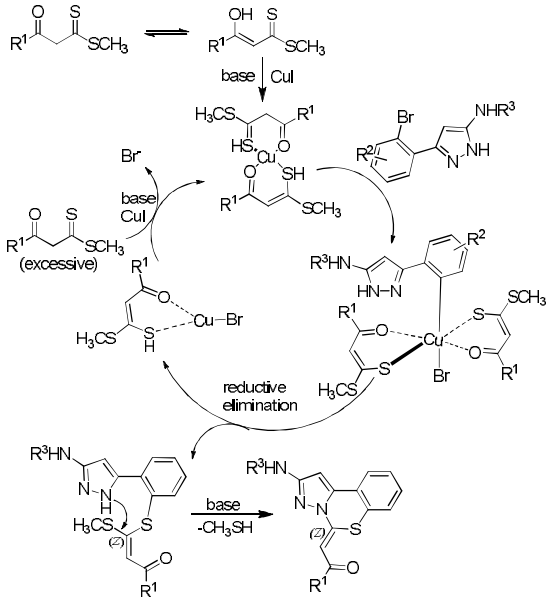
Scheme 34. Copper-catalyzed coupling modes involving β-oxodithioesters.

Singh and co-workers[29] devised a novel approach where an efficient and highly regioselective one-pot three-component synthesis of 3-(cycloalkyl/alkyl/arylamino)-5-aryl/alkylisoxazoles **45** has been achieved by the cyclocondensation of β-oxodithioesters, amines and hydroxylamine in ethanol at reflux (Scheme 36). This transformation proceeds *via* an *in situ* generated β-oxothioamide by the reaction of the β-oxodithioester and amine, which undergoes nucleophilic attack by hydroxylamine followed by intramolecular cyclization with the oxo functionality and subsequent dehydration to give 5-substituted 3-aminoisoxazoles as a single regioisomer in good yields. Furthermore, the mechanism of the reaction has been established experimentally and shown to be in agreement with the hard and soft (Lewis) acid and base (HSAB) theory.

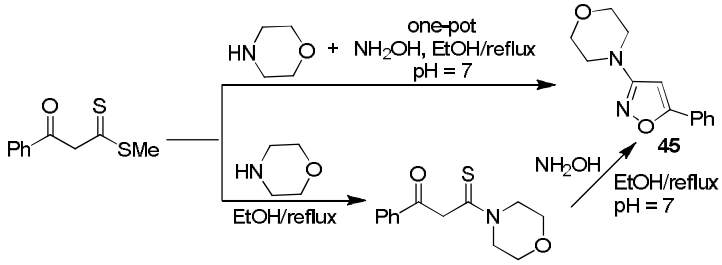
Nagaraju *et al.*[30] deduced a cost-effective and eco-friendly straightforward synthesis of highly diversified thiazoloquinoline scaffolds **46** *via* one-pot four-component cascade reaction utilizing α-enolic dithioesters, cysteamine, aldehydes, and cyclic 1,3-diketones in water-PEG-400 (Scheme 37). This protocol generates two rings by the concomitant formation of C−C (two), C−N (two), and C−S multiple bonds involving a sequence of *N,S*-acetal formation, Knoevenagel reaction, aza-ene reaction, imine-enamine/keto-enol tautomerization, and N-cyclization as key steps.

The first step involved in the formation of cyclic *N,S*-acetal by the reaction of α-enolic dithioester with cysteamine, next reaction of aldehyde with cyclic 1,3-diketone gives Knoevenagel product, a highly reactive *ortho*-quinonemethide intermediate that could not be isolated. Subsequently, the *N,S*-acetal undergoes a

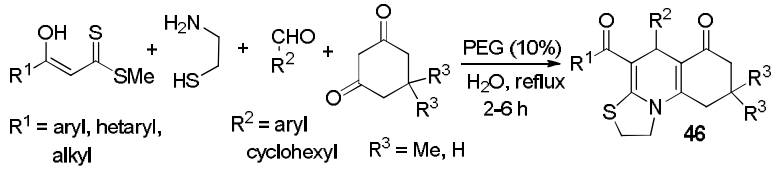
conjugate addition with *ortho*-quinonemethide intermediate *via* an aza-ene fashion to generate acyclic intermediate. Intermediate undergoes imine-enamine and keto-enol tautomerization to give intermediate, which rapidly undergoes intramolecular dehydrative N-cyclization to give the desired triheterocyclic product (Scheme 38).



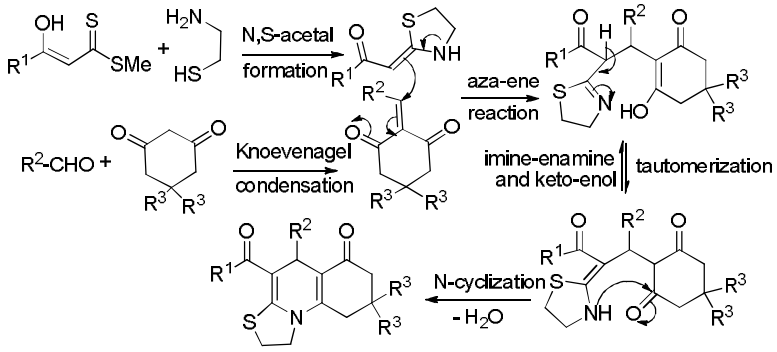
Scheme 35. Proposed mechanism.



Scheme 36. One-pot and stepwise synthesis of 3-morpholine-5-phenylisoxazole.

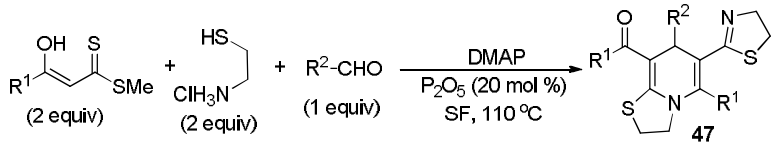


Scheme 37. One pot four-component synthesis of thiazoloquinolines.



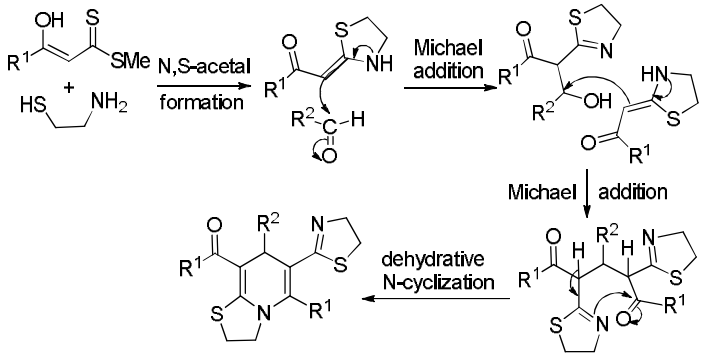
Scheme 38. Possible mechanism for formation of thiazoloquinolinone.

Singh and co-workers[31] reported an operationally and user-simple, a highly efficient one-pot three-component (5 molecules) reaction of α-enolic dithioesters, cysteamine hydrochloride and aldehydes, which furnished a range of thiazolopyridines **47** in high yields under metal-free and solvent-free conditions involving a sequence of *N,S*-acetal formation/double Michael addition/N-cyclization as key steps in a single operation (Scheme 39).



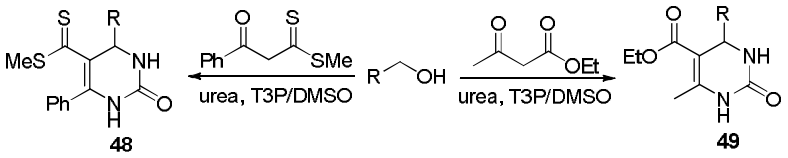
Scheme 39. Synthesis of highly functionalized thiazolopyridines.

The cyclic *N,S*-acetal thus obtained by a reaction of α-enolic dithioester with cysteamine will undergo reaction with aldehyde to gave intermediate, which further reacts with a second molecule of *N,S*-acetal to form new intermediate, which rapidly undergoes intramolecular dehydrative N-cyclization to furnish the desired thiazolopyridine **47** (Scheme 40).



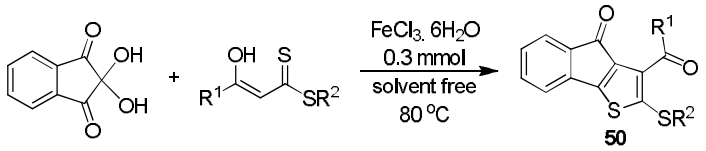
Scheme 40. Plausible mechanism for the formation of thiazolopyridines.

Mantelingu *et al*.[32] reported an efficient and highly convergent route to dihydropyrimidinones (DHPMs) **48** and **49** by one-pot three-component oxidative cyclocondensation employing a variety of alcohols, β-ketoesters/β-oxodithioester and urea (Scheme 41).



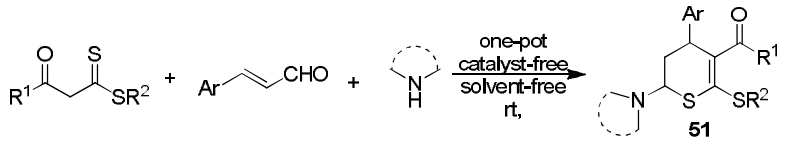
Scheme 41. Synthesis of dihydropyrimidinones.

It is most customary to generate thiophene or thiopyran from α-enolic dithioester. Recently, very important methods have been developed to access thiophene and thiopyran from α-enolic dithioester. Singh and co-workers[33] reported the synthesis of a broad range of indeno[1,2-*b*]thiophenes **50** through the annulation of α-enolic dithioesters with ninhydrin in the presence of $FeCl_3 \cdot 6H_2O$ under solvent-free conditions (Scheme 42). The method is economic with regard to the number of steps as well as to being a one-pot carbon-efficient process that is devoid of toxic reagents and solvents.



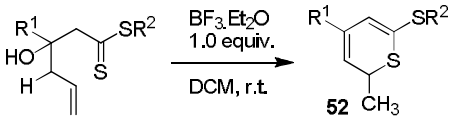
Scheme 42. Synthesis of indeno[1,2-*b*]thiophenes.

Koley *et al*.[34] reported a highly convergent and regioselective approach to synthetically demanding 6-cycloamino-2-(methyl/benzyl)sulfanyl-3-(aroyl/hetaroyl/alkanoyl)-4-aryl-5,6-dihydro-4*H*-thiopyrans **51**, which is achieved *via* one-pot three-component domino reaction of β-oxodithioesters, α,β-unsaturated aldehydes, and cyclic aliphatic secondary amines at room temperature under catalyst-free and solvent-free conditions (Scheme 43).



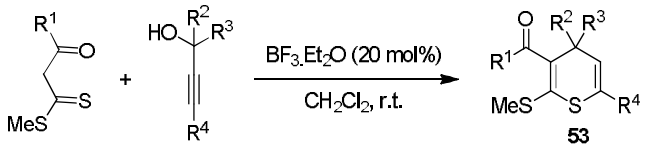
Scheme 43. Synthesis of 5,6-dihydro-4*H*-thiopyrans.

Chowdhury and co-workers[35] reported the synthesis of 2*H*-thiopyrans **52** from β-allyl-β-hydroxy dithioesters *via* regioselective intramolecular annulation strategy. Lewis acid $BF_3.Et_2O$ efficiently mediated the regioselective dehydration followed by intramolecular thio-annulation at room temperature (Scheme 44).



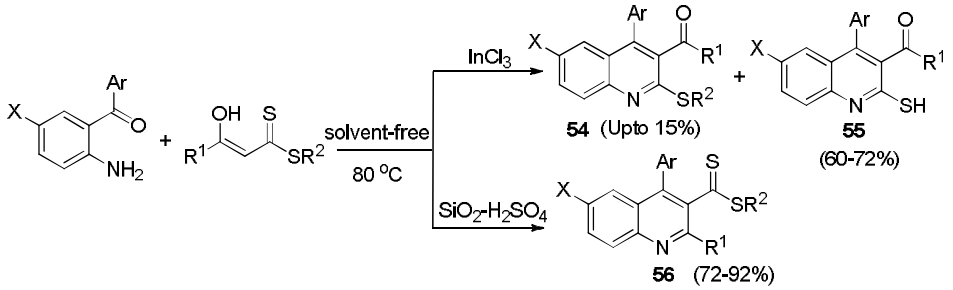
Scheme 44. Synthesis of thiopyrans.

Madabhushi *et al*.[36] reported a simple and efficient method for the synthesis of polyfunctionalized 4*H*-thiopyrans **53** via highly regioselective cyclocondensation of β-oxodithioesters with 1,1,3-trialkyl or aryl substituted prop-2-yn-1-ols using $BF_3.Et_2O$ as the catalyst (Scheme 45).



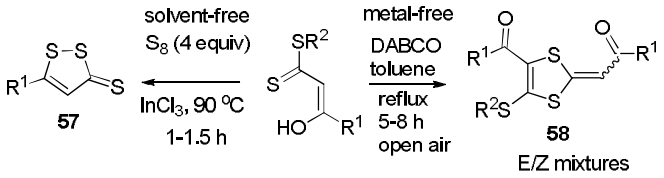
Scheme 45. Synthesis of polyfulctionalysed 4*H*-thiopyrans.

A straightforward approach for the chemodivergent synthesis of quinolines (**54**-**56**) is described through site-selective coupling of *ortho*-aminoaryl ketones with α-enolic dithioesters (DTEs) under solvent-free conditions. The operationally and user-simple one-pot methodology is based on the trifunctional nature of DTEs. Both the carbonyl and the thiocarbonyl moiety in α-enolic dithioesters were employed for the efficient construction of three differently substituted quinolines in a chemoselective manner simply by variation of easy to handle acid catalyst[37] (Scheme 46).



Scheme 46. Synthesis of diverse quinolines.

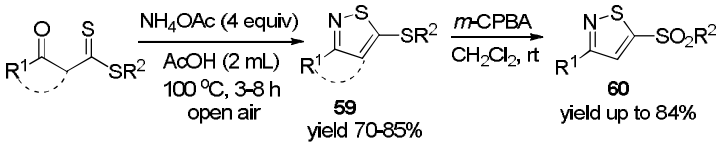
An operationally simple cascade protocol has been developed for the construction of 1,2- and 1,3-dithiole derivatives **57** and **58** from α-enolic dithioesters. 1,2-Dithioles are achieved by the reaction of dithioesters with elemental sulfur in the presence of $InCl_3$ under solvent-free conditions. 1,3-Dithioles have been constructed *via* DABCO mediated self-coupling of dithioesters in open air enabling the formation of two new C–S bonds and one ring in a single operation in contiguous fashion. The reactions proceeded smoothly affording the desired sulfur-rich heterocycles in good to excellent yields, exhibiting gram-scale ability and broad functional groups tolerance utilizing easy to handle cheap and easily available reagents. The probable mechanisms for the formation of 1,2- and 1,3-dithioles from α-enolic dithioesters have been suggested[38] (Scheme 47).



Scheme 47. Construction of 1,2- and 1,3-dithiole derivatives from α-enolic dithioesters.

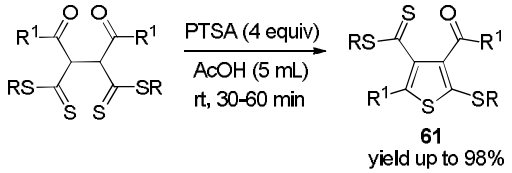
An user friendly new protocol for the synthesis of 3,5-disubstituted/annulated isothiazoles **59** is devised utilizing β-ketodithioesters/β-ketothioamides and NH_4OAc *via* C=O/C=S bond functionalization under metal and catalyst-free conditions.[39] The strategic [4+1]-annulation initiated by NH_4OAc is carbon-economic and relies on sequential imine formation/cyclization/aerial oxidation cascade forming consecutive C–N and S–N bonds in one pot. A wide range of previously inaccessible and synthetically

challenging isothiazoles are compatible with this transformation under non-toxic conditions with excellent functional group tolerance. The products bear useful synthetic handles for further functionalization. The isothiazoles thus obtained were further oxidized to the corresponding isothiazoles **60** by *m*-CPBA (Scheme 48).



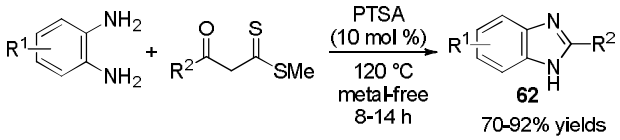
Scheme 48. Synthesis of 3,5-disubstituted/annulated isothiazoles.

Metal-free *para*-toluenesulfonic acid (PTSA) mediated straightforward synthesis of hitherto unreported tetrasubstituted thiophenes **61** has been achieved in quantitative yields by chemo- and regioselective dehydrative cyclization of α,α′-bis(β-oxodithioesters) at room temperature.[40] Notably, the dithioester group at 4-position of thiophene ring has been further transformed to thiazoline group (Scheme 49).



Scheme 49. Synthesis of tetrasubstituted thiophenes.

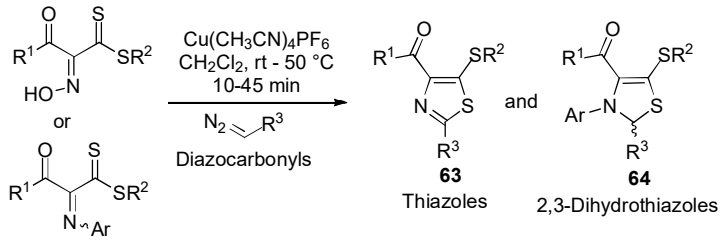
The benzofused nitrogen heterocycles have a great importance in drug discovery and materials, among them benzimidazole scaffold is of particular interest and has been categorized as a privileged scaffold. An operationally simple and user-friendly one-pot domino protocol for the synthesis of 2-aryl/hetaryl benzimidazoles **62** has been devised form easily available and inexpensive 1,2-phenylenediamines and β-oxodithioesters. The strategic [4+1]-heteroannulation initiated by Brønsted acid PTSA relies on remarkable domino sequence of condensation, cyclization and elimination.[41] The current approach enables N–H/N–H functionalization under solventless and metal-free conditions leading to diverse benzimidazoles. The reactions proceeded smoothly affording the desired products in good to excellent yields, exhibiting gram-scale ability and broad functional groups tolerance. Notably, the approach is highly chemo- and regioselective (Scheme 50).



Scheme 50. Synthesis of 2-aryl/hetaryl benzimidazoles.

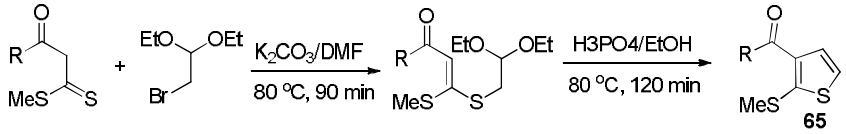
An efficient chemoselective practical route to fully substituted thiazoles **63** and 2,3-dihydrothiazoles **64** has been devised by [4+1]-heterocyclization of α-(*N*-hydroxy/aryl)imino-β-oxodithioesters with *in situ* generated Cu-carbenoids of diazocarbonyls.[42] The α-(*N*-hydroxy/aryl)imino-β-oxodithioesters are readily accessible by the reaction of β-oxodithioesters with nitrous acid/nitrosoarenes. The overall transformation involves sequential N–O/C–N bonds cleavage followed by cascade C–N/C–S bonds formation in one-pot. This new strategy allows full control over the introduction of various sensitive functional groups at different

positions of the thiazole ring, broadening the arsenal of synthetic methods to obtain such scaffolds (Scheme 51).



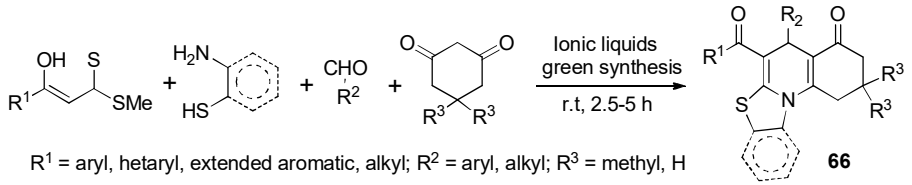
Scheme 51. Synthesis of fully substituted thiazoles and 2,3-dihydrothiazoles.

Junjappa *et al.*[43] introduced a method where β-oxodithioates react with bromoacetaldehyde diethylacetal in the presence of anhydrous potassium carbonate in dimethyl formamide at 80 °C to generate the corresponding mixed acetals. The corresponding acetals undergo cyclization in the presence of ethanolic orthophosphoric acid to afford the corresponding 2-methylthio-3-acyl/aroyl/heteroaroyl thiophenes **65** in good yields (Scheme 52).



Scheme 52. Formation of disubstituted thiophene.

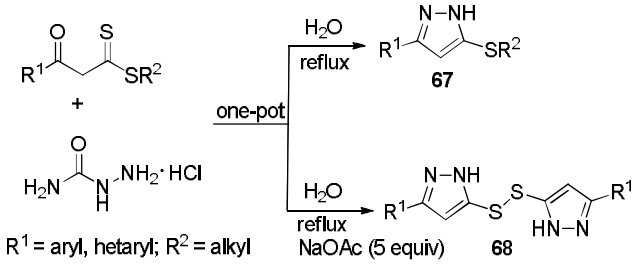
An efficient, eco-friendly and highly convergent one-pot route to privileged thiazoloquinolinone derivatives **66** has been developed *via* four-component cascade coupling (4CCC) of α-enolic dithioesters, cysteamine/2-aminothiophenols, aldehydes, and cyclic 1,3-diketones in recyclable [EMIM][$EtSO_4$] ionic liquid at room temperature for the first time (Scheme 53).[44] The reaction proceeds *via N,S*-acetal formation, Knoevenagel condensation, aza-ene reaction, imine-enamine/keto-enol tautomerization, and intramolecular N-cyclization cascade sequence. The merit of the protocol is highlighted by its efficacy of forming consecutive five new bonds (two C–C, two C–N and one C–S) and two rings with all reactants being efficiently utilized. The operational simplicity, sustainability, mild conditions, excellent yields, tolerance of wide functional groups and avoidance of expensive/toxic reagents are additional attributes to this domino four-component protocol. The modular character of this multicomponent approach and the availability of the starting compounds make this process potentially attractive for combinatorial chemistry and diversity-oriented synthesis (DOS).



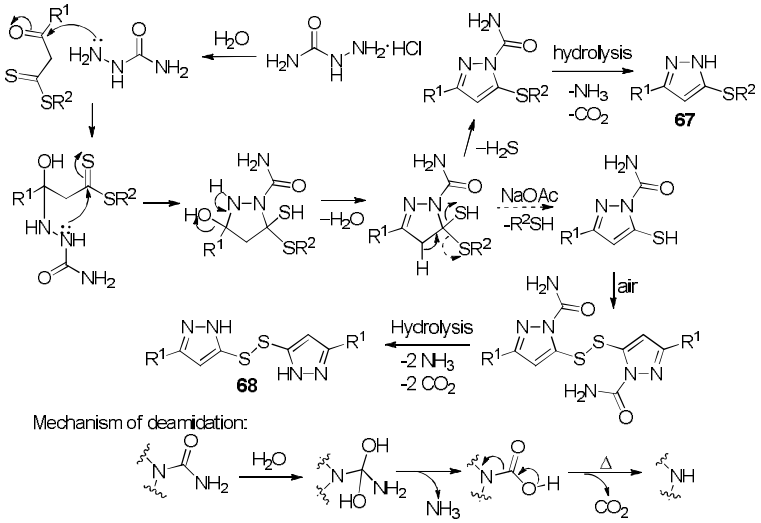
Scheme 53. Four-component synthesis of thiazoloquinolinone derivatives.

Recently, Koley *et al.*[45] developed a catalyst-free strategy to access diverse pyrazoles **67** and disulfide-tethered pyrazoles **68** by the reaction of β-ketodithioesters with semicarbazide hydrochloride in water (Scheme 54). This tandem [3+2]-heteroannulation features inexpensive and easily available substrates,

broad substrate scope, and good yields. The pH of the medium played a key role toward the selectivity switch, as refluxing in water led to the formation of pyrazoles, whereas addition of sodium acetate in water enabled the formation of disulfide-tethered pyrazoles. A mechanistic rationale for this regio-/chemoselective domino reaction is outlined, which is well supported and validated by density functional theory calculations (Scheme 55). Notably, this chemistry is general, mild and low cost, making this protocol a good alternative to existing ones.



Scheme 54. Construction of pyrazoles and 1,2-bis(pyrazol-5-yl)disulfanes in water under catalyst-free conditions.



Scheme 55. Tentative mechanism for the formation of pyrazoles and disulfide-tethered pyrazoles.

7. Conclusion and outlook

α-Enolic dithioesters have recently emerged as useful synthons in a variety of metal-catalyzed and metal-free reactions, which affords novel methodologies for the formation of carbon–carbon and carbon–heteroatom bonds. In this context, it has been found that α-enolic dithioesters, which display an exceptionally fine balance between stability and reactivity, could be used as versatile building blocks/synthons towards the construction of a wide range of cyclic frameworks. They also offer unique and multiple opportunities for the inclusion of sulfur-based functionalities into organic molecules, and are emerging as especially useful and versatile precursors for various organic synthesis. Recent breakthroughs in the utilization of these substrates have revitalized interest in diverse skeletally different heterocycles, and the recent past decade has witnessed an ever-increasing number of publications reporting the development of new reactions or synthetic sequences starting from α-enolic dithioesters. In this report, cyclization reactions

based on α-enolic dithioesters as substrates and major developments in this area have been discussed. The number of publications dealing with the use of α-enolic dithioesters for the development of new synthetic transformations and/or for the preparation of simple/complex molecules is increasing exponentially, thus creating what could be qualified as a real "α-enolic dithioester boom". Here, we have presented the power and diversity of domino/cascade reactions based on the use of β-keto/α-enolic dithioesters as key substrates, which have quickly become powerful, fascinating, and highly efficient intermediates in organic synthesis. The concept of domino sequences has allowed easily reaching high molecular complexity with very often excellent levels of selectivity with simple operational procedures, as well as advantages of savings in solvent, time, energy, and costs. These domino reactions proceed under relatively mild reaction conditions and tolerate a wide variety of functional groups, thus avoiding protection group chemistry. The resulting functionalized heterocycles can undergo various useful subsequent transformations to give highly substituted heterocycles with one or more than one hetero atom. Definitely, much more remains to be done in this field, and in the next few years, we will see many new, exciting findings in β-keto/α-enolic dithioesters chemistry. Thus, we hope this mini review would provid appropriate background for such developments and the encouragement to synthetic organic chemists to employ this valuable intermediate toward new heterocyclic scaffolds and in medicinal chemistry. On the other hand, some new synthetic approaches were developed for the specific aim of achieving a more sustainable transformation. Our attempts presented here might open a window for the future development of unprecedented asymmetric catalytic/non-catalytic multicomponent reactions, particularly using acids/bases as catalysts. The goal of this brief report on β-keto/α-enolic dithioesters is to provide appropriate background for synthetic, medicinal, material, and combinatorial developments, and in particular to Ph.D. and Master Students in related area. Further, it has been established to be versatile intermediates toward the construction of various important bioactive scaffolds and offer a promising route for rapid diversity oriented synthesis (DOS) of numerous useful molecules.

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