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Versatile α-oxoketene dithioacetals and analogues in heterocycle synthesis

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REVIEW

Versatile α-oxoketene dithioacetals and analogues in heterocycle synthesis

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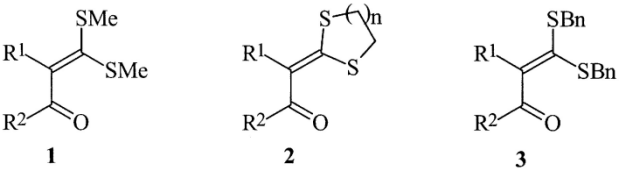
The synthetic utility of ketene dithioacetals is reported in a formal way. The title compounds are used as precursors for the synthesis of many heterocyclic rings. The reactions of the title compounds are subdivided into groups that cover reactions yielding monoheterocycles e.g., thiophenes, imidazolidines, pyrimidines, pyridines, pyrazoles and even fused heterocyclic e.g., pyrroloimidazoles, pyrazolopyridines and imidazopyridines.

Keywords: Ketene dithioacetals; Synthetic utility; Addition-elimination reactions; Cyclocondensation; Hydroxy enethiolates; Dithiane; Borane-pyridine complex; Steroidal heterocycles; Heteroannulated

1. Introduction

α-Oxoketene dithioacetals **1–3** especially the dimethylthioacetals **1** have recently received considerable attention due to their synthetic importance for the construction of a variety of alicyclic, aromatic and heterocyclic compounds [1, 2]. Ketene dithioacetals, in the presence of various regents, undergo different types of reactions to yield other heterocyclic compounds, e.g., thiophenes, pyrimidines, pyridines, etc. Consequently we were interested in surveying the synthetic utility of ketene dithioacetals.



Ketene dithioacetals

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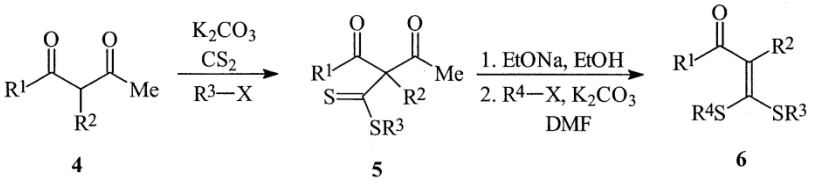
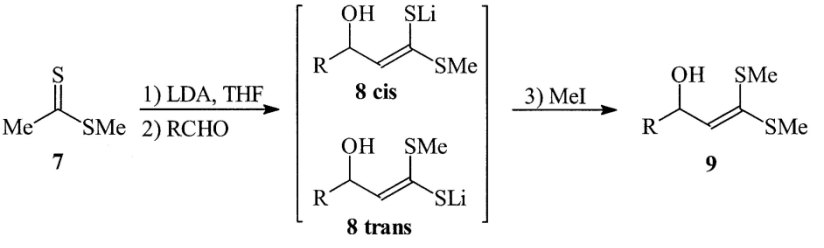
The method for preparation of α-oxoketene dithioacetals is common, the combination of an active methylene/methyl substrate, CS_2, RX, and a suitable base [1–3]. Lawesson and Larsson [4–6], Junjappa and Ila [7] have reported the synthesis of mixed dialkylketene dithioacetals from dithioesters which were prepared from ketone and dimethyl trithiocarbonate [8].

Q. Zhang *et al*. [9] have reported the preparation of single/mixed β-oxoketene dithioacetals from β-dicarbonyl compound **4** possessing an active methyne group. The method is based on the base decomposition of **5** and subsequent alkylation to afford the ketene dithioacetal compounds **6** (R^1 = OEt; R^2 = Et, allyl; R^3 = Et, Me, allyl, *n*-Bu; R^4 = Me, Et, *n*-Bu).



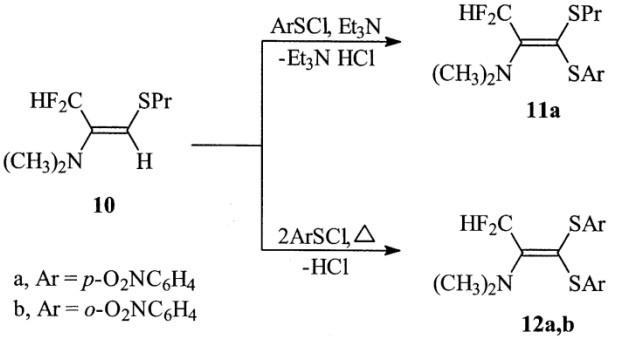
4 **5** **6**

The ketene dithioacetals **9** (R = Me, Et, Pr) were obtained from the condensation of methyl dithioacetate **7** with various aldehydes followed by alkylation of the produced hydroxy enethiolates **8** with methyl iodide [10].



7 **8 cis** **8 trans** **9**

Ketene dithioacetal **11a** was formed by the reaction of enamine **10** with *p*-nitrophenylsulfenyl chloride in the presence of triethylamine. Compounds **12a,b** were prepared by heating enamine **10** with two moles of *p*- and *o*-nitrophenylsulfenyl chloride [11].



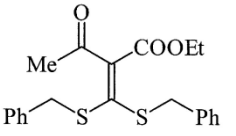
10 **11a** **12a,b**

Heterocyclic synthesis

1. *Thiophenes*

3,4-Disubstituted thiophenes were synthesized in moderate to good yields simply from the intramolecular Aldol type condensation of α-oxoketene dibenzylthioacetals [12]. For

example, the reaction of 3-oxobutanoic acid ethyl ester with carbon disulfide and benzyl chloride gave 2-bis[(phenylmethyl)thio]-methylene]-3-oxobutanoic acid ethyl ester **13**. The sodium hydroxide-catalyzed intramolecular cyclocondensation of **13** gave 1-[4-hydroxy-5-phenyl-2-[(phenylmethyl)-thio]-3-thienyl]ethanone **14**.



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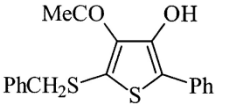
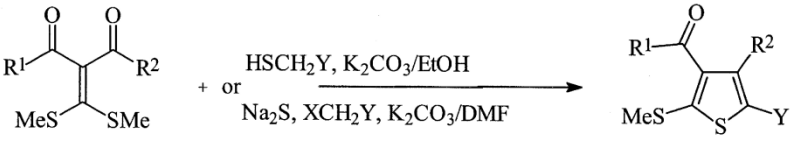


14

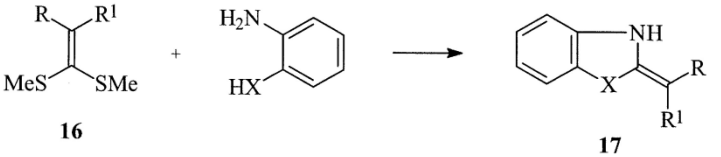
The formation of thiophenes from ketene dithioacetals **1** was described recently by Kirsch *et al.* [13] using ethyl thioglycolate in a basic medium. The ability of thioglycolate to replace a methylsulfanyl group of ketene dimethylacetals has been investigated to prepare 5-methylsulfanylthiophenes **15** in excellent yields.



1 **15**

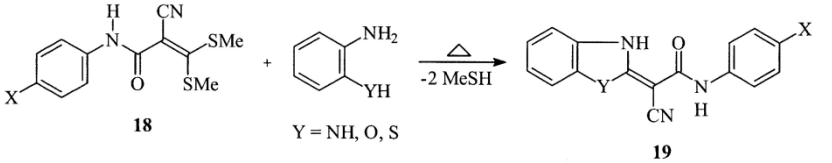
2. *Imidazolidines, oxazolidines and thiazolidines*

These 5-membered heterocyclic ring compounds containing two heteroatoms in the 1 and 3 positions are readily synthesized by reaction of ketene dithioacetals **16** with 1,2-diamines, 1,2-amino alcohols, and 1,2-amino thiols, respectively [14–15]. The aliphatic bifunctional nucleophiles lead to simple heterocyclic ring systems while the aromatic heteroatom nucleophiles afford annulated poly-aromatic heterocyclic ring systems e.g. **17** (R = Ac, OAc, COOEt, CN; R^1 = Ac, OAc, COOEt, CN, H; X = O, S). These substitution reactions proceed by two sequential conjugate addition-elimination reactions.



16 **17**

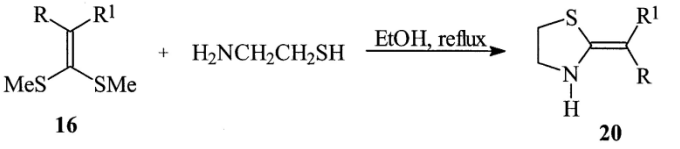
Ketene dithioacetals **18** reacted with *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol in refluxing absolute ethanol to afford the corresponding (benzoimidazol-2-ylidene-, benzoxazole-2-ylidene-, and benzothiazole-2-ylidene)cyanoacetanilides **18** in good yields [16].



18 Y = NH, O, S **19**

X = H, Cl, Me, OMe

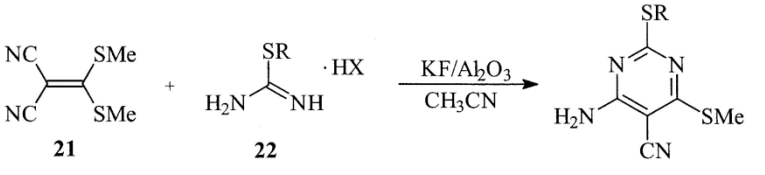
Ketene S,S-acetals **16** (R = H, COMe, COPh, COOMe, CN; R^1 = COMe, COPh, NO_2, COOMe, CN) react with $H_2NCH_2CH_2SH$ to afford the substituted 2-methylene thiazolidines **20** [17].



16 **20**

3. *Pyrimidines*

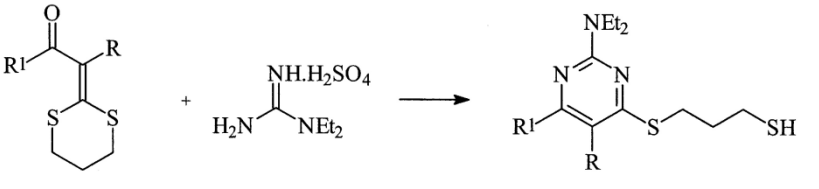
Yu and Cai [18] have reported the first use of $KF/A1_2O_3$ to catalyze the synthesis of 2-alkylthio-4-amino-5-cyano-6-methylthiopyrimidines **23** (R = Me, Et, *n*-Bu, *t*-Bu, n-$C_{12}H_{25}$ and $PhCH_2$) via the reaction of the ketene dithioacetal **21** with isothiouronium salts **22**. The highest yields could reach 83% when the reaction was carried out under the reflux condition in acetonitrile and the optimum amount of catalyst was 1.5 g of $KF/A1_2O_3$ for each of 5 mmol of **21**.



21 **22** **23**

X = $1/2H_2SO_4$, Br, Cl

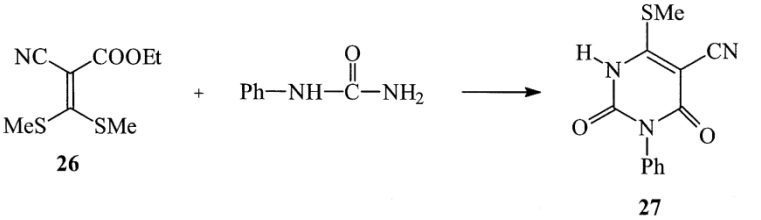
The reaction of α-oxoketene dithioacetals **24** with N,N-diethylguanidine sulfate was reported recently to facilitate the efficient synthesis of pyrimidines **25** [19] carrying a remote thiol group.



24 **25**

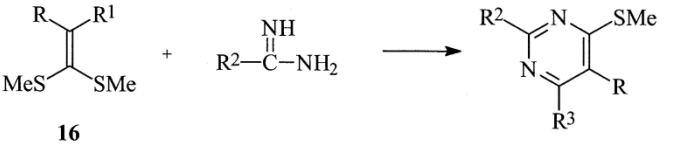
a; R = COMe, R^1 = Me
b; R = H, R^1 = CF_3

Cyclization of ethyl 2-cyano-3-bis(methylthio)acrylate **26** with phenylurea gave 3-phenyl-5-cyano-6-methylthio-pyrimidine-2,4-diones **27** [20].



26 **27**

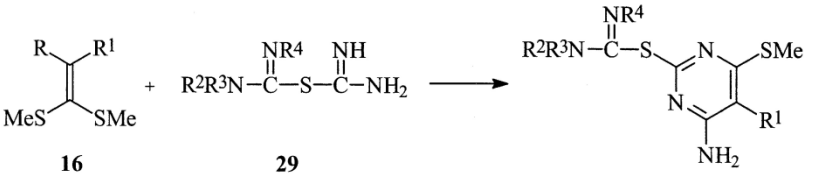
Pyrimidines **28** were obtained from the reaction of ketene dithioacetals **16** (R = CN, R^1 = CN, COOEt) with $R^2C(NH_2)$:NH (R^2 = morpholine) [21].



16 **28**

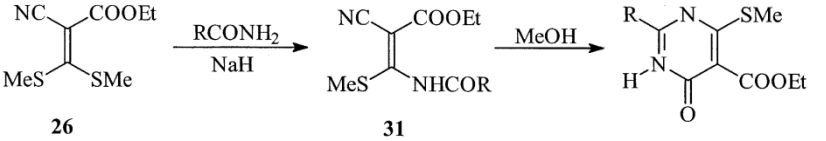
(R = CN; $R^3 = NH_2$, OH)

2-Isothioureido pyrimidines **30** (R^1 = CN, $CONH_2$, p-$O_2NC_6H_4$; $R^2 = R^4$ = Me, Et; R^3R^4 = $(CH_2)_4$; R^4 = p-$C1C_6H_4$, Ph) were prepared by reaction of thiobis-formamidine **29** with ketene dithioacetals **16** (R = CN; R^1 = CN, $CONH_2$, p-$O_2NC_6H_4$) [22].



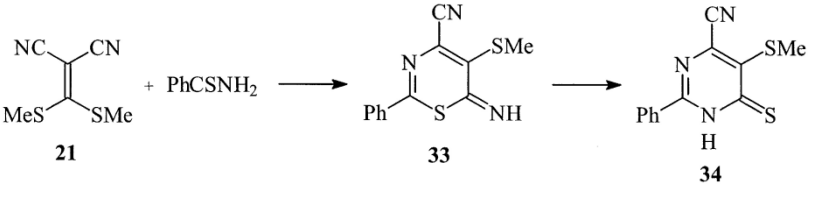
16 **29** **30**

Ethyl 2-cyano-3-bis(methylthio)acrylate **26** was reacted with $RCONH_2$ (R = Me, $C1CH_2$, Ph, substituted phenyl, PhCH=CH) in the presence of NaH to give the corresponding carboxamides **31**, which cyclized to the pyrimidinones **32** [23–24].



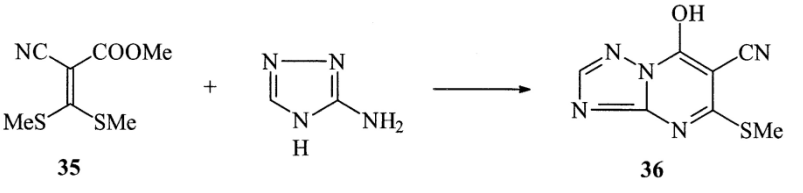
26 **31** **32**

Cyclocondensation of ketene dithioacetal **21** with thiobenzamides and $HC1O_4$ gave 6-amino-6H-1,3-thiazines **33**. Dimroth rearrangement of **33** in the presence of base gave thioxopyrimidines **34** [25].



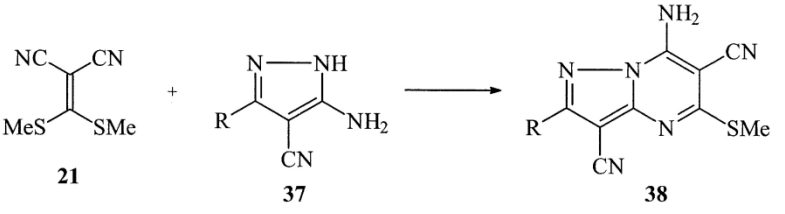
21 **33** **34**

Cyclocondensation of triazolamine with ketene dithioacetals **35** gave triazolopyrimidines **36** [26].

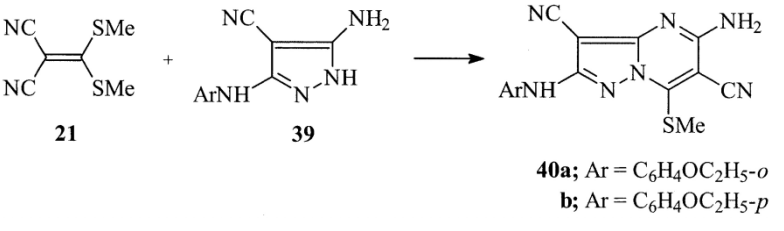


35 **36**

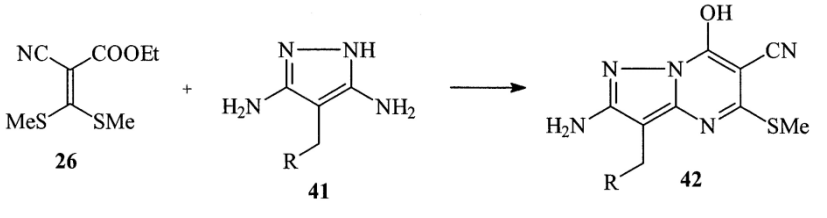
Condensation of 3-amino-1H-pyrazole-4-carbonitriles **37** (R = NH_2, 2,5-dimethyl-1-pyrryl, 4-morpholinyl, SMe) with bis(methylthio)methylene malononitrile **21** in the presence of triethylamine gave pyrazolo[1,5-a]pyrimidines **38** [27].



The reaction of ketene dithioacetal **21** with aminopyrazoles **39** in refluxing DMF containing a catalytic amount of triethylamine afforded the corresponding pyrazolo[1,5-a]pyrimidines **40** [28].

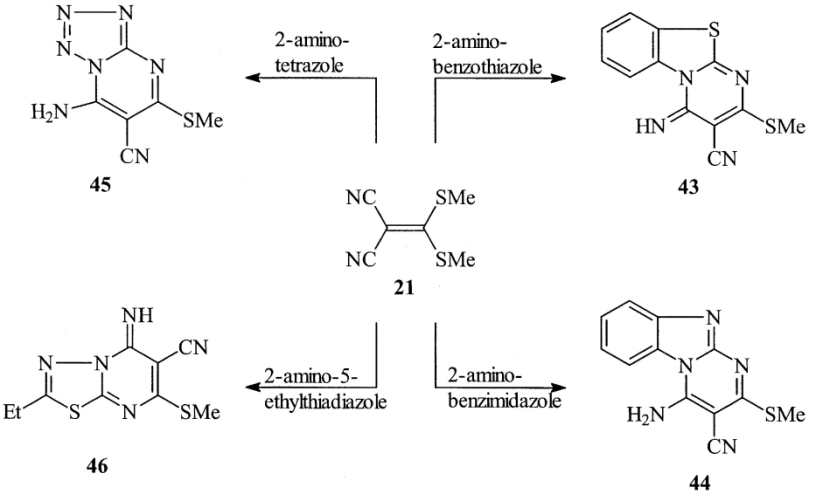


Cyclocondensation of 3,5-diaminopyrazoles **41** with ketene dithioacetals **26** in acidic and basic media yields pyrazolopyrimidines **42** [29] (R = 4-$MeOC_6H_4$, 4-$C1C_6H_4$, 4-MeC_6H_4).

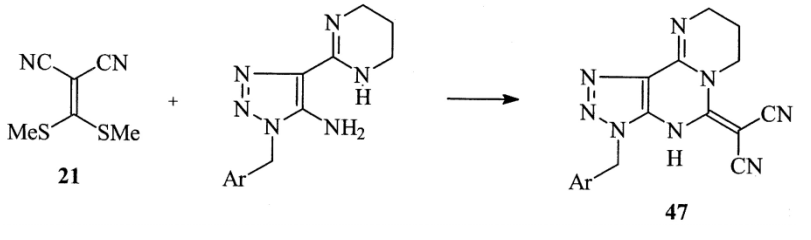


Metwally *et al*. reported the condensation of bis(methylthio)methylene malononitrile **21** with some amino azoles, namely 2-aminobenzothiazole, 2-aminobenzimidazole, 5-aminotetrazole monohydrate and 2-amino-5-ethylthiadiazole which resulted in the formation of bridgehead

nitrogen compounds **43**, **44**, **45** and **46** respectively [30].

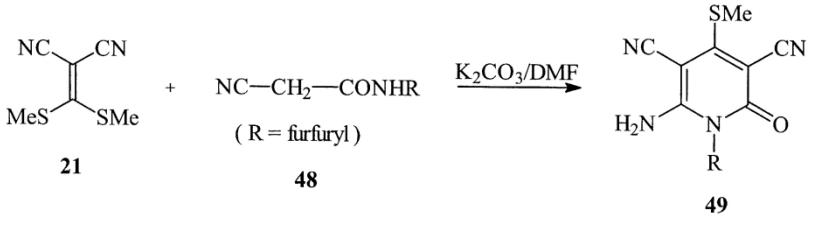


Aminotriazoles have been reacted with 2-cyano-3,3-bis(methylthio)-acrylonitrile **21** to give the corresponding new heteroannulated 8-azapurines **47** [31].



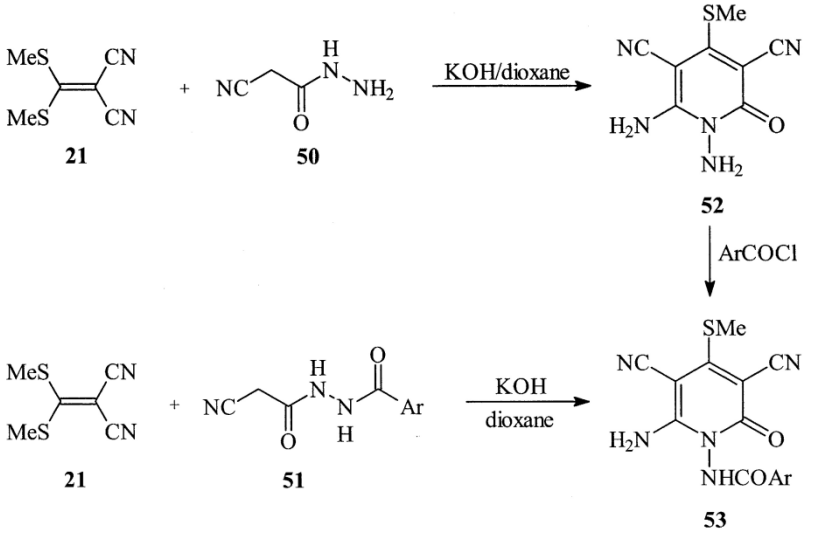
4. *Pyridines*

Secondary α-cyanoacetamide derivatives **48** have been reacted with 2-cyano-3,3-bis(methylthio)acrylonitrile **21** in DMF containing K_2CO_3 to afford the corresponding N-substituted pyridinones **49** [32].

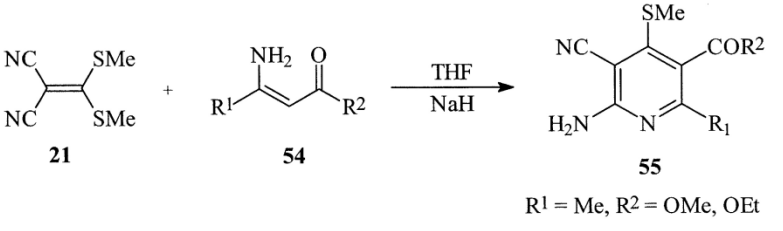


Ketene dithioacetal **21** was treated with cyanoacetohydrazide **50** and its N-aroyl derivatives **51** at room temperature in the presence of pulverized potassium hydroxide in 1,4-dioxane to give the corresponding *N*-amino-2-pyridones **52** and *N*-aroylamino-2-pyridones **53** respectively in

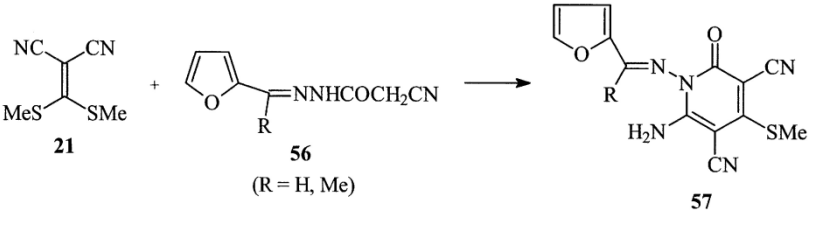
good yields. When **52** was left to react with aroyl chlorides in refluxing ethanol, the corresponding *N*-aroylamino-2-pyridones **53** were obtained [33].



The condensation of ketene dithioacetal **21** with β-amino crotonates **54** was carried out in THF in the presence of NaH to give 2-amino-3-cyano-2-alkyl-6-methylthio-5-pyridinecarboxylic acid derivatives **55** in moderate yield [34].

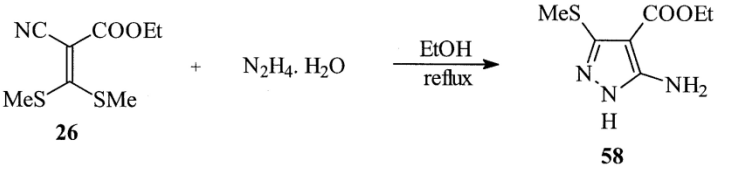


Hydrazones **56** were cyclized with bis(methylthio)methylene malononitrile **21** to give the substituted 1-[1-(fur-2-yl)alkylideneamino]-1,2-dihydropyridine-3,5-dicarbonitriles **57** [35].

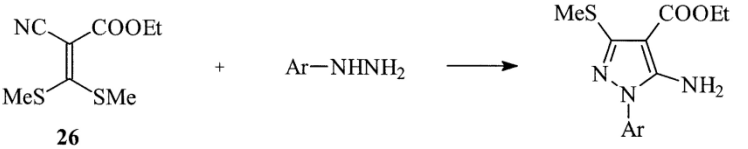


5. *Pyrazoles and isoxazoles*

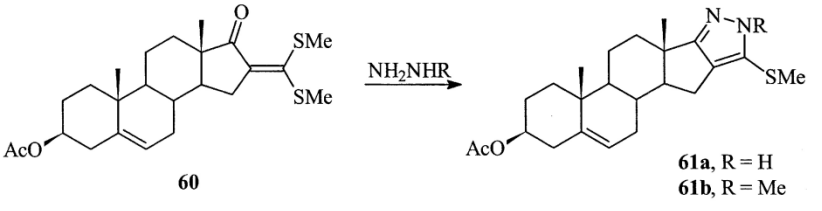
Ethyl-2-cyano-3,3-bis(methylthio)acrylate **26** has been reacted with hydrazine hydrate to afford ethyl 5-amino-3-methylthio-lH-pyrazol-4-carboxylate **58** [36].



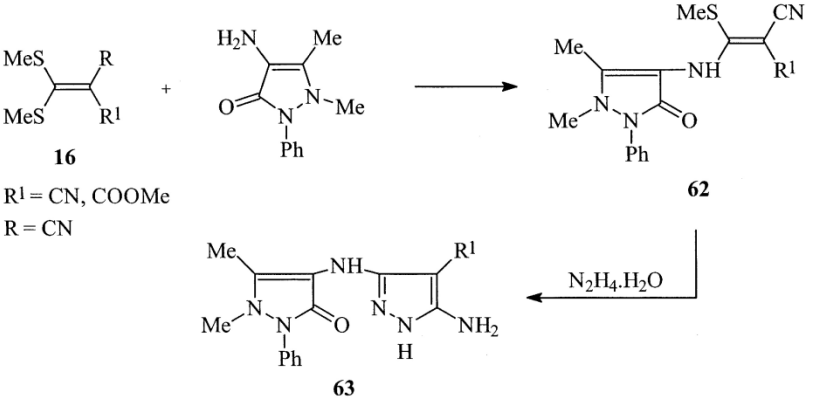
The reaction of 3,3-bis(methylthio)-2-cyanoacrylic acid ethyl ester **26** with different substituted phenylhydrazines afforded the pyrazole carboxylate derivatives **59** (Ar = 4-$O_2NC_6H_4$, 2,6-$(Cl)_2$-4-$CF_3C_6H_2$) [37–38].



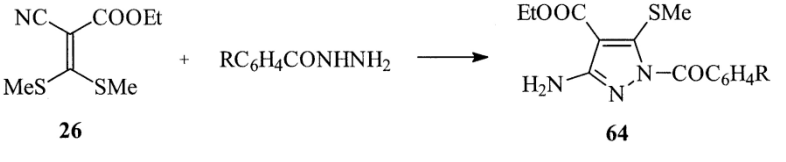
The synthesis of steroidal heterocycles **61a** and **61b** [39] containing the pyrazole ring fused to the 16,17-position of the steroid nucleus was achieved via the reaction of 3β-acetoxy-l6-[bis(methylthio)methylene]androst-5-en-17-one **60** with hydrazine and methylhydarzine, in boiling methanol, respectively.



Reaction of ketene derivatives **16** with 4-aminoantipyrine gives compound **62** which react with hydrazine to afford 1-phenyl-2,3-dimethyl-4-[3-(5-amino-4-substituted)-1H-pyrazolylamino]pyrazolin-5-one **63** (R^1 = CN, COOMe) [40].

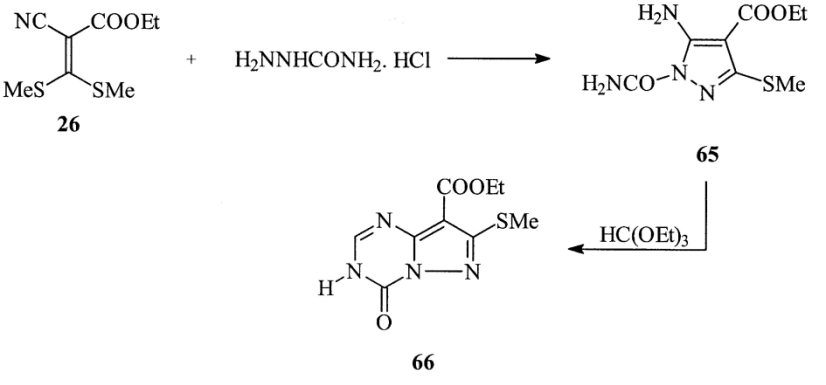


The reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate **26** [41–42] with carboxylic acid hydrazides gave substituted pyrazoles **64** (R = H, 4-OMe, 4-Cl, 4-NO_2).

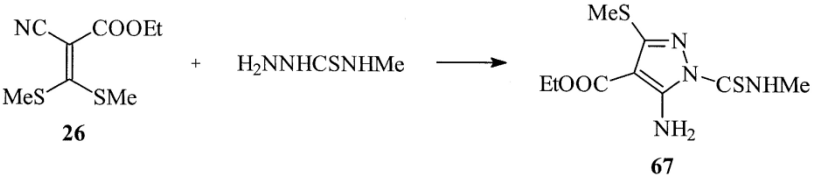


Cyclocondensation of ethyl-2-cyano-3,3-bis(methylthio)acrylate **26** with semicarbazide HCl in refluxing diethyl ether for one hour gave 54–80% substituted pyrazoles **65** which

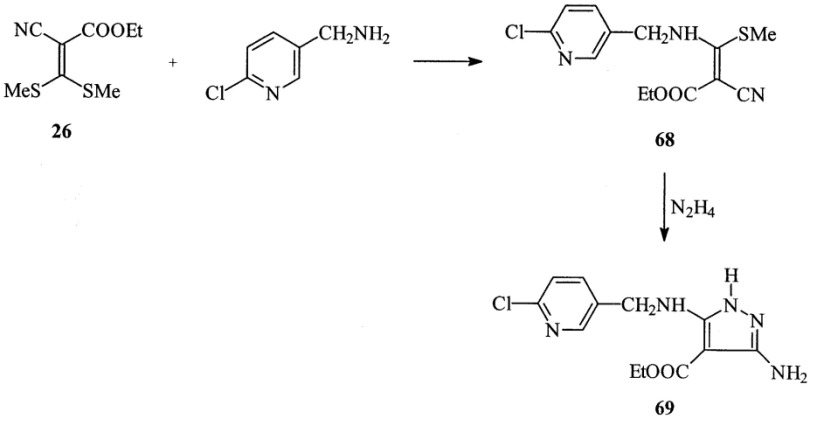
underwent cycloaddition with $HC(OEt)_3$ to yield 49–79% substituted pyrazolo[2,3-a]1,3,5-triazines **66** [43].



5-Amino-3-methylsulfanyl-l-methylthiocarbamoyl-lH-pyrazole-4-carboxylic acid ethyl ester **67** [44] was prepared by cyclocondensation of ethyl-2-cyano-3,3-bis(methylthio)acrylate **26** with methylthiosemicarbazide.

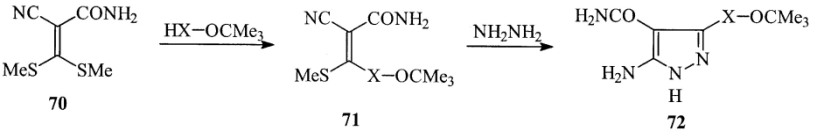


3-[(6-Chloropyridin-3-ylmethyl)-amino]-2-cyano-3-methylsulfanyl-acrylic acid ethyl ester **68** [45] was synthesized via the reaction of ketene dithioacetal **26** with C-(6-chloro-pyridin-3-yl)-methyl amine. Compound **68** reacted with hydrazine to give the corresponding aminopyrazole derivative **69**.



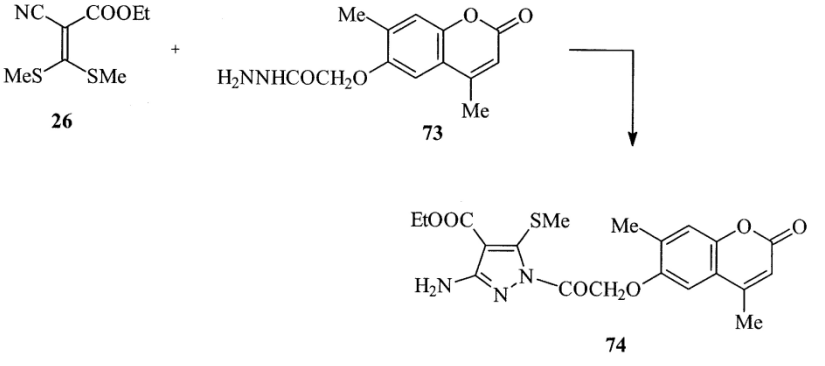
N-(5-Aminopyrazol-3-yl) amino acids **72** were prepared by treating 2-cyano-3,3-bis(methylthio)-2-propenamide **70** with H-X-$OCMe_3$ [X = Gly, Gly-Phe, Pro, Glu($OCMe_3$)]

and cyclizing the resulting propenamide **71** with hydrazine hydrate [46].



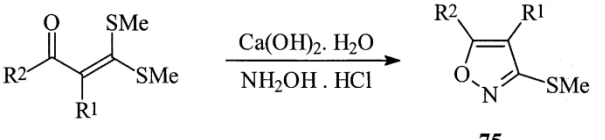
70 **71** **72**

Ethyl-2-cyano-3,3-bis(methylthio)acrylate **26** has been reacted with the coumarin derivative **73** to give the pyrazole derivative **74** [47].



26 **73** **74**

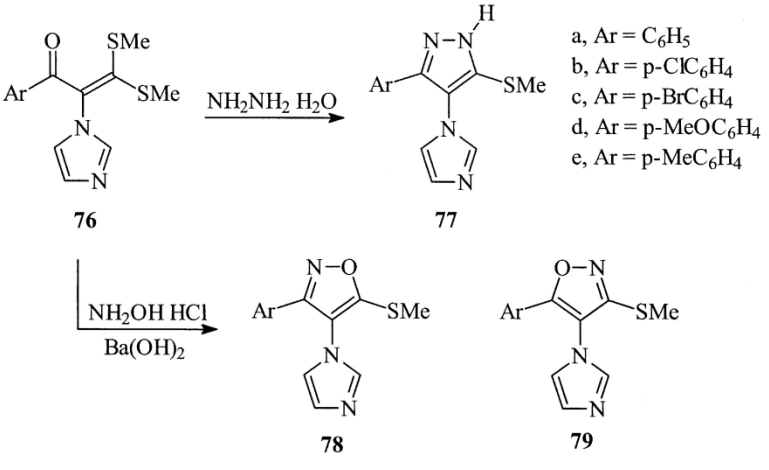
Reaction of conjugated ketene dithioacetals **1** with hydroxylamine gave the corresponding isoxazoles **75** [48–49].



1 **75**

R^1 = CN;
R^2 = Ph, 4-ClC_6H_4, 2-furyl

Substituted pyrazolylimidazole **77**, isoxazolylimidazole **78** and **79** were synthesized by cyclocondensation of α-oxo-α-imidazolylketene dithioacetal **76** with bifunctional nucleophiles such as hydrazine and hydroxylamine [50].



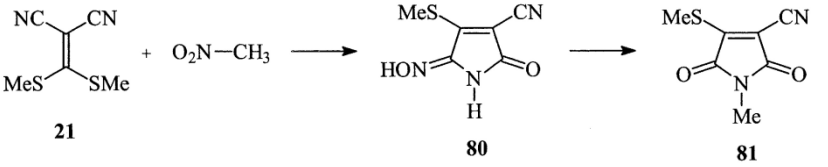
76 **77**

a, Ar = C_6H_5
b, Ar = p-ClC_6H_4
c, Ar = p-BrC_6H_4
d, Ar = p-$MeOC_6H_4$
e, Ar = p-MeC_6H_4

78 **79**

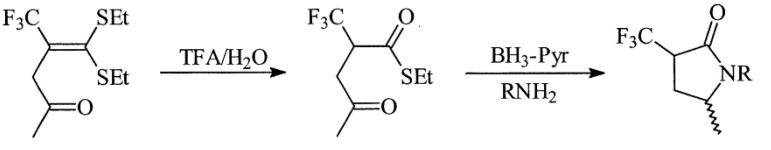
6. *Pyrroles*

The reaction of ketene dithioacetal **21** with nitromethane gave 2-hydroxyimino-4-cyano-3-(methylthio)maleimide **80** which was readily converted to the corresponding 4-cyano-3-(methylthio)maleimide **81** by methylation with dimethyl sulfate followed by hydrolysis with HCl [51].



21 **80** **81**

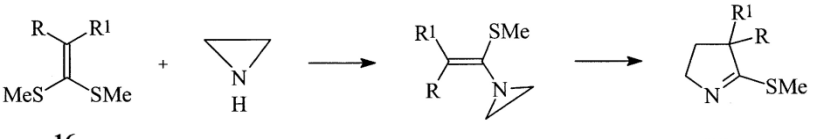
Thiolester **83** was obtained in almost quantitative yield by hydrolysis of ketene dithioacetal **82** in a 10/1 trifluoroacetic acid-water refluxing mixture. The nucleophilic attack of **83** by aniline or benzylamine) did occur selectively on the ketone function using the borane-pyridine complex to afford the lactam **84** [52].



82 **83** **84**

R = Ph, Bn

Ketene dithioacetals **16** have been reacted with aziridine in Et_2O to give the aziridino methylene compounds **85**, which underwent KI-catalyzed rearrangement to give pyrrolines **86** [53].

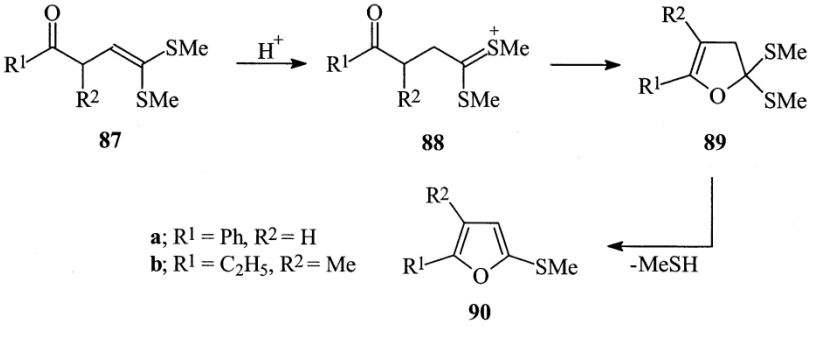


16 **85** **86**

R = CN; R1 = CN, COOEt, $CONH_2$

7. *Furans*

The acid-catalyzed reaction of β-oxoketene dithioacetals **87a** and **87b** gave furans **90a** and **90b** in 70% and 80% yield, respectively. The reaction presumably proceeds by a protonation-cyclization-elimination sequence [54].

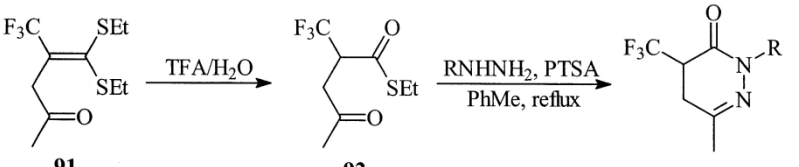


87 **88** **89**

90

8. *Pyridazines*

Ketene dithioacetal **91** undergoes acid hydrolysis to give the corresponding γ-keto thiolester **92** which underwent condensation with hydrazines under *p*-toluenesulfonic acid (PTSA) catalysis afforded the 4,5-dihydropyridazinones **93** [55]. Substituted hydrazines led regioselectivity to compounds substituted on N-2, indicating hydrazone formation in the first step.

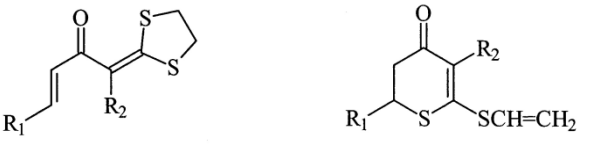


91 **92** **93**

R = H, Me, Ph

9. *Thiopyrans*

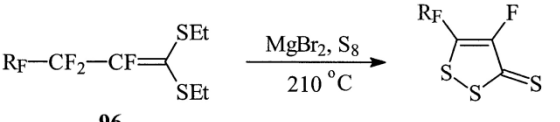
Dimsyl sodium induced anionic ring cleavage of 1-(1,3-dithiolan-2-ylidene)-4-aryl-3-buten-2-ones **94** (R_1 = Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-MeC_6H_4, R_2 = H; R_1 = Ph, 4-$MeOC_6H_4$, R_2 = Me) followed by intramolecular cyclization of the intermediate thiolate anion gave 2-aryl-6-(vinylsulfanyl)-2,3-dihydro-4H-thiopyran-4-ones **95** in good yields [56].



94 **95**

10. *Dithioles*

Excellent yield of 4-fluoro-l,2-dithiole-3-thiones **97** [57] was obtained (80–92%) was obtained in a one pot procedure by direct heating of **96**, magnesium bromide and elemental sulfur.

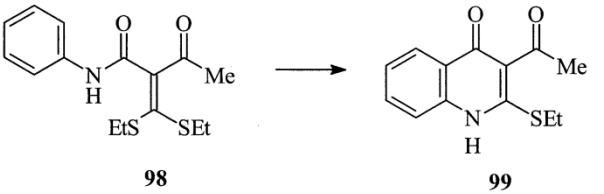


96 **97**

R_F = CF_3, $(CF_2)_2H$

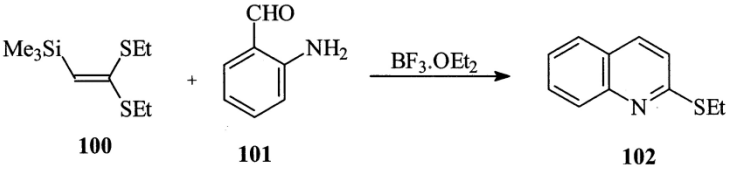
11. *Quinolines*

Thermal cyclization of ketene dithioacetal **98** was reported recently to give the corresponding quinolinone **99** [58]. The structure of the quinolinone obtained has been revised by X-ray crystallographic analysis as 4-quinolinone instead of 2-quinolinone.



98 **99**

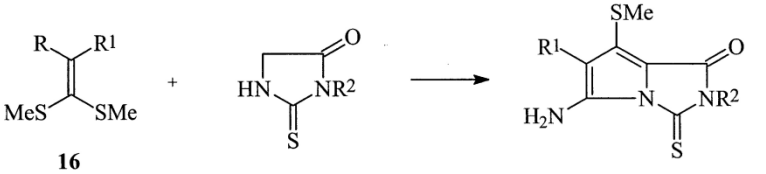
When a mixture of 2-aminobenzaldehyde **101** and $BF_3.OEt_2$ was treated with silylketene dithioacetal **100**, 2-ethylthioquinoline **102** was obtained interestingly in 40% yield [59].



100 **101** **102**

12. *Pyrroloimidazoles*

7-Alkylsulfanyrrolo[1,2-c]imidazoles **104** (R^1 = CN, COOEt; R^2 = H, Ph) [60] were prepared by the reaction of ketene dithioacetals **16** with 2-thioxohydantions **103**.



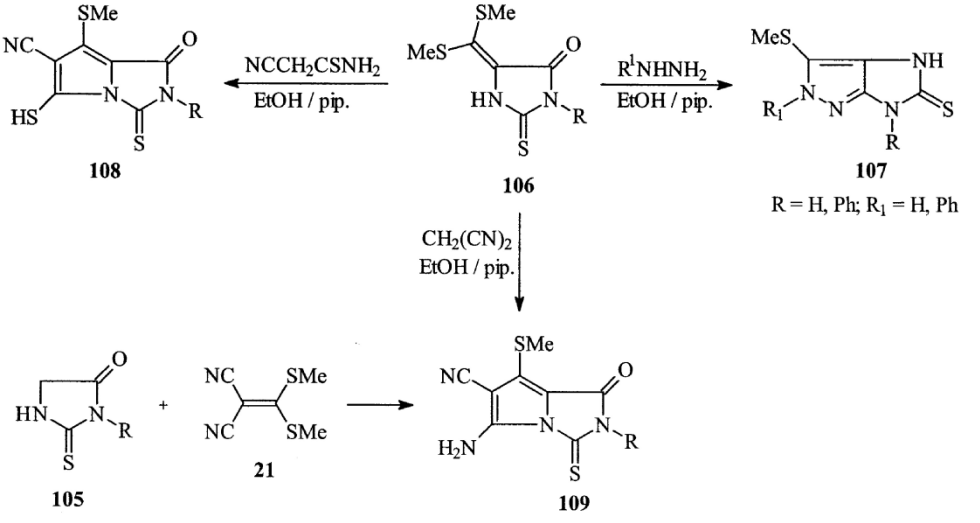
16
R = CN;
R1 = CN, COOEt

103
(R^2 = H, Ph)

104

Pyrrolo[1,2-c]imidazole derivatives **108** and **109** [61] were synthesized by the reaction of ketene dithioacetals **106** with cyanothioacetamide and malononitrile respectively. The formation of **109** from the reaction of **106** and malononitrile is assumed to proceed via the intermediacy of acyclic Michael adducts, which cyclize via MeSH elimination and addition to the cyano group to yield the final stable diazapentalene analogues **109**. The products **109** were obtained also from the reaction of 2-thioxohydantoin **105** and bis[(methylthio)methylene] malononitrile **21**.

The reaction of ketene dithioacetals **106** with substituted hydrazines in refluxing ethanol containing a catalytic amount of piperidine afforded the corresponding 4-methylsulfanylimidazo[5,4-c]pyrazoles **107** in good yields [61].



108

106

107
R = H, Ph; R_1 = H, Ph

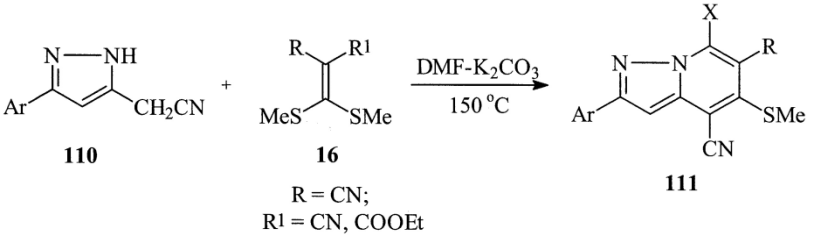
105

21

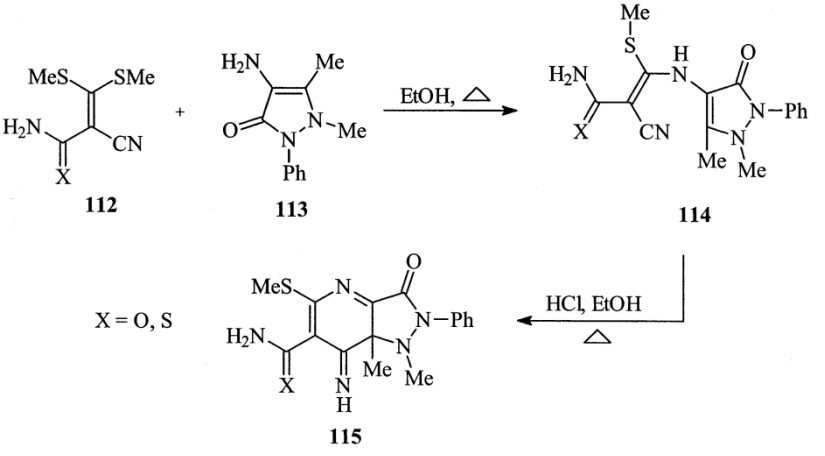
109

13. *Pyrazolopyridines*

Substituted pyrazolo[1,5-a]pyridines **111** [62] (Ar = substituted phenyl, 3-pyridyl, 4-pyridyl; X = OH, NH_2, Me; R = CN) were prepared from the reaction of 5-aryl-3-cyanomethyl-1*H*-pyrazole **110** with ketene dithioacetals.

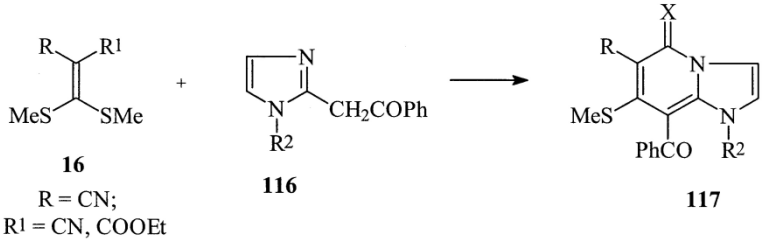


The reaction of ketene dithioacetals **112** with 4-amino-2,3-dimethyl-1-phenylpyrazolin-5-one **113** in refluxing ethanol containing catalytic amounts of piperidine was reported to yield the corresponding pyrazolone ketene *N*, *S*-acetal derivatives **114**. The latter undergo intramolecular cyclization to afford the corresponding pyrazolo[4,3-b]pyridine derivatives **115** [63].

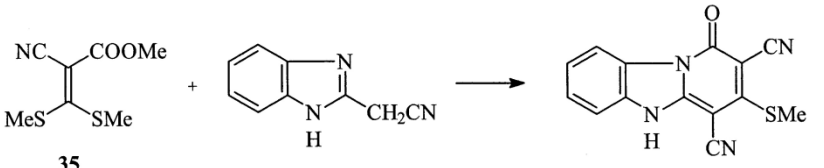


14. *Imidazopyridines*

Reaction of 2-benzoylmethyl imidazoles **116** with ketene dithioacetals **16** in the presence of K_2CO_3 gave the corresponding imidazo[1,2-a]pyridine derivatives **117** (R = CN, R^2 = H, Me; X = NH, O) [64].

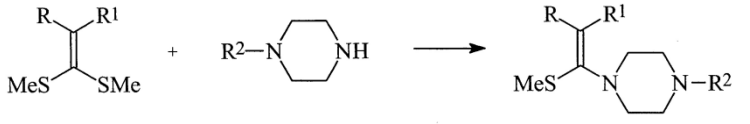


Reaction of 2-benzimidazolyl acetonitrile **118** with methyl-2-cyano-3,3-bis(methylthio) acrylate **35** gave the corresponding fused benzimidazole derivative **119** [65].



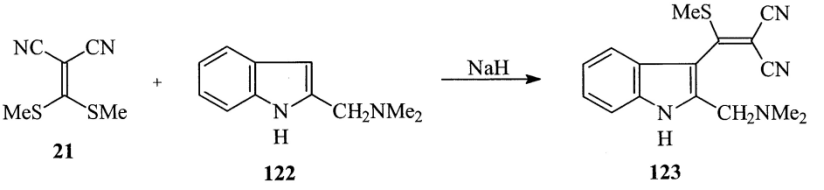
15. *Miscellaneous reactions*

Various 2-cyano-3-methylthio-3-piperazinylacrylonitriles and acrylamides **121** [66] were prepared by the reaction of ketene dithioacetals **16** with substituted piperazines **120**.

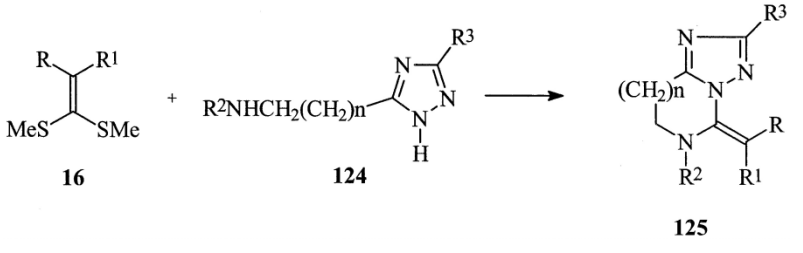


R = CN;
R1 = CN, COOEt

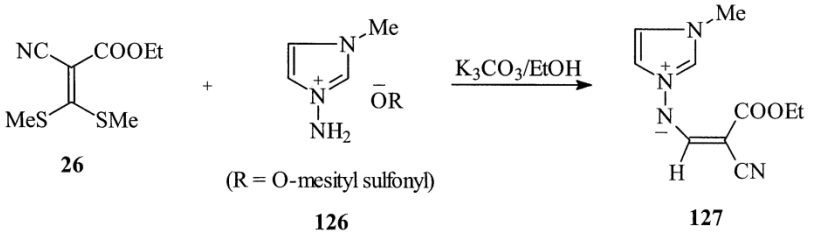
Reaction of indole derivative **122** with ketene dithioacetals **21**, in the presence of NaH or NaOH gave 3-(2-cyano-l-methylthio-vinyl)indole derivative **123** [67].



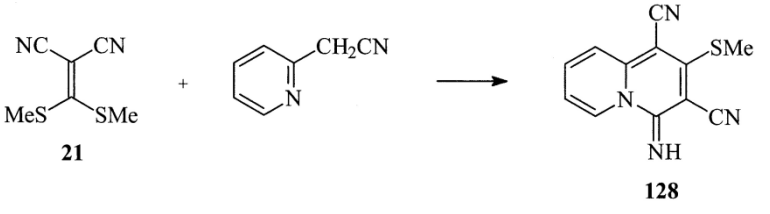
The reaction of ω-aminoalkyl-1,2,4-triazoles **124** with ketene dithioacetals **16** was reported to give the partially saturated pyrimidotriazoles **125** (R = CN; R^1 = CN, COOEt; R^2 = H, Me; R^3 = H, PhNH, 4-$MeOC_6H_4$) [68].



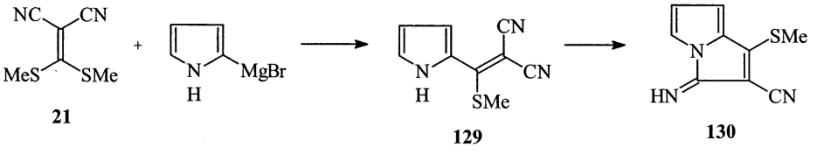
The reaction of *N*-amino-imidazolium salts **126** with ketene dithioacetal **26** as polarized olefin in the presence of K_2CO_3 in ethanol gave the corresponding imidazolium N-vinyl imino ylide **127** [69].



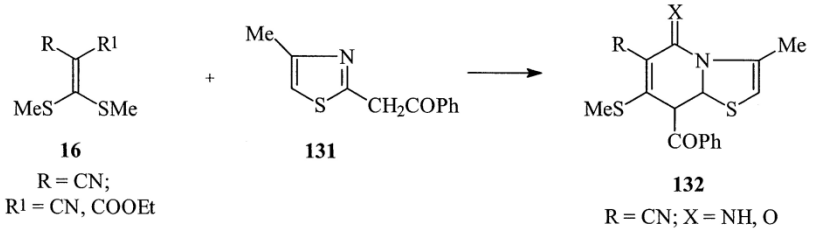
1,3-Dicyano-4-amino-2-methylthio-4H-quinolizine **128** was prepared from pyridin-2-ylacetonitrile and 2-cyano-3,3-bis(methylthio)acrylonitrile **21** [70].



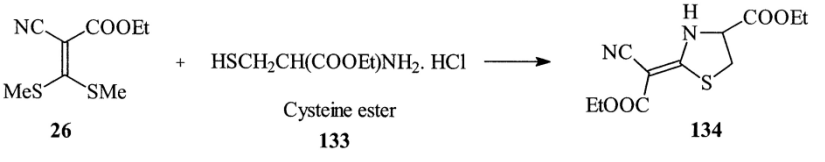
Condensation of 1-pyrrolyl magnesium bromide with 2-cyano-3,3-bis(methylthio) acrylonitrile **21** in non-polar solvents gave the dinitriles **129**, which on heating in the presence of catalytic amounts of amines were cyclized to give the pyrrolizines **130** [71].



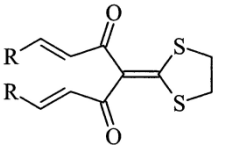
Reaction of 2-(4-methylthiazol-2-yl)-1-phenylethanone **131** with ketene dithioacetals **16** gave the corresponding thiazolo[3,2-a]pyridines **132** [72].



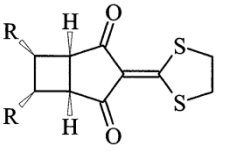
2-(Cyano-ethoxycarbonyl-methylene)-thiazolidine-4-carboxylic acid ethyl ester **134** was synthesized by the reaction of ketene *S*, *S*-acetal **26** with cysteine ethyl ester hydrochloride **133** in the presence of a base [73].



Irradiation of bis(alkenoyl)ketenedithioacetals **135** (R = Ph, 4-$MeOC_6H_4$, 4-$C1C_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_4$, thienyl) in solution leads to facile and stereospecific intramolecular [2+2] photocycloaddition [74] resulting in the formation of substituted bicyclo [3.2.0]heptane-2,4-diones **136**, the observed conformational rigidity of which is attributed to the push-pull character of the ketene dithioacetal group.



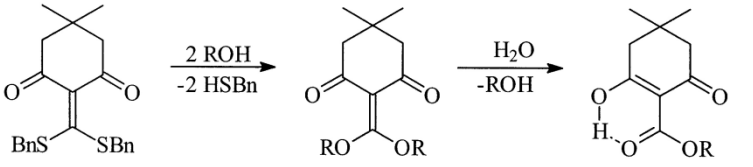
135



136

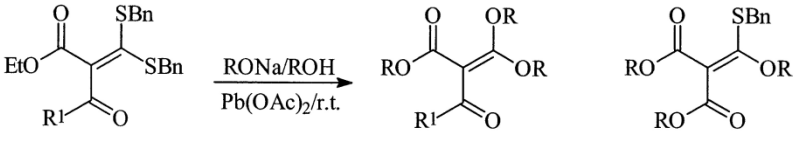
When α, α'-dioxoketene dibenzylthioacetal **137A** was subjected to recrystallization in hot alkanols for purification, the alkanol esters **139a-c** were produced respectively in good yields. The formation of **139a-c** could be expressed only by the sequential nucleophilic addition of alkanol (or water) and elimination benzylthio units. Diisopropylacetal **138c** was obtained as the only *O*, *O*-acetal product in the parallel experiments by refluxing **137A** in absolutely anhydrous isopropanol at N_2 atmosphere for 30 minutes then cooling to room temperature. Comparatively, the corresponding esters **139a** and **139b** were obtained respectively with methanol and ethanol as the solvent. These results might indicate that **138c** is more stable than **138a** and **138b** when exposed to the air due to its steric hindrance to further transformation [75].

Compared with **137A**, acyclic analogues **137B** and **137C** are not sensitive to hot alkanols. Whereas, when using sodium alkoxides as nucleophiles and catalyzed by lead acetate at room temperature, the two benzylthio groups of **137B** could be displaced by ethoxy and isopropoxy groups respectively to yield the corresponding *O*, *O*-acetal **140a** and **140b**. The mono-substituted products as *O*, *S*-acetal **141a** and **141b** were also yielded from **137B** when the reaction time was limited. When **137C** was used as substrate, only in sodium ethoxide-ethanol medium and catalyzed by $Pb(OAc)_2$, *O*, *O*-acetal **140c** was obtained [75].



137A **138** **139**

a; R = Me **b;** R = Et **c;** R = i-Pr



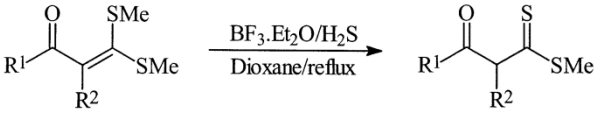
137B; R1 = OEt
C; R1 = Me

140a; R1 = OEt, R = Et
140b; R1 = Oi-Pr, R = i-Pr
140c; R1 = Me, R = Et

141a; R = Me
141b; R = Et

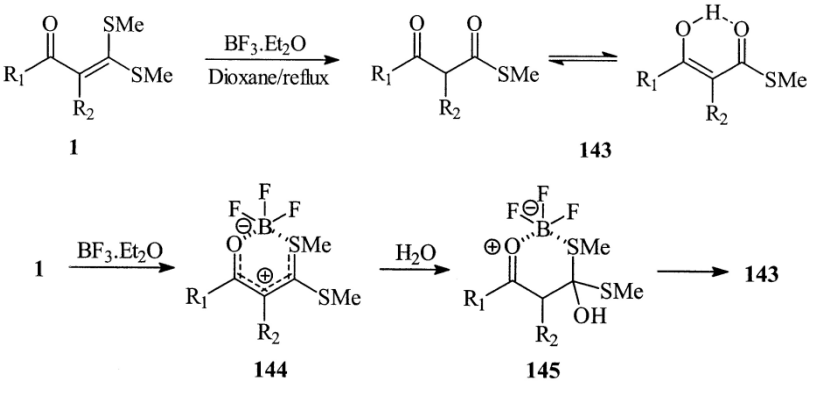
When α-oxoketene dithioacetals **1** were treated with hydrogen sulfide in refluxing dioxane in the presence of boron trifuoride etherate, the corresponding substituted dithiocarboxylates **142** (R^1 = methyl, phenyl, substituted phenyl, 2-naphthyl, 2-thienyl, R^2 = H; $R^1R^2 = C_4H_8$) were isolated in good yields. The method has been found to be general to a variety of substituted ketene dithioacetals and several substituted β-oxodithioesters could be synthesized.

The reaction apparently involves the complexation of the carbonyl group of the α-oxoketene dithioacetals with Lewis acid, thus activating the β-carbon atom towards the nucleophilic attack of hydrogen sulfide [76].

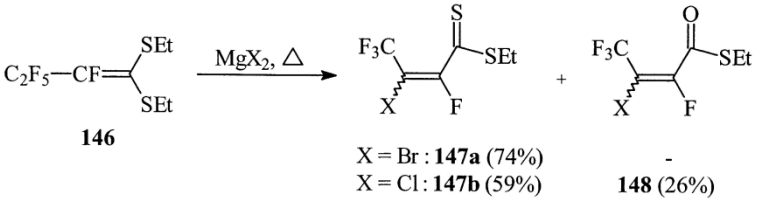


1 **142**

Refluxing of ketene dithioacetals **1** in dioxane in the presence of an equivalent amount boron trifuoride etherate and then treatment with water gave the thiolesters **143** in moderate to good yields. The Lewis acid assisted partial hydrolysis of acyl ketene dithioacetals could involve the initial formation of a complex **144** with boron trifuoride etherate. Addition of water to this complex during work-up to give **145**, followed by loss of methylthio group, would lead to the formation of β-oxothiolester **143** [77].

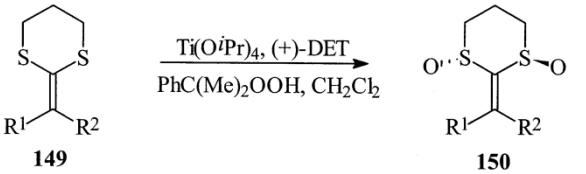


1,1-bis(ethylsulfanyl)perfluorobut-l-ene **146**, on heating with magnesium bromide, was converted into the ethyl β-bromo dithiocrotonate **147a** in 74% isolated yield [78]. A similar reaction occurred with magnesium chloride afforded the corresponding β-chloro dithiocrotonate **147b** (59%) except that thiolester **148** (26%) was obtained as a by-product.



146

The ketene dithioacetal bis-sulfoxides **150** were prepared directly in high yield by asymmetric oxidation of ketene dithioacetals **149** [79].

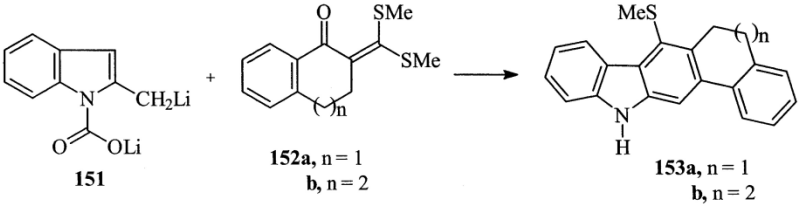


149 **150**

R^1 = H, cyclo-$(CH_2)_5$, Ph, Me

R^2 = $(CH_2)_3CH_3$, C_8H_{11}, cyclo-$(CH_2)_5$, Ph, *p*-$MeOC_6H_4$

Dianion **151** was generated and reacted with α-oxoketene dithioacetals **152a** and **152b** derived from tetralone and benzsuberone to afford the corresponding carbazoles **153a** and **153b** in 64% and 68% yields respectively [80].



151 **152a,** n = 1 **b,** n = 2 **153a,** n = 1 **b,** n = 2

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