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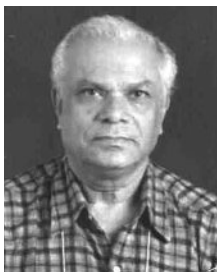
# Molecular Diversity through Novel Organosulfur Synthons: Versatile Templates for Heterocycle Synthesis

Hiriyakkanavar Ila*[a] and Hiriyakkanavar Junjappa[b]

*Abstract:* This review highlights some of our recent work on design and development of new synthetic methods for diverse classes of heterocycles employing novel organosulfur synthons *i.e.* polarized ketene dithioacetals, N,S-acetals, β-oxodithioesters and 2,3-(hetero)aryl-3-(methylthio)acrylonitriles, easily accessible from a wide range of active methylene compounds.

**Keywords:** N,S-Acetals · β-Oxodithioesters · Polarized ketene dithioacetals · Substituted and fused five- and six-membered heterocycles



***Hiriyakkanavar Ila*** received her PhD in 1968 from Indian Institute of Technology (IIT), Kanpur, India. After postdoctoral research at Purdue University, USA (1969), she joined Central Drug Research institute (CDRI), Lucknow (1970) as research scientist and married (1971) ***Hiriyakkanavar Junjappa***, also an organic chemist and scientist at CDRI. In 1977, both of them moved to new North Eastern Hill University, Shillong and established a School of Chemistry there and continued research together. She became professor in 1986 and joined Department of Chemistry, IIT Kanpur in end of 1995. In 2007, she moved to Bangalore and joined Jubilant Biosys Ltd. Bangalore as Principal Advisor-Chemistry. In beginning of 2010, she moved to Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bangalore as INSA Senior Scientist and honorary professor. Her research interest currently focuses on design and development of new synthetic methods for biologically important heterocycles, domino reactions and multicomponent reactions.

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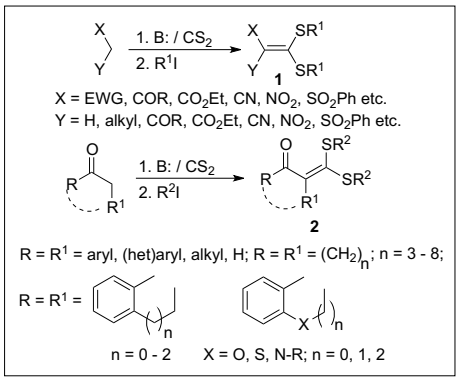
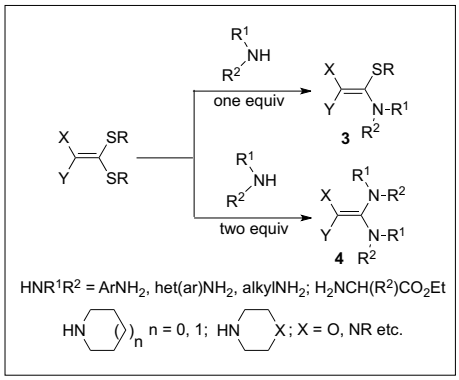
## 1. Introduction

We started our professional career in India at Central Drug Research Institute (CDRI), Lucknow in early 1970s. Medicinal chemistry and drug discovery research in India were in a preliminary stage at that time, and most of the medicinal chemists were engaged in synthesizing compounds related to known drugs (structure–activity relationship) by reported methods. Research in organic chemistry in India, at that time, was mainly centered around natural product chemistry. Only a few research groups were involved in synthetic organic chemistry concentrating mainly on synthesis of natural products like steroids, alkaloids and terpenes. Similarly, most of the universities were involved in teaching of organic chemistry in a classical way starting from synthesis of various organic compounds and their physical and chemical properties. The Department of Chemistry, Indian Institute of Technology (IIT), Kanpur was among the first few premier institutes in India, which introduced teaching of modern organic chemistry with emphasis on structural and mechanistic organic chemistry. I was fortunate to be admitted among the first batch of Ph.D. students in the Department of Chemistry, IIT Kanpur and received rigorous training in structural and mechanistic organic chemistry along with related branches like chemical binding, molecular orbital theory, chemical thermodynamics, spectroscopic methods in organic chemistry including $^1$H NMR and mass spectroscopy.

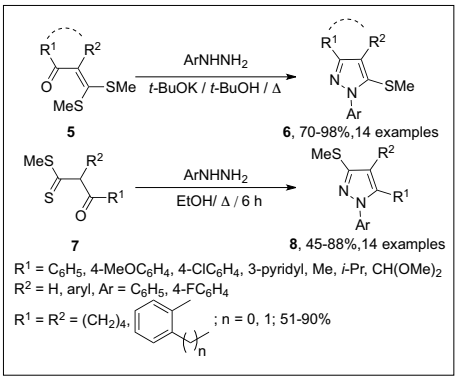
Therefore, with a strong background in mechanistic organic chemistry, along with overwhelming demand for submitting new compounds for biological screening in CDRI, we were looking for a new source of diversity in terms of readily available substrates, which can be utilized for designing new reactions for developing new synthetic methods especially for five and six membered heterocycles. At this stage, we came across a new class of organosulfur compounds known as polarized ketene dithioacetals **1** and **2** (Scheme 1). We were especially attracted by their stability at room temperature and their ready accessibility from a broad range of active methylene compounds in simple one-pot reaction by treatment with base, carbon disulfide and subsequent alkylation of dithiolate salt with alkyl halides (Scheme 1). Also, the two labile alkylthio groups (generally methylthio) at the β-position of these intermediates could be easily displaced by one or two equivalents of primary and secondary amines yielding novel functionalized enamines known as polarized ketene N,S- and N,N-acetals of the general structures **3** and **4** (Scheme 2). Our literature survey at this stage revealed that although several of these substrates have been synthesized by few research groups,[1] their reactivity profile in terms of their synthetic applications was virtually unexplored except for a few



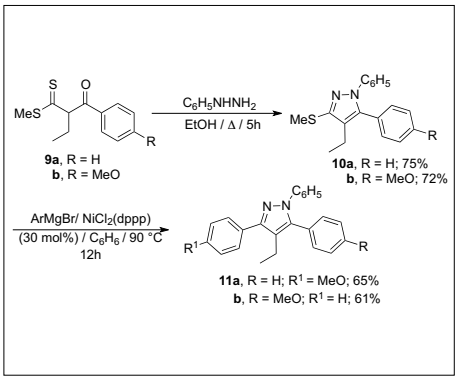

Scheme 1. Synthesis of polarized ketene dithioacetals.




Scheme 2. Synthesis of polarized ketene N,S- and N,N-acetals.




Scheme 3. Regioselective synthesis of 1-aryl-3,4-(or 4,5-) substituted/annulated 5-(or 3-)-(methylthio)pyrazoles.




Scheme 4. Regioselective synthesis of selective estrogen receptor ligands.

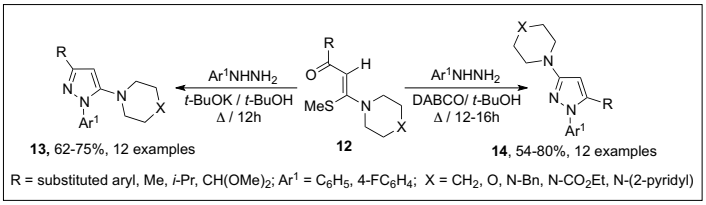
reactions reported by earlier workers.[2]

We therefore undertook a systematic investigation of this broad class of intermediates, especially α-oxoketene dithioacetals derived from active methylene ketones and the related N,S- and N,N-acetals with special emphasis on design and development of new synthetic methods for biologically relevant novel five- and six-membered heterocycles by making use of their varying reactivity pattern.[3] During the course of this research work, we also explored other organosulfur synthons such as β-oxodithioesters, 1-(methyldithiocarbonyl)imidazole and α-(2-bromohetero)aryl-β-(hetero)aryl/alkyl-β-(methylthioacrylonitriles) (see Scheme 14 later). The present account mainly highlights selected work of the last six years along with some earlier important work demonstrating the versatility of these useful intermediates and the products derived from them.

### 2.1 α-Oxoketene Dithioacetals as Versatile 1,3-Electrophilic Three-carbon Synthons: Regioselective Synthesis of Tri/tetrasubstituted Pyrazoles

One of the most general and practical methods for the synthesis of N-substituted pyrazoles utilizes cyclocondensation of 1,3-diketones or their equivalents[4a] with N-substituted hydrazines. However the method suffers from a regioselectivity problem with unsymmetrically substituted 1,3-diketones yielding isomeric mixtures of substituted pyrazoles. We have successfully developed a regiocontrolled synthesis of either 1-aryl-3,4-substituted/annulated-5-(methylthio) pyrazoles **6** or their 3-(methylthio)-regioisomers **8** by reacting both acyclic and cyclic α-oxoketenedithioacetals **5** or the corresponding β-oxodithioesters **7** with various arylhydrazines (Scheme 3) under optimized reaction conditions.[4a] Also, these 5-(or 3-)-methylthiopyrazoles could be transformed to the corresponding isomeric 5-(or 3-) alkyl/arylpyrazoles by nickel-catalyzed cross-coupling of 5-(or 3-) methylthio group with alkyl/aryl Grignard reagents. The methodology is utilized for regiocontrolled synthesis of pyrazole-based selective estrogen receptor ligands **11** (Scheme 4).[4a]

Similarly, we have demonstrated that by proper manipulation of the reaction conditions and choice of base, it was possible to synthesize either 3-(or 5)-(cycloamino)-1,3 (or 1,5)-diaryl/alkyl substituted pyrazoles **13** or **14** respectively in highly regioselective fashion from the common α-oxoketene-N,S-acetal precursors **12** by their reaction with various arylhydrazines (Scheme 5).[5a]



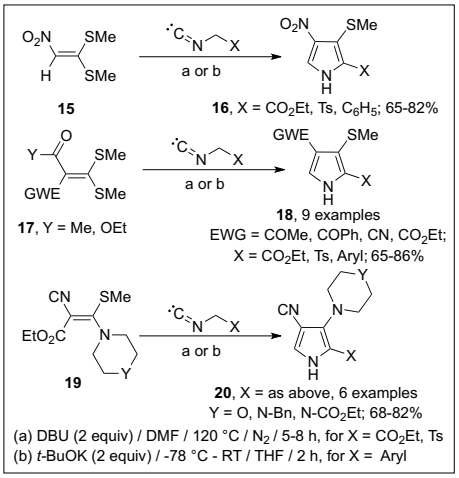

Scheme 5. Regioselective synthesis of 1-aryl-3(or 5)-aryl/alkyl-5(or 3)-(N-cycloamino) pyrazoles.

### 2.2 Reactivity of Activated Double Bonds: Efficient Synthesis of 2,3,4-Trisubstituted Pyrroles by Formal Cycloaddition of Polarized Ketene Dithioacetals with Activated Methylene Isocyanide Anions

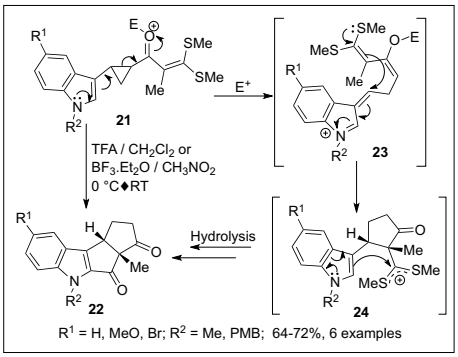
The diverse reactivity pattern of polarized ketene dithioacetals was further demonstrated by designing an efficient and versatile protocol for regioselective synthesis of 2,3,4-trisubstituted pyrroles by base-induced formal cycloaddition of activated double bonds of various polarized ketene S,S- and few N,S-acetals with activated methylene isocyanide anions (Scheme 6).[6] The methodology allows precise control over the introduction of a variety of substituents and functionalities (tosyl, carboalkoxy, aryl, cyano, nitro, acetyl, benzoyl, cyclic amines, *etc*.) at the 3- and 5-positions of pyrrole ring. The reaction of nitroketenedithioacetal **15** with activated methylene isocyanides is particularly noteworthy, since the nitro group is retained in the 3-position of pyrroles **16** unlike in the Barton-Zard reaction, where it acts as the leaving group (Scheme 6).[7]

### 2.3 Ketene Dithioacetal Functionality as Cationic Cyclization Initiator/Terminator in Domino Carbocationic Rearrangements of α-[Bis(methylthio)methylene] alkyl-2-(aryl/heteroaryl)cyclopropyl Ketones

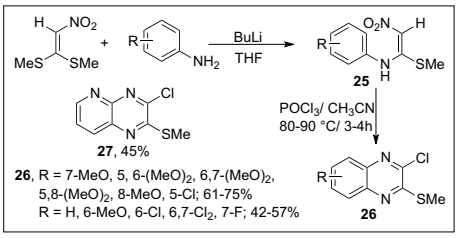
The ability of the two sulfur atoms in the ketene dithioacetal moiety to stabilize a positive charge makes it a useful functionality as a potential cationic cyclization initiator or terminator group in polyene cyclizations.[3a] We have demonstrated in our earlier studies, that domino carbocationic rearrangements of newly designed aryl and heteroarylcyclopropyl ketones bearing an




Scheme 6. Synthesis of 2,3,4- trisubstituted pyrroles.




Scheme 7. Domino carbocationic rearrangement of cyclopropyl ketones **21** to pentaleno[*b*] indole diketones **22**.




Scheme 8. Synthesis of substituted 2-(methylthio)-4-chloroquinoxalines.

α-bis(methylthio)methylene functionality allow construction of a variety of carbocyclic and heterocyclic scaffolds such as substituted cyclopentanones, cyclopenta[b] indanes, diquinanes, 1-arylindanes, bicyclo[3.2.1]octene, and other cyclopentano-fused heterocycles.[8] In a recent paper, we have shown that carbocationic rearrangement of α-[bis(methylthio)methylene] alkyl-2-(3/2-indolyl)cyclopropyl ketones of the general structure **21** in the presence of trifluoroacetic acid or other Lewis acids provides a direct approach to pentalenofused indolodiketones such as **22** involving the appendage of two cyclopentanone rings in a cascade process in one-pot operation (Scheme 7).[8]

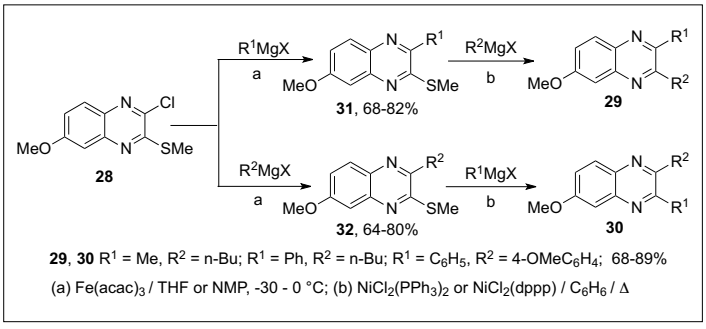
### 2.4 *Reactivity of Polarized Ketene N,S-Acetals: $POCl_3$-induced Intramolecular Cyclocondensation of Nitroketene N,S-Arylaminoacetals: A Novel Highly Regioselective Synthesis of Unsymmetrical 2,3-Substituted Quinoxalines and Imidazo[1,5-a] quinoxaline-3-carboxylates*

Polarized ketene N,S- and N,N-acetals can be considered as the second generation of reactive intermediates derived from polarized ketene dithioacetals *via* replacement of one or both methylthio groups by primary or secondary aliphatic or aromatic amines (Scheme 2). We have extensively explored these N,S-acetals in the past, for the synthesis of novel functionalized five- and six-membered heterocycles by making use of their diverse reactivity profile either as functionalized enamines or as three-carbon 1,3 electrophilic fragments.[3e,f,9] A few years back, we reported a novel general highly regioselective synthesis of unsymmetrically substituted 2-methylthio-3-chloroquinoxalines of the general structure **26** by $POCl_3$-mediated intramolecular cyclocondensation of a broad range of nitroketene N,S-arylaminoacetals **25** (Scheme 8).[9] The 2-methylthio- and 3-chloro functionalities in these quinoxalines could be further elaborated for the synthesis of regioisomeric unsymmetrically substituted 2,3-aryl/alkyl quinoxalines such as **29** and **30** by sequential iron- or nickel-catalyzed cross-coupling with various aryl/alkyl Grignard reagents in a highly regiocontrolled fashion (Scheme 9),[9] thus overcoming regioselectivity problems encountered in previous syntheses (Hinsberg condensation) of unsymmetrically substituted quinoxalines.

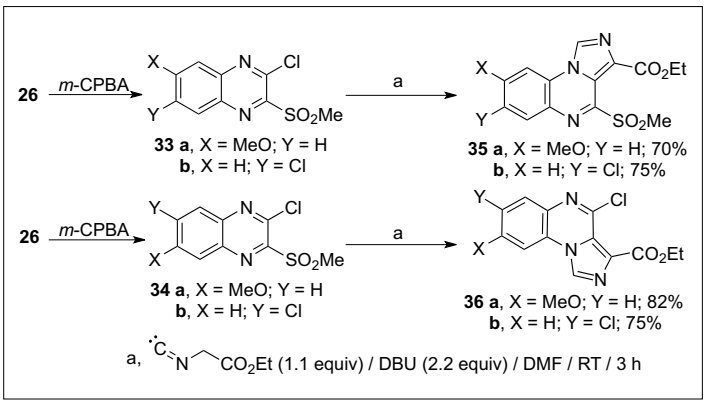
In a subsequent study, we also reported an efficient regio- and chemoselective synthesis of novel biologically relevant 3-(carboethoxy)imidazo[1,5-*a*]quinoxalines such as **35** and **36** by subjecting the unsymmetrically substituted 2-methylsulfonyl-quinoxalines **33** and **34** to base-induced formal cycloaddition with ethyl isocyanoacetate on N=C bond (Scheme 10).[10]

### 2.5 *4-Bis(methythio)methylene-2-phenyloxazol-5-one: Versatile Template for Diversity Oriented Synthesis of 2-Phenyl-4,5-functionalized Oxazoles and Related Heterocycles*

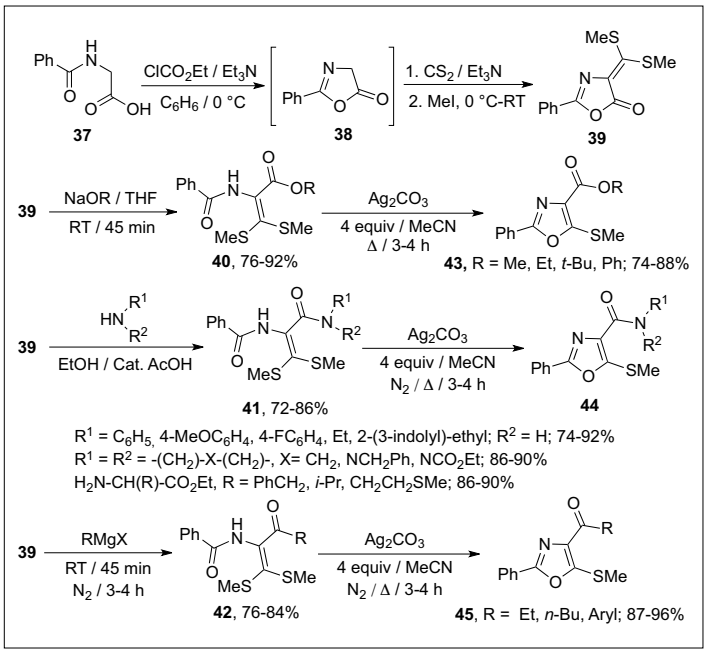
In a recent paper, we set out to explore the feasibility of utilizing ketene dithioacetal **39** derived from 2-phenyl-4,5-dihydrooxazol-5-one (**38**) as a versatile template to access a broad range of heterocycles with diverse functionalities. A close look at the structure **39** reveals that it contains many



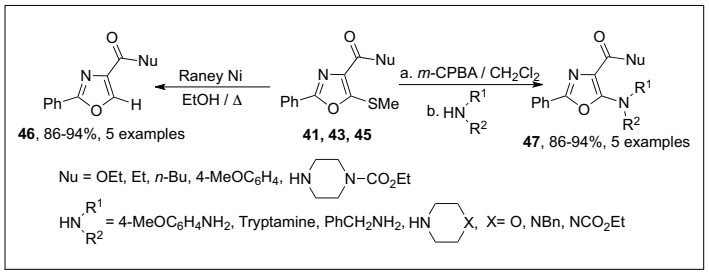

Scheme 9. Regioselective synthesis of unsymmetrical 2,3-diaryl/alkyl quinoxalines.



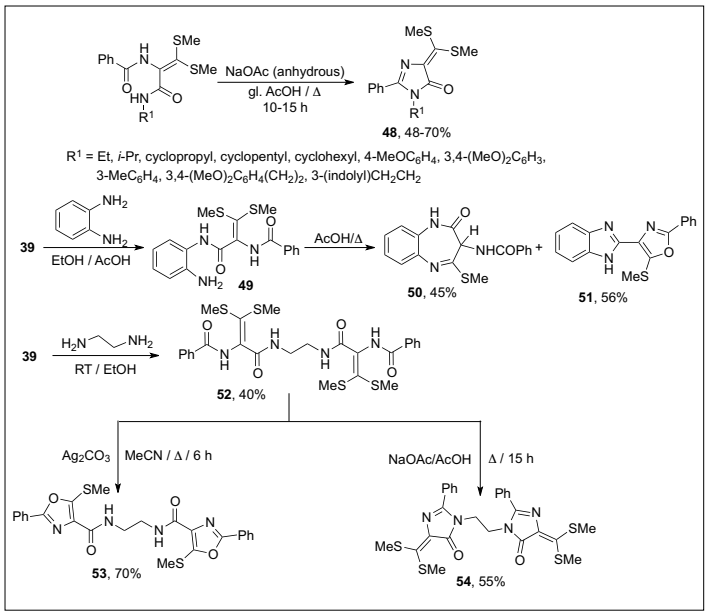

Scheme 10. Regio- and chemoselective synthesis of substituted imidazo[1,5-*a*]quinoxaline-3-carboxylates.



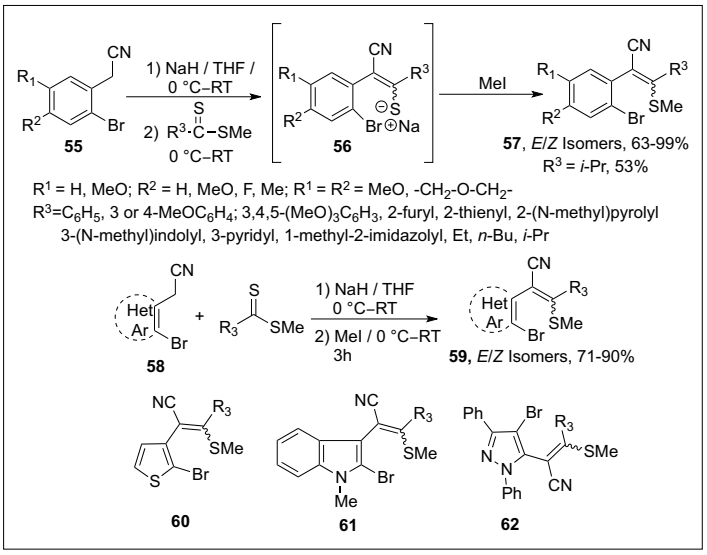

Scheme 11. Synthesis of 2-phenyl-4,5-functionalized oxazoles.



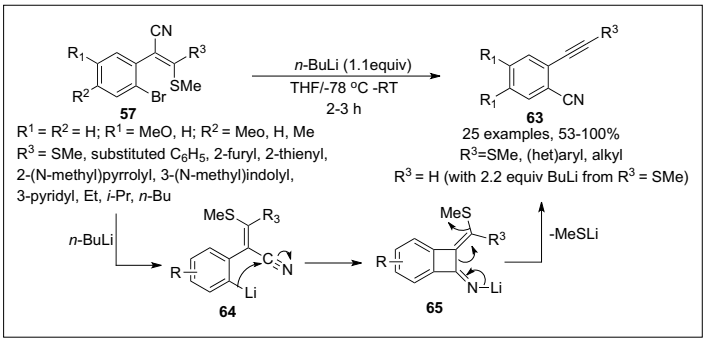

Scheme 12. Synthesis of 2-phenyl-4-functionalized-5-unsubstituted/aminooxazoles.




Scheme 13. Further transformation of 2-phenyl-4-bis(methylthio)methyleneoxazole-5-one.




Scheme 14. Synthesis of novel 2-[2-bromo(hetero)aryl]-3-(methylthio)-3-hetero(aryl)/alkylacrylonitrile precursors **57** and **60**–**62**.




Scheme 15. Synthesis of 1-[*o*-cyanoaryl]-2-[(hetero)aryl/alkyl/methylthio) acetylenes.

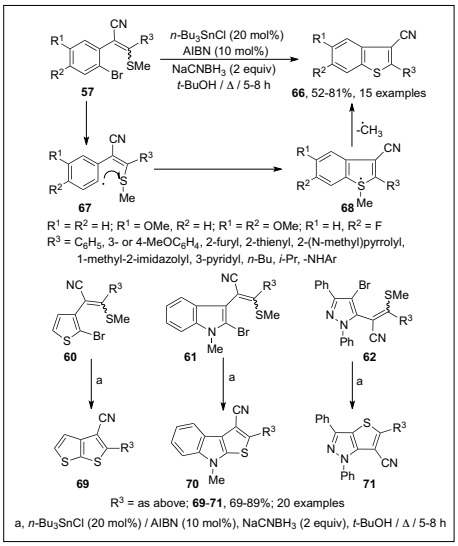
reactive sites allowing for a diverse set of possible transformations. We have utilized this intermediate for diversity-oriented synthesis of 2-phenyl-4,5-functionalized oxazoles as shown in Scheme 11.[11a] Thus oxazolone **39** undergoes facile ring opening with various oxygen (alkoxides), nitrogen (amines and amino acid esters) and carbon (alkyl/aryl Grignard reagents) nucleophiles yielding highly functionalized enamides of the general structures **40**–**42** respectively with multiple reactive sites. These enamide precursors undergo efficient silver carbonate-mediated 5-*endo* cyclization, furnishing a variety of 2-phenyl-5-methylthio-4-carboalkoxy/carbamoyl/acyloxazoles **43**–**45** in excellent yields.[11a] The 5-methylthio group in oxazoles **43**–**45** could be either desulfurized with Raney nickel yielding 5-unsubstituted oxazoles **46** or transformed into 5-aminooxazoles **47** by the oxidation of the 5-methylthio group to a methylsulphonyl group (*m*-CPBA) and its subsequent replacement by primary and secondary amines (Scheme 12).[11a]

We have further shown that enamides **41** obtained from ring opening of **39** by primary amines could be cyclodehydrated (NaOAc/AcOH) to novel 4-bis(methylthio) methylene-2-phenyl-1-alkyl/arylimidazol-5(4*H*)ones **48** in good yields (Scheme 13).[12] Similarly enamides derived from bisamines like *o*-phenylenediamines and ethylenediamine afford a variety of novel heterocycles **50**-**54** in the presence of various acidic and basic cyclizing agents as depicted in Scheme 13.[12]

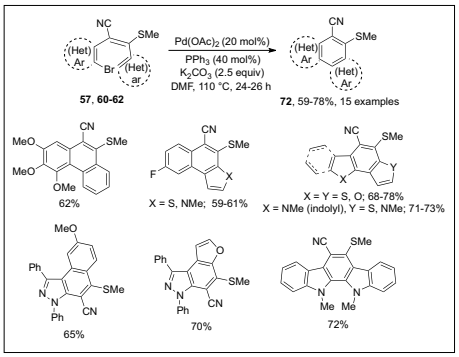
### 2.6 *2-[(2-Bromo(hetero)aryl)]-3-(methylthio)-3-(hetero)aryl/alkyl Acrylonitriles: Versatile Intermediates for Synthesis of Fused Heterocycles and Substituted Acetylenes*

During the course of our continued investigation on polarized ketene dithioacetals and β-oxodithioesters, we became interested in design and developement of a new class of organosulfur synthons such as **57** and explored their synthetic applications (Scheme 14–18). Thus we envisaged the replacement of one of the methylthio groups of polarized ketene dithioacetals (derived from 2-bromoarylacetonitriles) by an aryl/heteroaryl group with a view to add further diversity to these precursors. Besides, the presence of a halogen atom (Br) in the 2-position of aryl/heteroaryl group can trigger a variety of reactions (*i.e.* generation of an organolithium species, carbon-centered radical or aryl palladium/copper species), which could be modulated to provide new synthetic routes for novel heterocycles as well as other new entities. The desired precursors **57** and their heterocyclic variants **60**–**62** were synthesized in high yields by base-induced condensation of the corresponding 2-bromoaryl(or heteroaryl)acetonitriles **55** or **58** with aryl/heteroaryl dithioesters followed by *in situ* alkylation of the resulting thiolate salts **56** with methyl iodide (Scheme 14). These intermediates were found to be stable at room temperature and shown to exist as a thermally labile mixture of *E*/*Z* stereoisomers from their $^1$H NMR spectra.

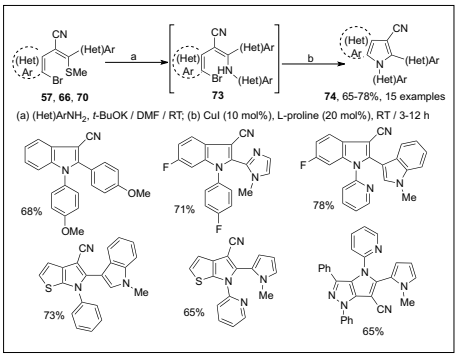
The reaction of **57** [and its bis(methylthio) analog, R$^3$ = SMe] with butyl lithium was first examined in the presence of an electrophile such as benzonitrile (Scheme 15). Surprisingly, the products obtained were found to be 1-(*o*-cyanoaryl)-2-methylthio/(hetero)aryl/alkylacetylenes **63** formed by an interesting anionic domino rearrangement (without participation of benzonitrile) involving migration of the cyano group through a benzocyclobutene intermediate **65** [**64**→**65**] and its subsequent ring opening and elimination of lithium methylthiolate (Scheme 15).[13]



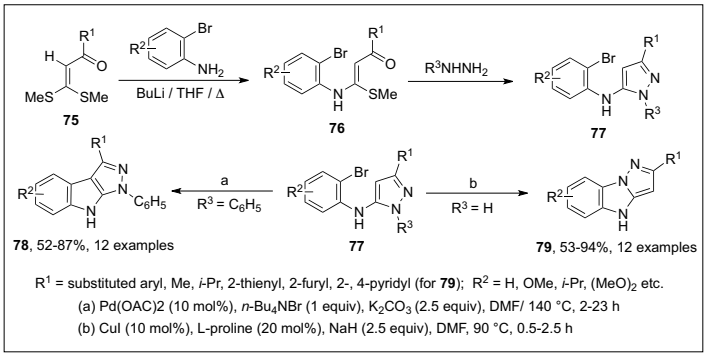

Scheme 16. Synthesis of substituted benzo[*b*] thiophenes and heterofused thiophenes.




Scheme 17. Synthesis of novel substituted phenanthrenes and polycyclic heteroarenes.




Scheme 18. Synthesis of substituted indoles and heterofused pyrroles.




Scheme 19. Synthesis of pyrazolo[3,4-*b*]indoles and pyrazolo[1,5-*a*] benzimidazoles.

We next explored the generation of a carbon-centered aryl radical by treatment of **57** with tributyltin hydride. It was anticipated that aryl radical species **67** would attack intramolecularly the sulfur atom of the favorably situated methylthio group to give intermediate radical **68**, which on fragmentation and loss of an alkyl radical would furnish benzo[*b*]thiophenes **66** (Scheme 16).[14] Indeed, to our delight, the reaction proceeded according to our design in the presence of catalytic tributyltin chloride and cyanoborohydride (yields of **66** were lower with TBTH) yielding substituted 2-hetero(aryl)/amino-3-cyanobenzothiophenes **66** in excellent yields (Scheme 16).[14]

This new methodology was found to be equally facile for the synthesis of other thieno-fused heterocycles such as 3-cyano-2-(hetero)aryl substituted thieno[2,3-*b*] thiophenes **69**, thieno[2,3-*b*]indoles **70** and thieno[3,2-*c*]pyrazoles **71** in high yields *via* intramolecular radical cyclization of the corresponding 2-[2-bromo(hetero) aryl-3-(methylthio)-3-(hetero)arylacrylonitrile precursors **60**–**62** as depicted in Scheme 16.[15]

With a diverse range of readily accessible novel 2-bromo(hetero)aryl-3-(methylthio)-3-hetero(aryl)acrylonitrile precursors (**57**, **60**–**62**) in hand, we next examined Pd-catalyzed direct intramolecular C–H (hetero)arylation of these intermediates with a view to develop a new route to a variety of highly functionalized polycyclic arenes and heteroarenes (Scheme 17).[16] We successfully achieved this goal by subjecting **57** and their heteroaryl analogs **60**–**62** to intramolecular cyclization in the presence of palladium acetate (20 mol%) and triphenylphosphine (40 mol%) furnishing the substituted pheananthrene **72** and a variety of substituted/fused heteroarene motifs such as naphtho[2,1-*b*]furan/thiophene, benzo[*e*]indole, thieno[2,3-*e*] benzo[*b*]thiophene/furan, thieno[3,2-*a*]- and pyrrolo[3,2-*a*]carbazoles, benzo[*e*]indazole, furo[3,2-*e*]indazole and indolo[2,3-*a*]carbazole derivatives in high yields as shown in Scheme 17.[16]

Finally, the versatility of these newly synthesized [2-bromo(hetro)aryl]acrylonitrile precursors was further evident by their facile copper-catalyzed intermolecular heteroannulation with various aryl/heteroarylamines (through intermediacy of N,S-acetals **73**) yielding a diverse range of novel 3-cyano-2-(hetero)aryl-1-N-(hetero)arylindoles and the corresponding thieno[2,3-*b*]pyrroles and pyrrolo[3,2-*c*] pyrazole derivatives **74** in high yields in a one-pot transformation involving formation of two C–N bonds (Scheme 18).[17]

### 2.7 *From one Precursor to another Precursor to Novel Heterocyclic Entities: Synthesis of 2-Bromoanilino-pyrazoles from N,S-Acetals and their Intramolecular Pd- and Copper-catalyzed Cyclization to Pyrazolo-fused Heterocycles*

The versatility and broad application of polarized ketene dithioacetals as useful synthons for diversity-oriented synthesis of novel heterocycles derives from the fact that besides themselves being useful precursors (first-generation precursors), they can be smoothly transformed into a broad range of N,S- and N,N-acetals (second-generation precursors) by replacement of one or both alkylthio groups by a large number of primary or secondary amines, thus providing a fertile ground for designing new transformations for heterocycle synthesis, depending on the choice and nature of the amines. Further, these N,S-acetals can be again converted into useful precursors (third generation) which can be further elaborated to develop new reactions for the synthesis of novel heterocyclic entities. We have successfully demonstrated this strategy in designing two efficient protocols for the construction of two classes of heterocyclics *i.e.* pyrazolo[3,4-b]indoles **78** and pyrazolo[1,5-a]benzimidazoles **79** from common heterocyclic precursors *i.e.* 1-aryl(or unsubstituted)-5-(2-bromoanilino)-pyrazoles **77** *via* Pd-catalyzed intramolecular CH heteroarylation and copper-catalyzed intramolecular C–N bond formation respectively as shown in Scheme 19.[18] Compounds **77** are obtained by cyclocondensation of hydrazine or arylhydrazine with the α-oxo-N-aryl-S-acetals **76**, (prepared from the ketendithioacetals **75**) by replacement of one of the (methylthio) groups by various 2-bromoanilines in the presence of BuLi (Scheme 19).[19]

## 3. Conclusion

In the foregoing discussion, we have attempted to summarize some of our recent research work displaying versatile applications of polarized ketene S,S-acetals

(or the precursors derived from them) and the related organosulfur synthons[20] in the design and developement of new efficient general synthetic methods for a range of substituted and fused heterocycles by making use of their varied reactivity pattern. The sulfur being a soft nucleophile, and the ability of a sulfur atom to stabilize both positive and negative charges, as well as the alkylthio group being a good leaving group along with unique electronic properties of the thiocarbonyl group (*vs.* carbonyl group) make these intermediates useful substrates for probing new reactions, which has been a central theme of our research group for several years. A few research groups in India[21] and China[22] have also been investigating these intermediates for the synthesis of various heterocyclic, carbocyclic and aromatic compounds. There were no research groups in India working in the area of heterocyclic chemistry when we started this work. Several research groups are now engaged in this area in view of the importance of small molecule heterocycles in drug discovery research.

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