



**2-[BIS(METHYLTHIO)METHYLENE]MALONONITRILE: A VERSATILE REAGENT IN THE DIVERSITY-ORIENTED SYNTHESIS OF COMPLEX HETEROCYCLIC SCAFFOLDS**

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**Abstract:**

2-[Bis(methylthio)methylene]malononitrile extensively applied as a synthon in the diversity-oriented synthesis of diverse heterocyclic compounds. These include mono/polycyclic-heterocyclic compounds, fused heterocyclic compounds, bicyclic bridged nitrogen, sulphur, oxygen-containing heterocycles, substituted heterocycles, and pyrimido-heterocycles. These compounds are synthesized via various reactions, such as cyclo-condensation, cyclo-addition, cascade reactions, and multi-component reactions. The compound's versatility and high reactivity as a multi-functional reagent stem from its easily available structure, featuring electron-withdrawing two cyano functional groups, two methylthio as the best leaving groups, and an  $\alpha$ ,  $\beta$ -unsaturated alkene part. Its unparalleled potential for crafting complex and functional heterocyclic frameworks has prompted us to compile a comprehensive review on the synthetic utility of 2-[Bis(methylthio)methylene]malononitrile, highlighting its role as a potent reagent in the synthesis of heterocyclic scaffolds.

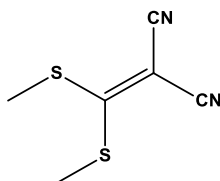
**Keywords:**

2-[Bis(methylthio)methylene]malononitrile, Potent reagent, Multi-component reactions, Synthetic utility, Heterocyclic scaffolds.

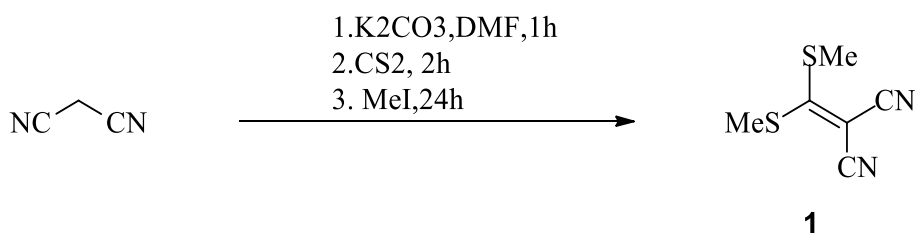
**Introduction:**

2-[Bis(methylthio)methylene]malononitrile (**1**), alternatively referred to as [Bis(methylthio)methylene] Propanedinitrile or [Bis(methylthio)methylidene]propanedinitrile.

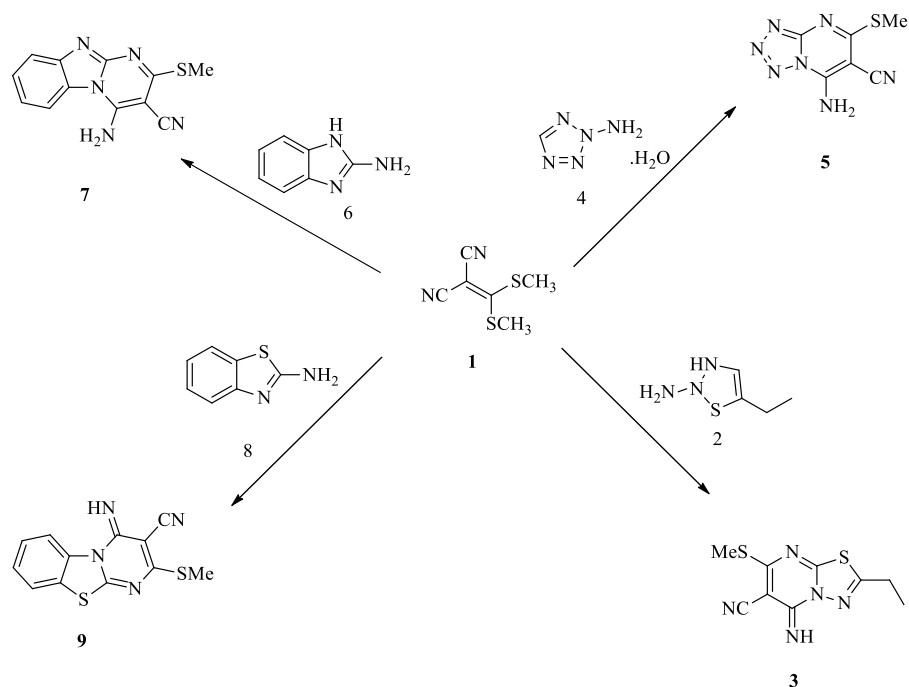
This versatile reagent is solid with a white-yellow colour, and its melting point falls within the range of 79 to 84°C. With a chemical formula of C<sub>6</sub>H<sub>6</sub>N<sub>2</sub>S<sub>2</sub> and a molecular weight of 170 g, it can be readily synthesized in the laboratory. The preparation method for 2-[Bis(methylthio)methylene]malononitrile is straightforward and commonly involves combining an active methylene compound, CS<sub>2</sub>, alkyl halide, and an appropriate base [i-iv]. Over an extended period, this compound has garnered significant attention owing to its crucial role in synthesizing a wide array of heterocyclic, alicyclic, and aromatic compounds [v-vi]. The compound's versatility and high reactivity stem from the combination of two powerful electron-withdrawing -CN functional groups, two readily detachable methylthio groups, and an α, β-unsaturated alkene segment. As a multi-functional reagent, it exhibits exceptional flexibility. It can readily undergo condensation reactions with various nucleophiles/bi-nucleophiles, leading to the formation of diverse heterocyclic compounds [vii-viii]. While there are numerous reviews on the synthesis of heterocyclic compounds using various reagents [ix-x], there seems to be limited literature on the specific utilization of 2-[Bis(methylthio)methylene]malononitrile for the synthesis of organic compounds, particularly heterocycles. In light of this, our review aims to explore the synthetic potential of this compound as a potent reagent in the formation of diverse heterocyclic scaffolds.

**2-(bis(methylthio)methylene)malononitrile (1)**

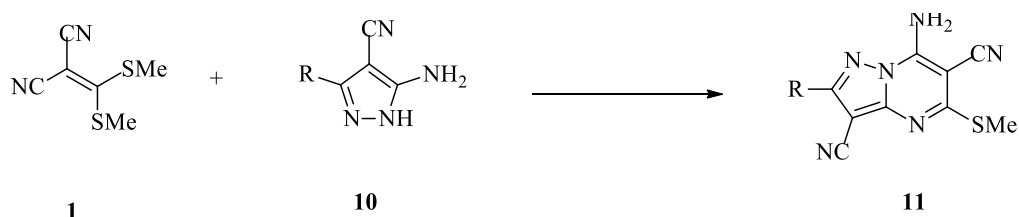
In a study by Wedad M. Al-Adiwish et al. [xi], the synthesis of 2-[bis(methylthio)methylene]propanedinitrile or 2-bis(methylthio)methylene malononitrile was documented, starting from malononitrile.

**Heterocyclic synthesis:**

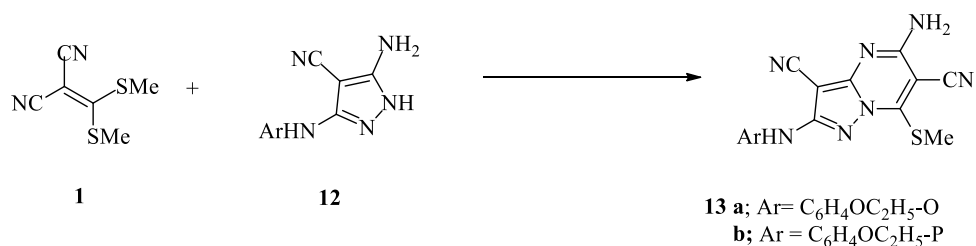
Metwally et al. conducted a study wherein they condensed bis(methylthio)methylene malononitrile **1** with certain amino azoles, specifically 2-amino-5-ethyl thiadiazole **2**, 5-aminotetrazole monohydrate **4**, 2-aminobenzimidazole **6**, and 2-aminobenzothiazole **8**. This reaction yielded bridgehead nitrogen compounds **3**, **5**, **7**, and **9** [xii].



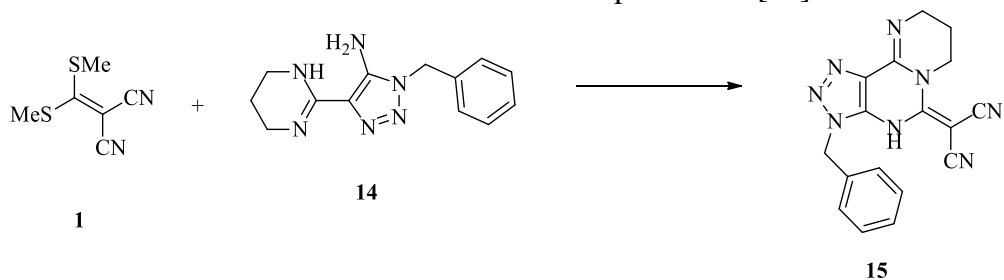
Pyrazolo[1,5-a]pyrimidines **11** were synthesized through the condensation of 3-amino-1H-pyrazole-4-carbonitriles **10** (where R = NH<sub>2</sub>, 2, 5-dimethyl-1-pyrrolyl, 4-morpholinyl, or -SMe) with bis(methylthio)methylene malononitrile **1** in the presence of triethylamine [xiii].



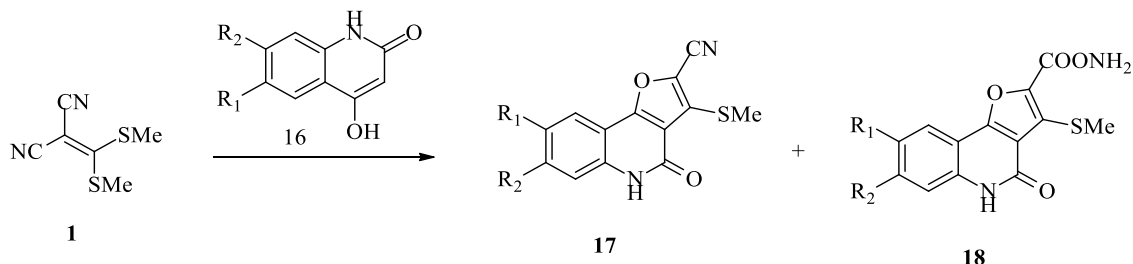
Pyrazolo [1, 5-a] pyrimidines **13a** and **13b** were obtained through the reaction of ketene dithioacetals **1** with aminopyrazoles **12** in DMF (dimethylformamide) under reflux conditions, with the addition of a catalytic amount of triethylamine [xiv].



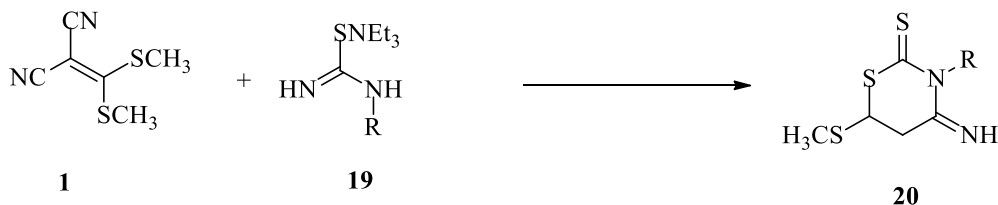
The reaction of aminotriazoles **14** with 2-cyano-3, 3-bis(methylthio)-acrylonitrile **1** resulted in the formation of novel heteroannulated 8-azapurines **15** [xv].



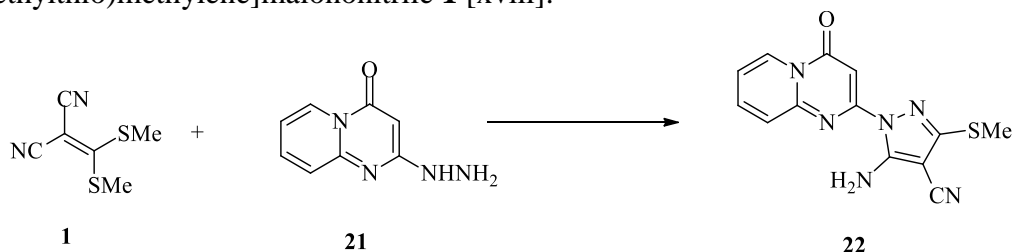
Upon reacting quinoline-2,4-diones **16** with 2-[bis(methylthio)methylene]malononitrile **1** in DMF/Et<sub>3</sub>N, the products obtained were 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-c]quinolone-2-carbonitriles **17** and 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-c]quinolone-2-carboxamides **18**. These compounds were observed instead of the expected 2-imino-substituted 4-(methylthio)-5,6-dihydro-2H-pyrano[3,2-c]quinolone-3-carbonitriles [xvi].



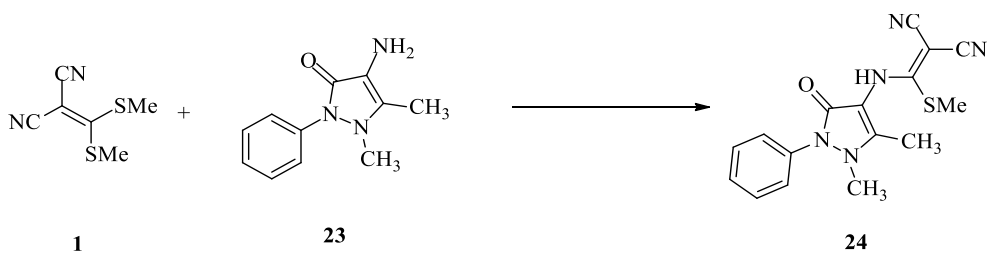
The reaction between dithiocarbamates **19** and 2-[bis(methylthio)-methylene]malononitrile **1** resulted in the formation of 1,3-thiazine-2-thione derivatives **20** [xvii].



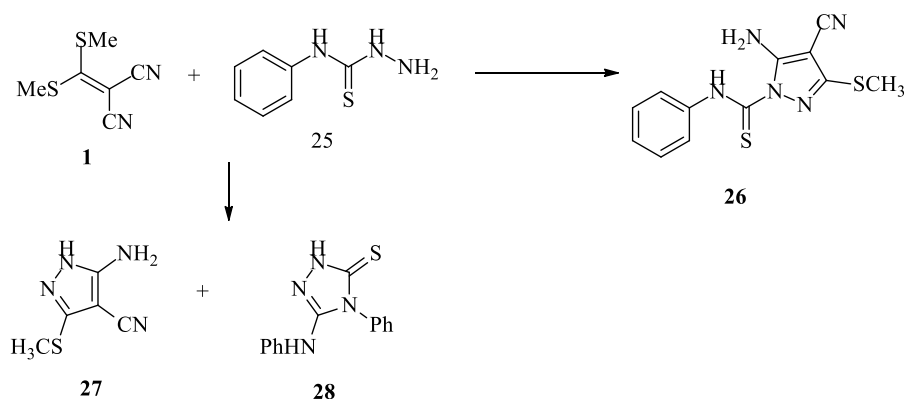
The formation of 1-substituted 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitriles **22** was reported through a reaction starting from hydrazines **21** and [bis(methylthio)methylene]malononitrile **1** [xviii].



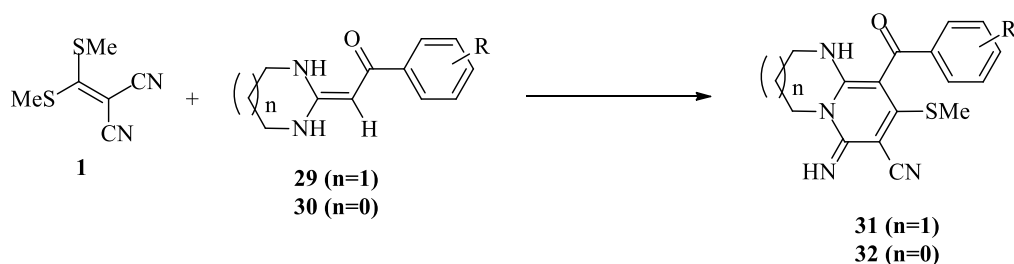
Under reflux conditions in ethanol, the crucial building block 2-(((1,5-Dimethyl-3-oxo-2-phenyl 2,3-dihydro-1H-pyrazol-4-yl)amino))(methylthio)methylene)malononitrile **24** was synthesized by reacting 2-(bis(methylthio)methylene)malononitrile **1** with 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one **23** [xix].



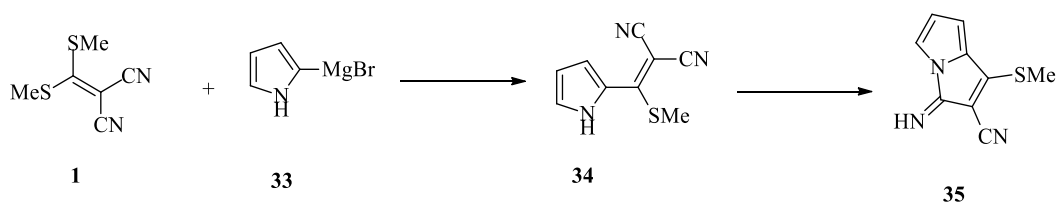
In the presence of ethyl alcohol/Et<sub>3</sub>NH<sub>3</sub> at room temperature, the reaction between N-substituted hydrazinecarbothioamides **25** and 2-bis(methylthio)methylene malononitrile **1** resulted in the formation of compound **26**. However, when the reaction was conducted under heating conditions, a mixture of compounds **27** and **28** was obtained [xx].



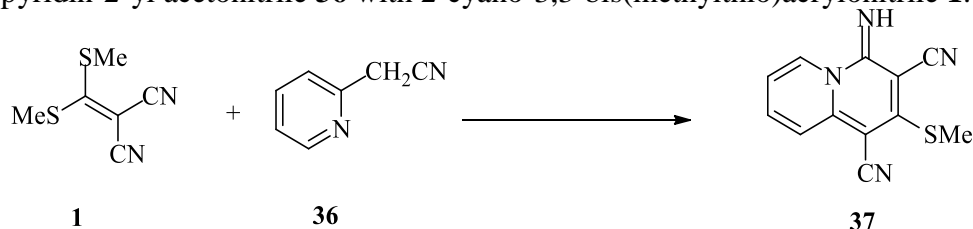
A novel approach has been introduced to produce polyfunctionalized pyridine-fused 1,3-diazaheterocycles **31** and **32**. This method involves reacting heterocyclic ketene animals (HKAs) **29** and **30** with bis(methylthio)methylene malononitrile **1**, facilitating the synthesis process. [xxi]



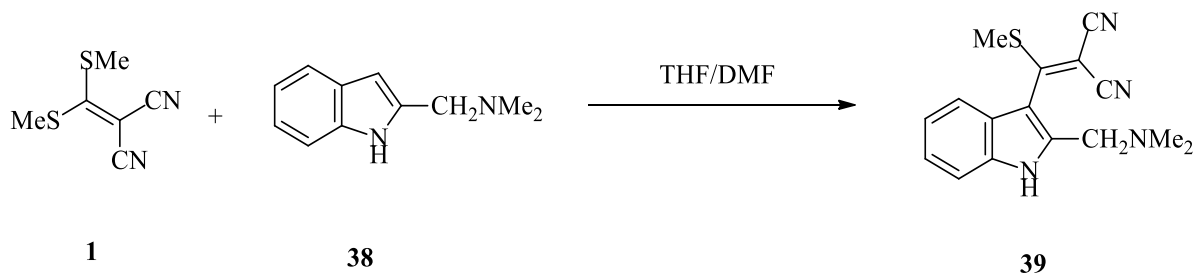
Heating the condensation product of 1-pyrrolyl magnesium bromide **33** with 2-cyano-3,3-bis(methylthio) acrylonitrile **1** in non-polar solvents resulted in the formation of dinitriles **34**. Subsequently, upon further heating in the presence of catalytic amounts of amines, these dinitriles underwent cyclization to yield pyrrolizines **35**. [xxii]



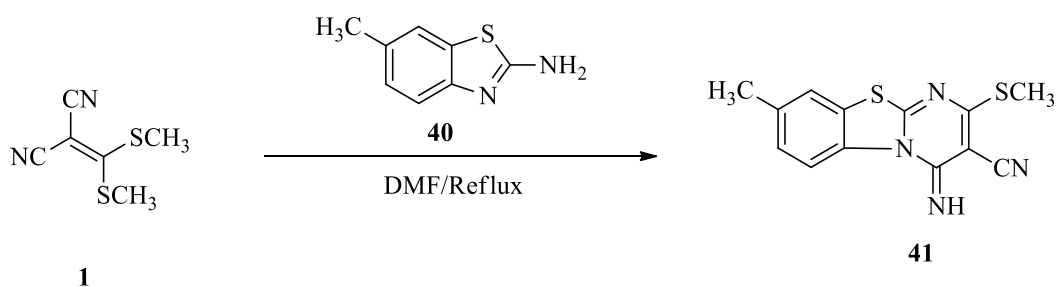
The synthesis of 1,3-dicyano-4-amino-2-methylthio-4H-quinolizine **37** was achieved by reacting pyridin-2-yl acetonitrile **36** with 2-cyano-3,3-bis(methylthio)acrylonitrile **1**. [xxiii]



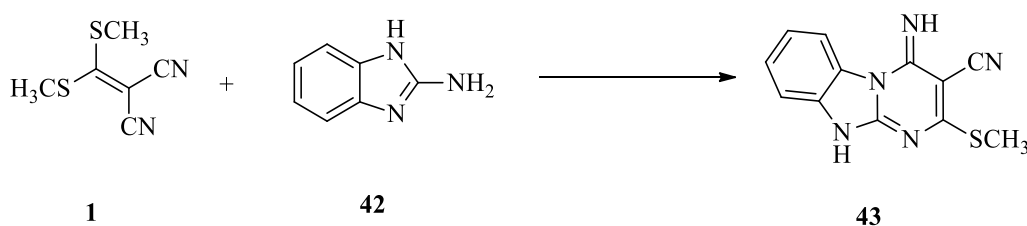
When indole derivative **38** was subjected to a reaction with ketene dithioacetals **1** in the presence of NaH or NaOH, it resulted in the formation of 3-(2-cyano-1-methylthio-vinyl)indole derivative **39**. [xxiv]



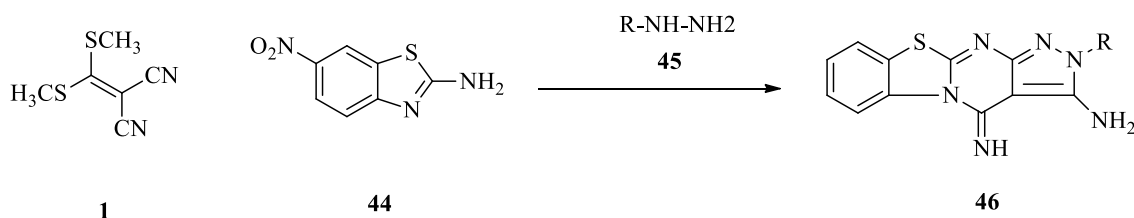
To obtain 3-cyano-4-imino-2-methylthio-8-methyl-4H-pyrimido[2,1-b]benzothiazole **41**, a reaction was carried out between 2-amino-6-methyl benzothiazole **40** and bis(methylthio)methylene malononitrile **1**. This reaction took place under reflux conditions in DMF (dimethylformamide) with potassium carbonate as the catalyst. [xxv]



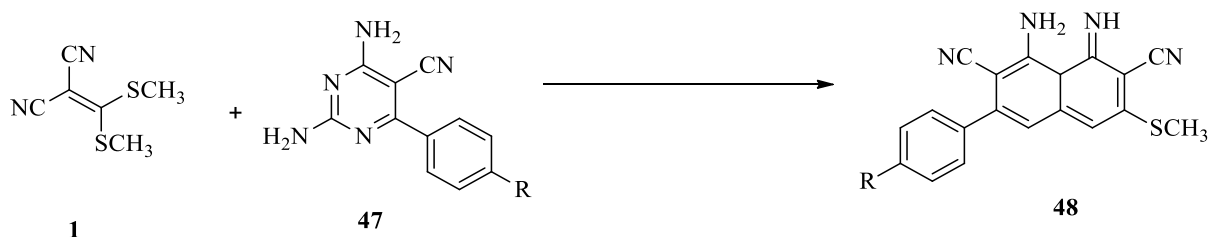
The synthesis of 3-cyano-4-imino-2-methylthio-4H-pyrimido[1,2-a]benzimidazole **43** was accomplished by refluxing 2-amino benzimidazole **42** with bis(methylthio)methylene malononitrile **1** in the presence of potassium carbonate in N, N'-dimethylformamide. [xxvi]



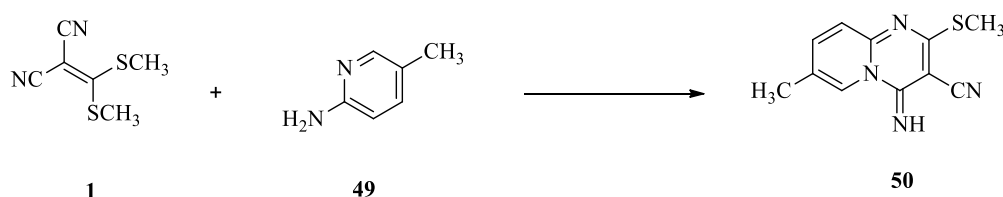
The multicomponent reaction between 2-amino-6-nitrobenzothiazole **44** and bis(methylthio)methylene malononitrile **1** was conducted by refluxing the two compounds in the presence of hydrazine hydrate **45**. The reaction took place with the addition of 5 ml of dimethylformamide and a pinch of anhydrous  $\text{K}_2\text{CO}_3$ . This synthesis yielded the corresponding 2-substituted derivatives of 3-amino-4-imino-8-nitro-pyrazolo[3,4-e]pyrimido[2,3-b][1,3]benzothiazole **46**. [xxvii].



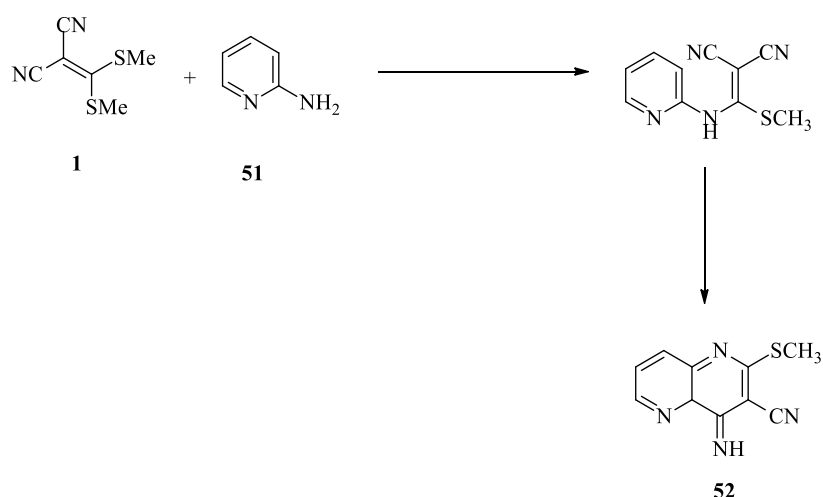
A novel heterocyclic system, comprising of two fused rings, was successfully synthesized. This system, named 6-amino-4-imino-8-(4'-substituted phenyl)-2-(methylthio)pyrimido[1,2-b]pyrimidine-3,7-dicarbonitrile **48**, was obtained through the reaction of 2,4-diamino-6-(4'-substituted phenyl)pyrimidine-5-carbonitrile **47** with bis(methylthio)methylene malononitrile **1** in the presence of anhydrous  $\text{K}_2\text{CO}_3$ , using DMF as the solvent. [xxviii]



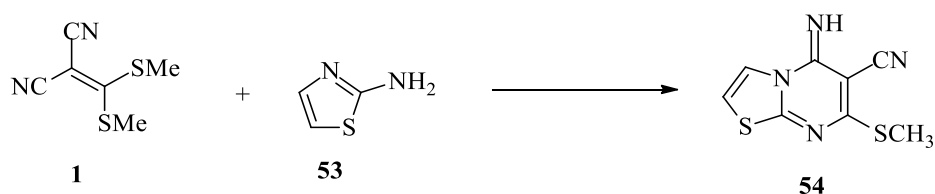
3-cyano-4-imino-7-methyl-2-(methylthio)-4H-pyrido[1,2-a]pyrimidine **50** was synthesized by reacting bis(methylthio)methylene malononitrile **1** with 2-amino-5-methylpyridine **49**. [xxix]



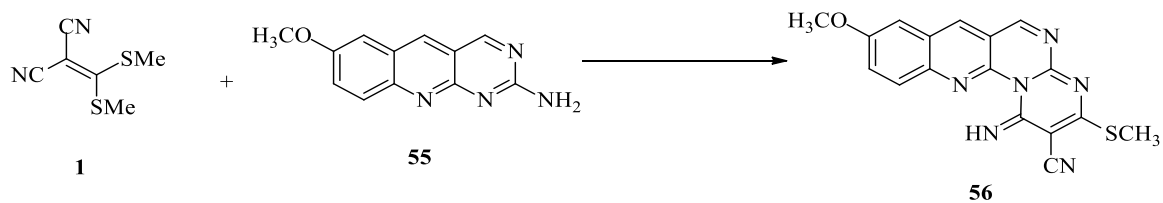
When bis(methylthio)methylene malononitrile **1** is subjected to a reaction with 2-aminopyridine **51** in the presence of N,N-dimethylformamide (DMF) and anhydrous potassium carbonate, it yields 3-cyano-4-imino-2-(methylthio)-4H-pyrido[1,2-a]pyrimidine **52**. [xxx]



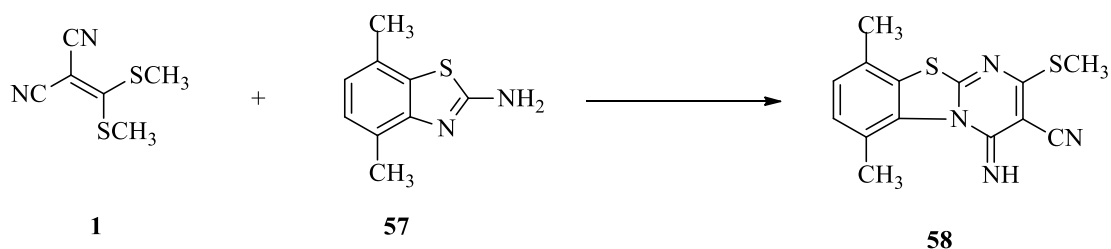
The reaction between 2-aminothiazole **53** and bis(methylthio)methylene malononitrile **1** resulted in the formation of 6-cyano-5-imino-7-(methylthio)-5H-thiazolo[3,2-a]pyrimidine **54**. [xxxii]



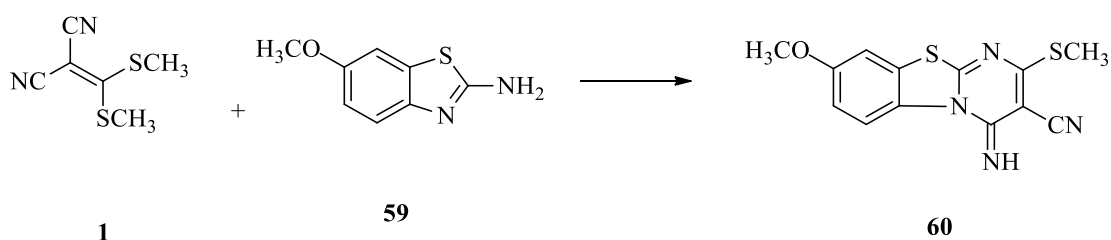
When 2-amino-7-methoxypyrimido[4,5-b]quinoline **55** is reacted with bis(methylthio)methylene malononitrile **1** in ethyl alcohol and catalytic amounts of TEA (triethylamine), the product obtained is 3-cyano-4-imino-9-methoxy-2-methylthio-4H-pyrimido[2,1-b]pyrimido[4,5-b]quinoline **56**. [xxxiii]



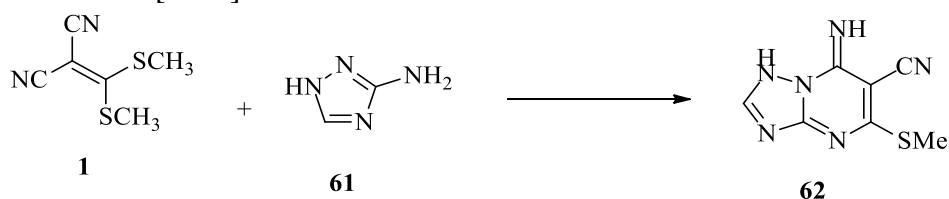
A novel heterocycle, namely 3-cyano-6,9-dimethyl-4-imino-2-methylthio-4H-pyrimido[2,1-b][1,3]benzothiazole **58**, was synthesized by reacting 2-amino-4,7-dimethylbenzothiazole **57** with bis-methylthio methylene malononitrile **1**. [xxxiii]



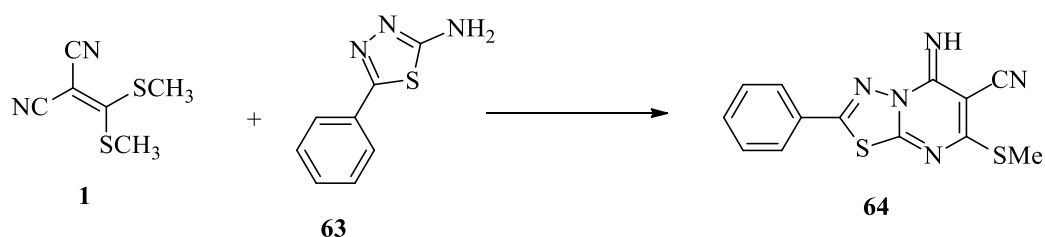
3-cyano-4-imino-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole **60** was obtained by treating 2-amino-6-methoxybenzothiazole **59** with bis(methylthio)methylene malononitrile **1** in the presence of dimethylformamide and a catalytic amount of anhydrous potassium carbonate. [xxxiv]



7-imino-5-(methylsulfanyl)-1,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile **62** was synthesized through a reaction between 2-[bis(methylsulfanyl)methylidene]malononitrile **1** and 1H-1,2,4-triazol-3-amine **61** in N,N-dimethylformamide in the presence of anhydrous potassium carbonate. [xxxv]

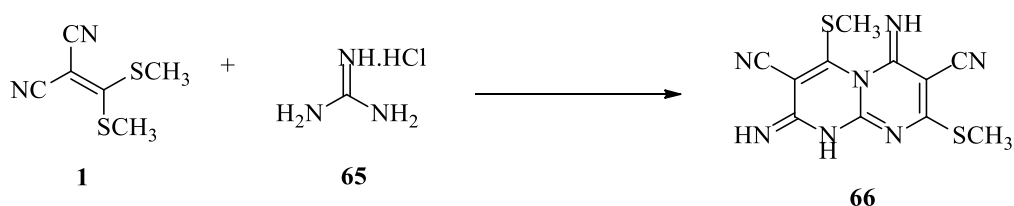


3-cyano-4-imino-2-methylthio-7-phenyl-4H-pyrimido[2,3-d]-1,3,4-thiadiazole **64** was synthesized by reacting bis(methylthio)methylene malononitrile **1** with 2-amino-5-phenyl-1,3,4-thiadiazole **63**. [xxxvi]

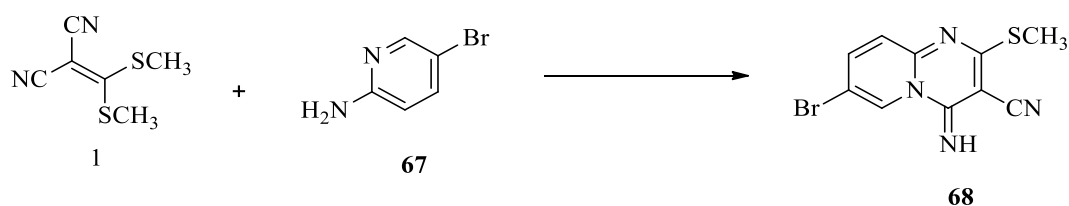




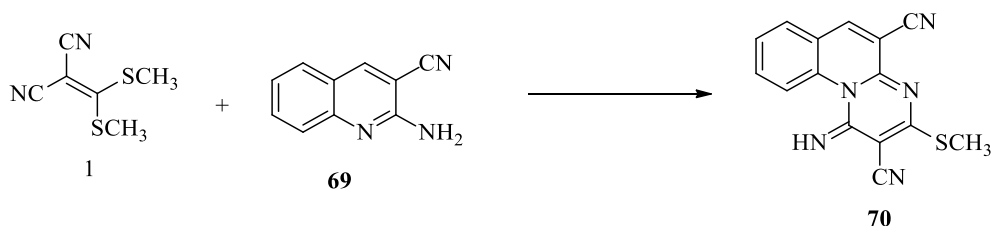
When guanidine hydrochloride **65** is subjected to a reaction with bis(methylthio)methylene malononitrile **1** in the presence of N,N-dimethylformamide (DMF) and a catalytic amount of anhydrous potassium carbonate, it yields diimino pyrimido pyrimidine **66**. [xxxvii]



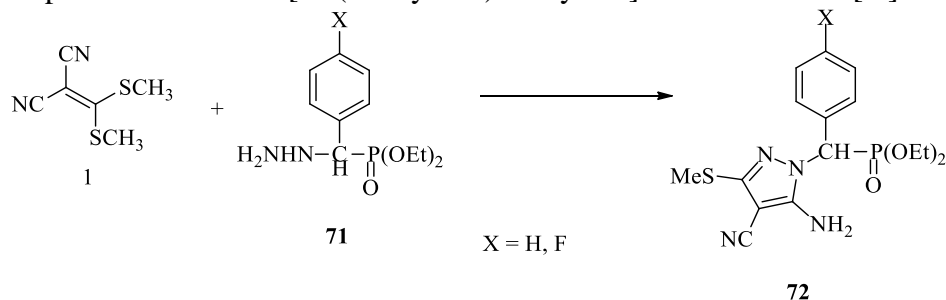
Compound 7-bromo-3-cyano-4-imino-2-methylthio-4H-pyrido[1,2-a]pyrimidine **68** was obtained by reacting 2-amino-5-bromopyridine **67** with bis(methylthio)methylene malononitrile **1**. [xxxviii]



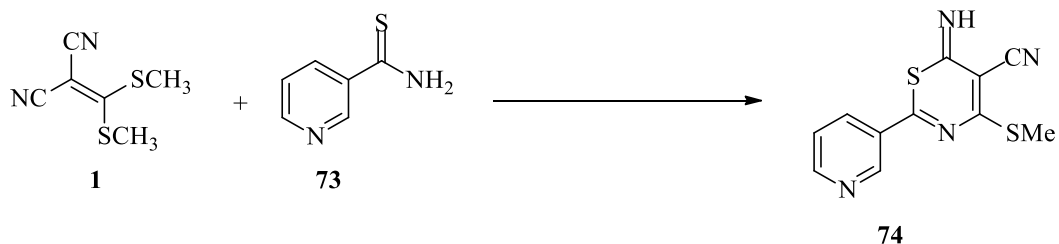
By refluxing 2-amino-3-cyanoquinoline **69** and bis(methylthio)methylene malononitrile **1** in the presence of a catalytic amount of anhydrous potassium carbonate in N,N-dimethylformamide (DMF), 3,11-dicyano-4-imino-2-methylthio-4H-pyrimido[1,2-a]quinoline **70** was obtained. [xxxix]



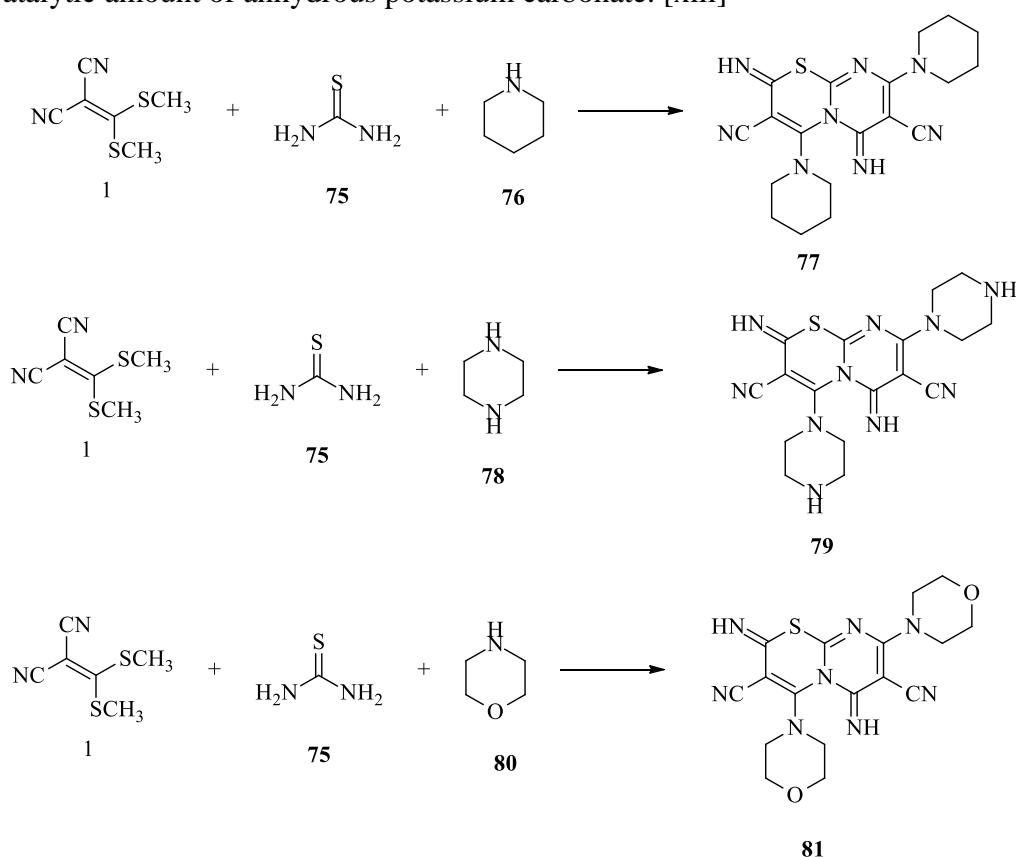
Diethyl[5-amino-4-cyano-3-(methylthio)-1H-pyrazol-1-yl]substitutedphenylmethyl phosphonates **72** were successfully prepared by condensing (1-hydrazino) substituted phenyl methyl phosphonates **71** with 2[bis(methylthio)methylene]malononitrile **1**. [xli]



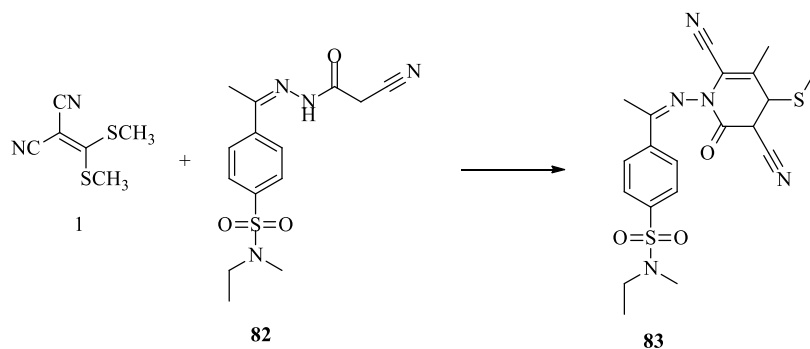
A novel heterocyclic compound, 6-imino-4-(methylthio)-2-(pyridin-3-yl)-6H-1,3-thiazine-5-carbonitrile **74**, was synthesized through the condensation of thionicotinamide **73** with bis(methylthio)methylene malononitrile **1**. The reaction took place in DMF with potassium carbonate serving as the catalyst. [xli]



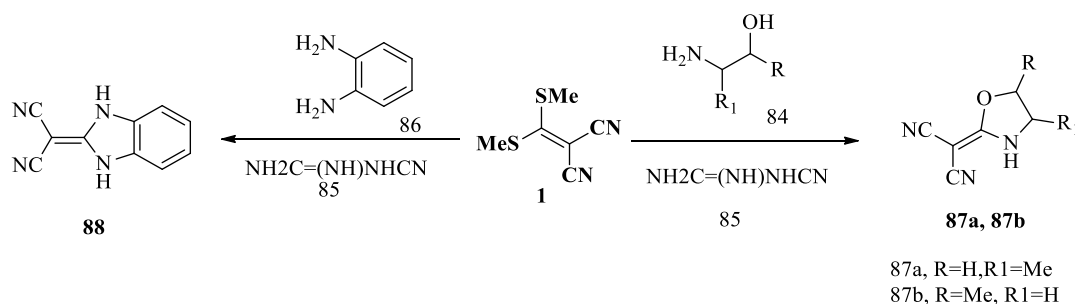
Through a one-step multicomponent reaction, substituted derivatives of 2,6-dihydro-2,6-diimino-4,8-bis(methylthio)pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile, namely compounds **77**, **79**, and **81**, were prepared. This was achieved by heating a mixture of bis(methylthio)methylene malononitrile **1** and thiourea **75** with different heteroaryl amines **76**, **78**, and **80**, respectively. The reaction took place in the presence of dimethylformamide and a catalytic amount of anhydrous potassium carbonate. [xlii]



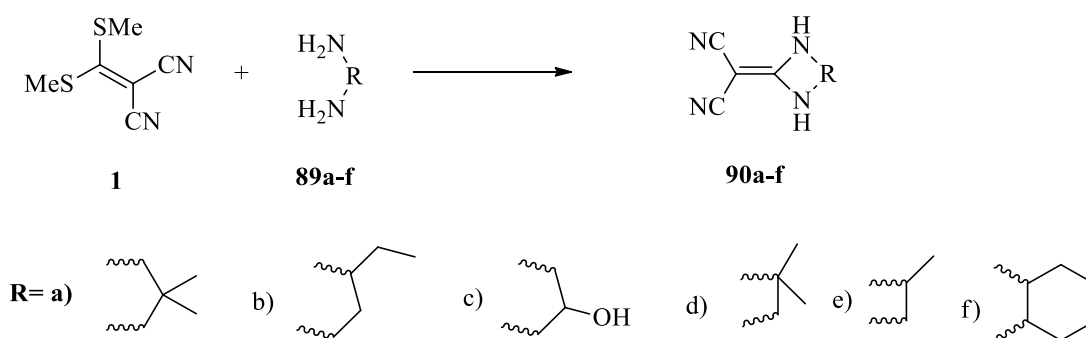
The reaction between 1-(2-(2-cyanoacetyl)hydrazino)ethyl derivative **82** and bis(methylthio)methylene malononitrile **1** was carried out in dimethylformamide (DMF) with the presence of anhydrous potassium carbonate. This reaction resulted in the formation of 2-oxopyridine-3,6-dicarbonitrile derivative **83**. [xliii]



Oxazolines **87a** and **87b**, as well as 1,3-dihydro-2H-benzimidazole **88**, were efficiently synthesized through a one-pot multicomponent reaction. This reaction involved bis(methylthio)methylene malononitrile **1**, cyanoguanidine **84**, and bifunctional nucleophiles such as  $\beta$ -hydroxyamines **85** and orthophenylenediamine **86**. [xlv]



A series of novel 2-(imidazolidin or tetrahydropyrimidin-2-ylidene) malononitrile derivatives **89a-f** were efficiently synthesized with good yields. This synthesis involved the cyclocondensation of 2[bis(methylthio) methylene]malononitrile **1** with diaminoalkanes **89a-f**. [xlv]



### Conclusion:

This review provides a comprehensive overview of the significant synthetic versatility of bis(methylthio)methylene malononitrile in the construction of intricate and functional heterocyclic structures. It highlights its applicability in various reactions, including cycloaddition, cyclocondensation, cascade reactions, and multicomponent reactions. The aim of this review is to encourage further research and exploration in this field, as it holds promising prospects for the development of new compounds and applications.

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**Conflict of Interest:** The authors hereby declare that they have no conflicts of interest associated with the publication of the review article.

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