Yoshinori Tominaga* and Yoshiro Matsuda

Faculty of Pharmaceutical Sciences, Nagasaki University, 1-14, Bunkyo-machi, Nagasaki 852, Japan

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This review describes developments in the synthesis of heterocyclic compounds using the nitro ketene dithioacetal 1-nitro-2,2-bis(methylthio)ethylene (**3**).

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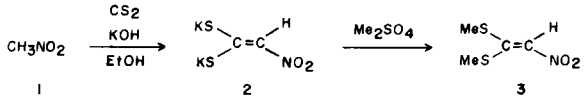
Contents.

1) Introduction.

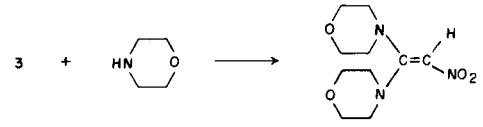
Ketene dithioacetals appropriately functionalized (cyano, methoxycarbonyl, sulfonyl, nitro, acyl, *etc.*) are versatile reagents which have been extensively utilised in heterocyclic synthesis [1-133]. One of these, the nitro ketene dithioacetal 1-nitro-2,2-bis(methylthio)ethylene (**3**), is also an extremely interesting synthon and is used as a two carbon fragment for the synthesis of heterocyclic compounds having nitro or amino groups. This ketene dithioacetal is readily prepared by the condensation of nitromethane with carbon disulfide in ethanol in the presence of potassium hydroxide followed by methylation with dimethyl sulfate [134, 135].

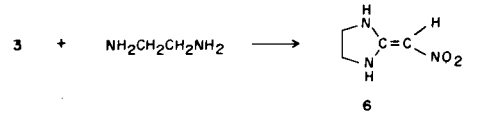


Despite numerous reports concerning the utility of this compound in the synthesis of heterocycles, to our knowledge it has never been reviewed in the literature. This review primarily describes the synthetic use of nitro ketene dithioacetal in the preparation of heterocyclic compounds. Work done in our own laboratory at Nagasaki University will be emphasized with additional references to the interesting and important results from the laboratories of other groups.

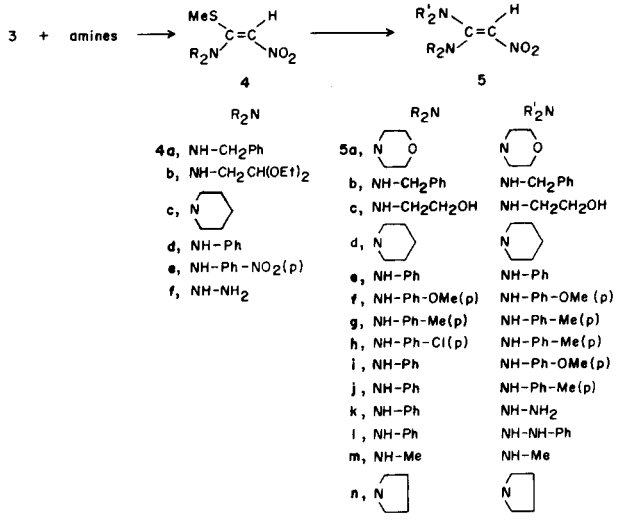
2) Reaction of **3** with Amines.

Gompper and Schäfer originally showed that nucleophilic substitution of **3** with morpholine or ethylenediamine affords nitro ketene aminals (**5a** and **6**) in 90% and 89% yield, respectively [135].





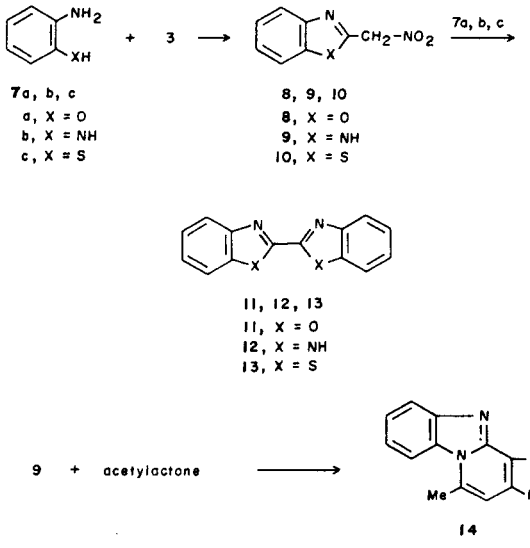
Later, Schäfer *et al.*, reported the reaction of **3** with various amines to give the corresponding mono- and di-replacement products in good yield [136, 137]. Generally, reaction of **3** with one gram equivalent weight of amine gives the corresponding mono displacement products **4a-f** in good yield. Further reaction of **4** with excess amine gives the corresponding ketene aminals **5a-n**.



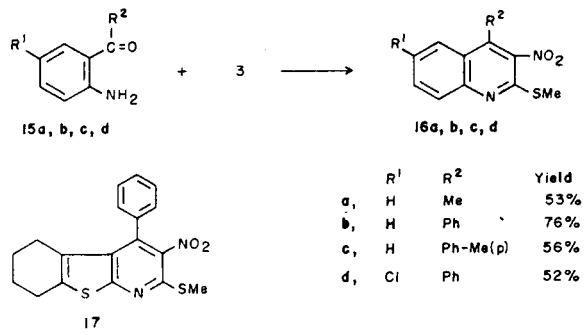
o-Aminophenol (**7a**) reacts with **3** to give 2-nitromethylbenzoxazole (**8**) in 86% yield. Similarly, 2-nitromethylbenzimidazole (**9**) is prepared from *o*-phenylenediamine (**7b**) in 89% yield. The reaction of *o*-aminothiophenol (**7c**) with **3** gives the intermediate **10** which on heating results in the formation of bis(2,2′-benzothiazole) (**13**) [138]. 2,2′-Bis (benzoxazole) (**11**) and 2,2′-bis(benzimidazole) (**12**) are obtained by the condensation of **8** with *o*-aminophen-

ole and **9** with *o*-phenylenediamine, respectively.

The reaction of **9** with acetylacetone results in the formation of 4-nitro-1,3-dimethylpyrido[1,2-*a*]benzimidazole (**14**) [138].

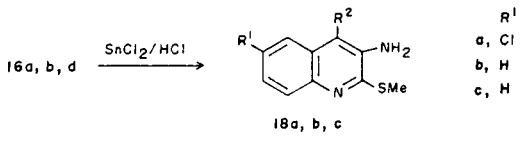


Compound **3** reacts with *o*-aminophenyl ketones **15a,b,c,d** in the presence of acid to give 3-nitroquinolines **16a,b,c,d** [139]. The condensed thiophene derivative **17** was prepared in a similar manner.

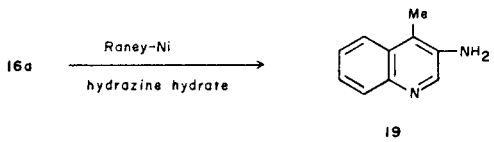


	R^1	R^2	Yield
a,	H	Me	53%
b,	H	Ph	76%
c,	H	Ph-Me(p)	56%
d,	Cl	Ph	52%

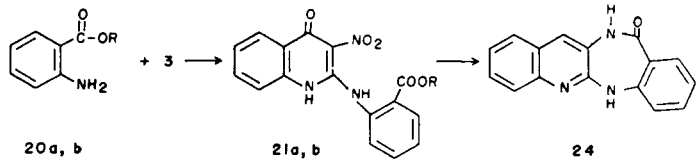
The reaction of **16a,b,c,d** with stannous chloride/hydrochloric acid yields 3-amino-2-methylthioquinolines **18a,b,c**. Treatment of **16a** with Raney-nickel/hydrazine hydrate leads to desulfurization and affords 3-aminoquinoline (**19**).

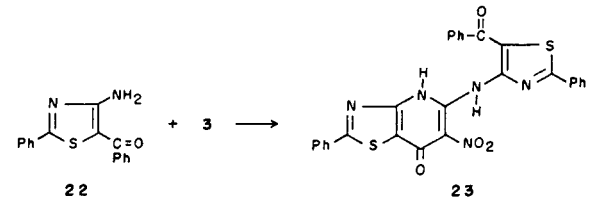


	R^1	R^2	Yield
a,	Cl	Ph	82%
b,	H	Ph	65%
c,	H	Me	82%

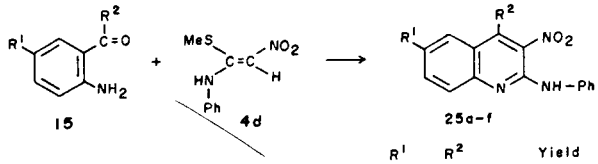


The use of anthranilic ester **20a,b** instead of the aminoketones results in the formation of the 2-anilino-3-nitro-4-quinolone derivatives **21a,b**. Similarly, 4-amino-5-benzoyl-1-phenylthiazole (**22**) reacts with **3** to give the corresponding pyrido[2,3-*d*]thiazole (**23**). The treatment of **21a** with Raney-nickel-hydrazine yields the diazepinone **24** in 15% yield [139].

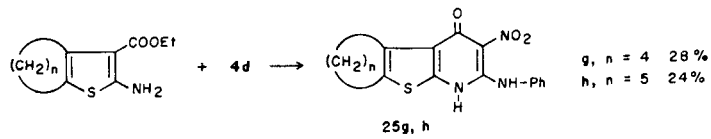




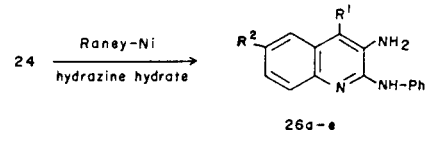
A variation of this reaction makes use of the mono replacement product of **3**, 1-anilino-1-methylthio-2-nitroethylene (**4d**) as the nitro-synthon. This leads to the 2-anilino-3-nitroquinoline (**25a-f**). The yield is best when carried out in acetic acid. The condensed thiophene derivatives **25g,h** have been similarly prepared [139].



	R^1	R^2	Yield
a,	Cl	Ph	46%
b,	H	Me	42%
c,	Br	Ph	65%
d,	H	Ph	73%
e,	H	Ph-Me(p)	57%
f,	H	OH	44%

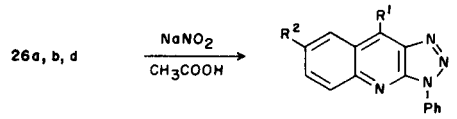


Compounds **25a-h** are key compouds for 2,3-diaminoquinolines which are used extensively to prepare fused quinoline derivatives. Schäfer, Gewald, and Seifert have reported the synthesis of 2-anilino-3-aminoquinolines **26a-e** by the reduction of the nitro group of **24** and **25** with Raney-nickel/hydrazine hydrate [139].



	R^1	R^2	Yield
a,	Ph	Cl	76%
b,	Me	H	86%
c,	Ph	Br	83%
d,	Ph	H	81%
e,	Ph-Me(p)	H	89%

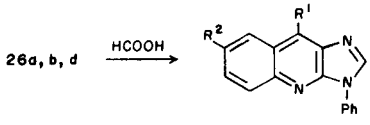
The treatment of **26a,b** and **d** with sodium nitrate in acetic acid gives the corresponding triazolo[5,4-*b*]quinolines **27a,b,c** [139].



27a, b, c

	R^1	R^2	Yield
a,	Ph	Cl	93%
b,	Ph	H	86%
c,	Me	H	36%

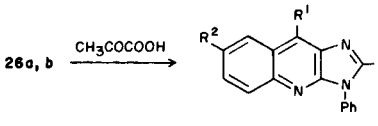
Compounds **26a,b** and **d**, on reaction with formic acid undergo cyclization giving rise to imidazo[5,4-*b*]quinolines **28a,b,c** [139].



	R^1	R^2	Yield
a,	Ph	Cl	95%
b,	Ph	H	76%
c,	Me	H	83%

28a, b, c

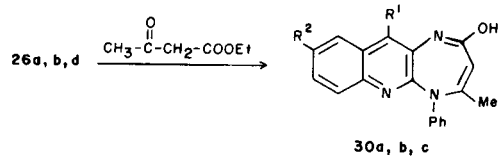
Reaction of **26a** and **b** with pyruvic acid also yields 2-methylimidazo[5,4-*b*]quinolines **29a,b** without the formation of pyrazino[2,3-*b*]quinolines [139].



	R^1	R^2	Yield
a,	Ph	Cl	89%
b,	Me	H	94%

29a, b

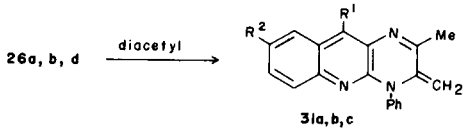
Condensation of **26a,b**, and **d** with ethyl acetoacetate gives 1,4-diazepino[2,3-*b*]quinoline derivatives **30a,b,c** [139].



30a, b, c

	R^1	R^2	Yield
a,	Ph	Cl	82%
b,	Ph	H	84%
c,	Me	H	86%

The treatment of **26a,b**, and **d** with diacetyl gives the corresponding 2-methyl-3-methylenepyrazino[2,3-*b*]quinolines **31a,b,c** [139].



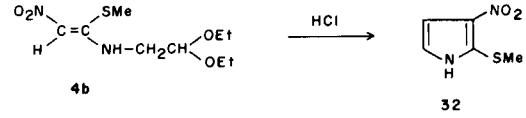
	R^1	R^2	Yield
a,	Ph	Cl	96%
b,	Ph	H	94%
c,	Me	H	86%

31a, b, c

3) Nitro Enamine Derivatives in the Synthesis of Heterocyclic Compounds.

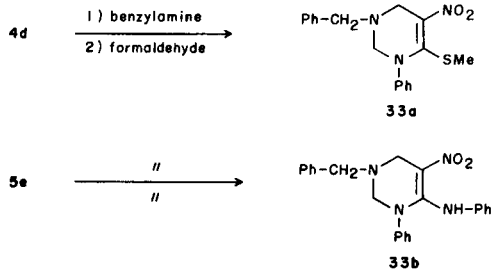
Ketene *S,N*-acetals and *N,N*-acetals which are prepared by the reaction of **3** with amines are nitro enamines. These nitro-synthons have found to be of great utility in the synthesis of heterocyclic compounds.

Treatment of **4b** with hydrochloric acid gives 2-methylthio-3-nitropyrrole (**32**) in 70% yield [136, 141]. This reaction suggests the condensation of **4** or **5** with various types of aldehydes, carbonyl compounds, and other electrophilic reagents to give the corresponding heterocyclic nitro compounds directly.



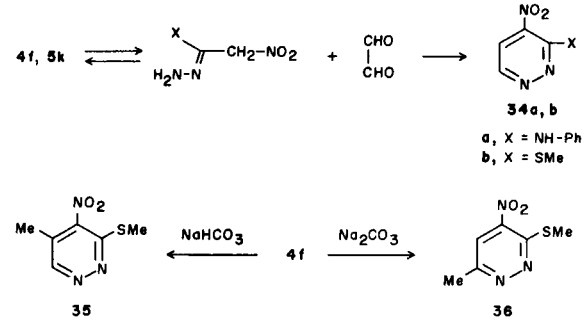
4b 32

We have demonstrated the Mannich reaction of **4d** or **5e** with formaldehyde and benzylamine to give 1,2,3,6-tetrahydropyrimidine derivatives **33a,b** in good yield [136].



33a 33b

Hamberger has reported that the nitro-amidrazones **4f**, **5k** react with glyoxal in the presence of base to give the 4-nitropyridazines **34a,b** in 40-50% yield. The methylthio derivative **4f** gives a low yield of the pyridazine **34b** with glyoxal and with pyruvaldehyde it gives two isomers **35** and **36** depending on the base employed [142].

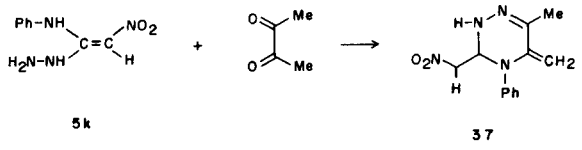


34a, b

a, X = NH-Ph
b, X = SMe

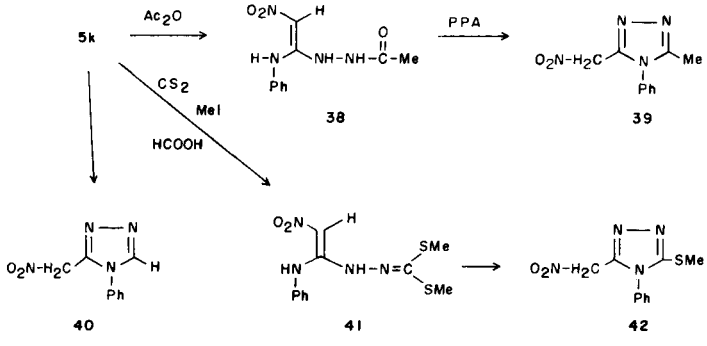
35 36

Condensation of **5k** with diacetyl gives triazine derivative (**37**) which differs from the compound prepared by Hamberger [142].



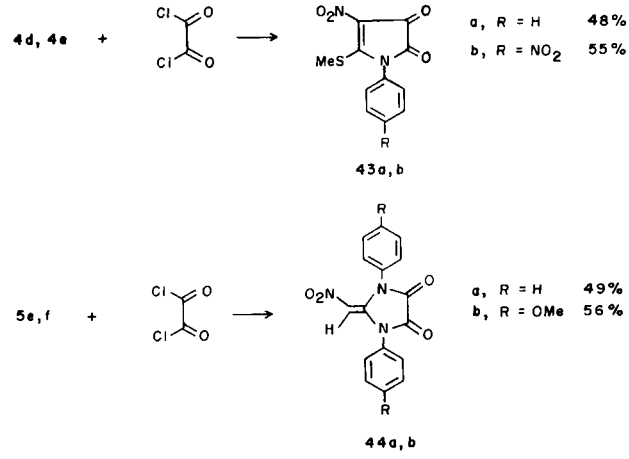
5k 37

The treatment of **5k** with acetic anhydride followed by cyclization with polyphosphoric acid results in the formation of 3-nitromethyl-5-methyltriazole (**39**). A mixture of **5k** and formic acid under refluxing conditions also gives the triazole derivative **40**. Reaction of **5k** with carbon disulfide in the presence of potassium hydroxide followed by methylation with methyl iodide affords the *N*-bis(methylthio)methylene derivative **41** which is converted into the triazole compound **42** by treatment with perchlorate [140].



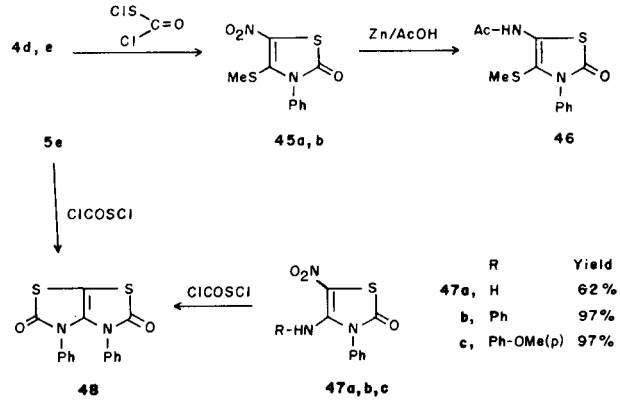
40 41 42

Compound **4d** or **4e** reacts with oxalyl chloride in benzene at 50-60° to form 3-nitro-2-methylthio-1-phenylpyrrol-4,5-diones **43a,b** in 48% and 55% yields, respectively. However, reaction of **5e** or **5f** with oxalyl chloride gives 2-nitromethyleneimidazole-4,5-diones **44a,b** in 49% and 56% yields respectively [140].



43a,b 44a,b

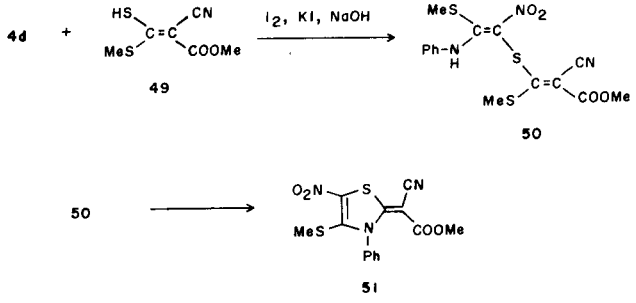
Reaction of **4d** or **4e** with chlorothioformylchloride gives 5-nitro-4-methylthio-3-phenylthiazol-2-ones **45a,b** in 83% and 80% yields respectively which are reduced with zinc dust in acetic acid to give the corresponding 5-amino derivatives. Subsequent acetylation with acetic acid yields 5-acetylaminothiazol-2-one (**46**). The methylthio group of **45** is highly reactive with nucleophilic reagents such as amines. Compound **45a** reacts with amines in dimethylformamide and ethanol under reflux to give the corresponding replacement products **47a,b,c** in good yield [140]. Compound **5e** reacts with chlorothioformylchloride to yield 2,3,4,5-tetrahydro-3,4-diphenylthiazolo[4,5-*d*]thiazole-2,5-dione which can also be prepared in like manner starting with **5e** [140].



	R	Yield
47a,	H	62%
b,	Ph	97%
c,	Ph-OMe(p)	97%

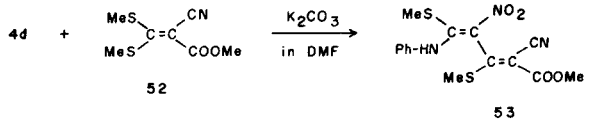
48 47a,b,c

We have shown that the reaction of **4d** with the mercapto derivative **49** in the presence of iodine, potassium iodide and sodium hydroxide in methanol produces the ketene dithioacetal derivative (**50**) which on refluxing in methanol gives the corresponding thiazole derivative **51** [136].



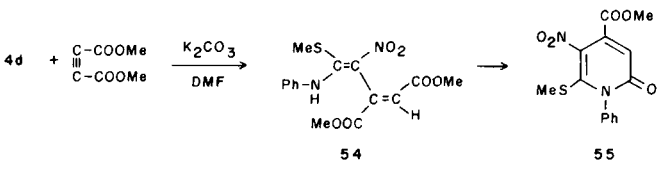
49 50 51

Compound **4d** also reacts with ketene dithioacetal **52** to give **53** in 40% yield [136].

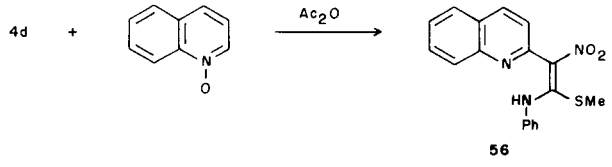


52 53

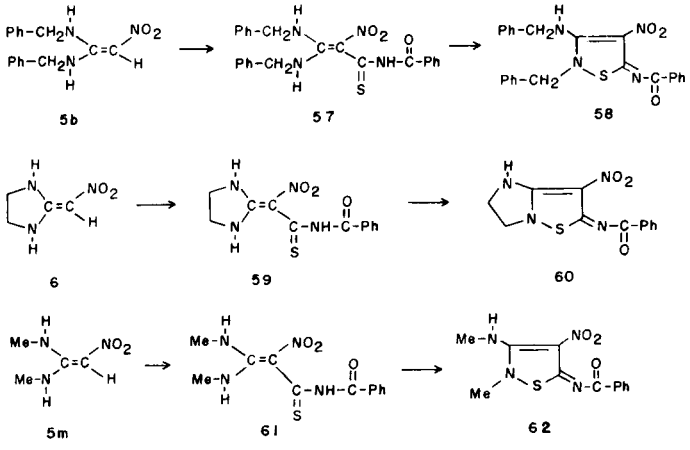
Michael reaction of **4d** with dimethyl acetylenedicarboxylate gives the corresponding addition reaction product (**54**) which is treated with hydrochoric acid solution in methanol to yield the 2-pyridone derivative **55** [136].



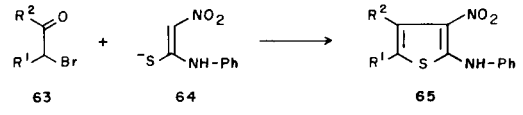
Reaction of **4d** with quinoline *N*-oxide in the presence of acetic anhydride gives **56** [136]. This reaction can not be run without an acylating reagent.



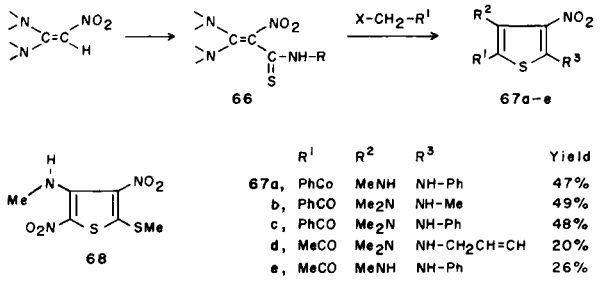
It is well known that enamines react with carbon disulfide or isothiocyanate compounds to give the corresponding vinyl dithiocarboxylic acids or vinyl thioamide derivatives [143]. Condensation of nitro ketene aminals with isothiocyanates followed by N-S bond formation using bromine leads to the isothiazole derivatives **58**, **60**, **61** [149].



Schäfer and Gewald have shown that the sodium salt of 1-anilino-1-mercapto-2-nitroethylene (**64**) reacts with α-haloketones to form 2-anilino-3-nitrothiophenes **65** [150].

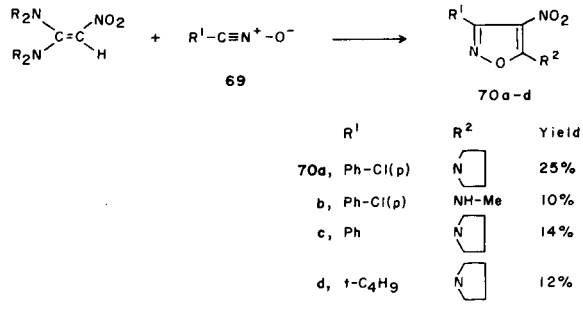


Similarly, nitro ketene aminals are first treated with aliphatic or aromatic isothiocyanates to form the adducts **66**. Reaction of **66** with α-haloketone then leads to the 5-acetyl-3-nitrothiophenes **67a-e** [151]. Reaction of the nitro ketene aminal **5m** with isothiocyanate adducts of bromonitro methane has given the 2,4-dinitrothiophene **68** in moderate yield.



	R^1	R^2	R^3	Yield
67a,	PhCo	MeNH	NH-Ph	47%
b,	PhCO	Me_2N	NH-Me	49%
c,	PhCO	Me_2N	NH-Ph	48%
d,	MeCO	Me_2N	$NH-CH_2CH=CH$	20%
e,	MeCO	MeNH	NH-Ph	26%

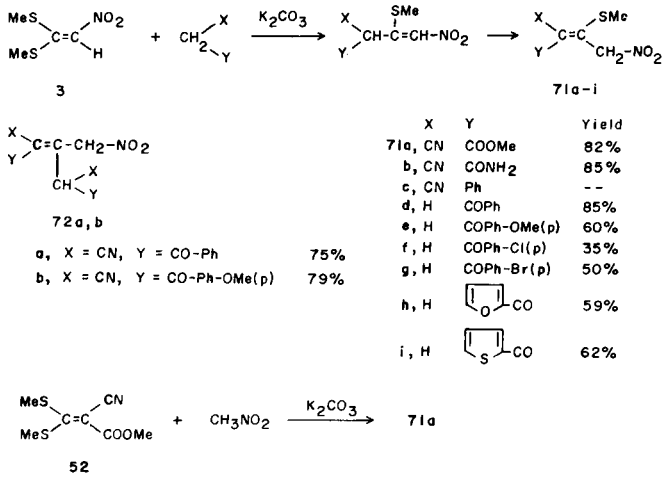
In an interesting sequence of reactions, Rajjapa and coworkers have prepared 5-amino-4-nitroisoxazole derivatives **70a-d** by a 1,3-dipolar cycloaddition reaction [152].



	R^1	R^2	Yield
70a,	Ph-Cl(p)	N	25%
b,	Ph-Cl(p)	NH-Me	10%
c,	Ph	N	14%
d,	t-C_4H_9	N	12%

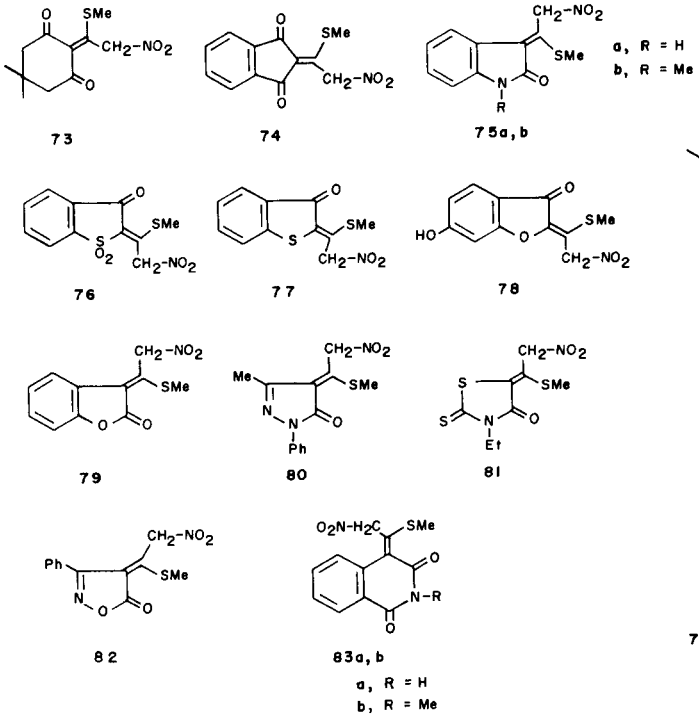
4) Reactin of **3** with Active Methylene Compounds.

Compound **3** also react with active methylene compounds to give the corresponding replacement products in good yield [153]. Generally, this reaction is carried out using potassium carbonate as a base.

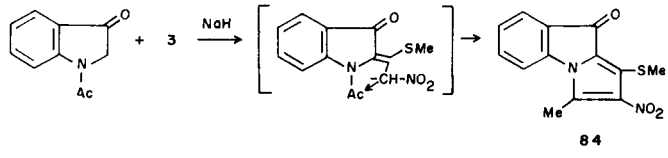


	X	Y	Yield
71a,	CN	COOMe	82%
b,	CN	$CONH_2$	85%
c,	CN	Ph	--
d,	H	COPh	85%
e,	H	COPh-OMe(p)	60%
f,	H	COPh-Cl(p)	35%
g,	H	COPh-Br(p)	50%
h,	H		59%
i,	H		62%

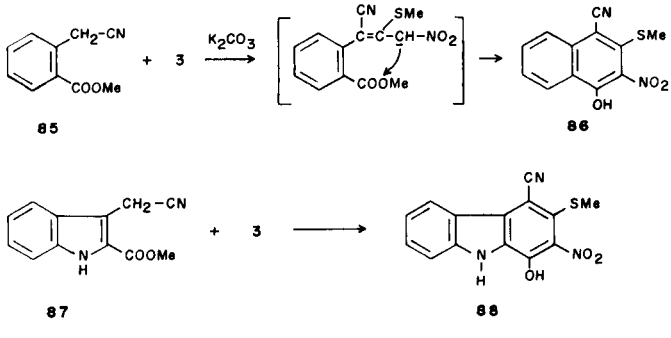
Compound **71a** is also obtained by the reaction of nitromethane with ketene dithioacetal **52** [153]. This reaction is carried out in the presence of potassium carbonate at room temperature and is superior to the reaction of **3** with methyl cyanoacetate. Similarly, cyclic ketones (dimedon and 1,3-indadione) are reacted with **3** to yield the corresponding nitroethylidene compounds **73** and **74** [128, 99]. The reaction has been applied to prepared various heterocyclic ethylidene derivatives **75-83** [153, 95].



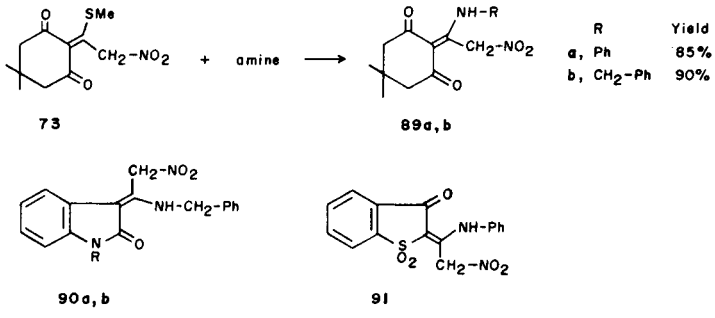
Further, 1-acetylindoxyl is allowed to react with **3** in the presence of sodium hydride in tetrahydrofuran to give the pyrrolo[1,2-*a*]indol-9-one derivative **84** [156].



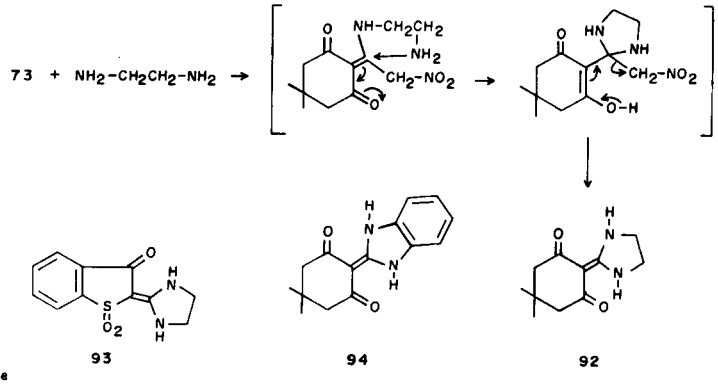
Reaction of methyl 2-cyanomethylbenzoate (**85**) with **3** in the presence of potassium carbonate gives the polyfunctionalized naphthalene **86** [156]. Similarly, the carbazole derivative **88** is obtained from methyl 3-cyanomethylindole-3-carboxylate (**87**) [82].



The methylthio group of the displacement product **73** shows reactivity with nucleophilic reagents such as amines. A few examples the reaction of **73**, **75a**, **b**, or **76** with an amine (benzylamine or aniline) to give the corresponding (α-amino)nitroethylidene compounds **90a**,**b**,**91** in good yield have also been shown below.

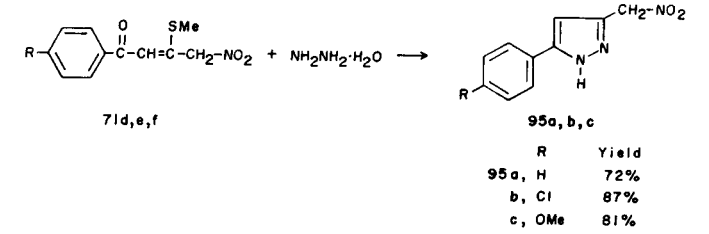


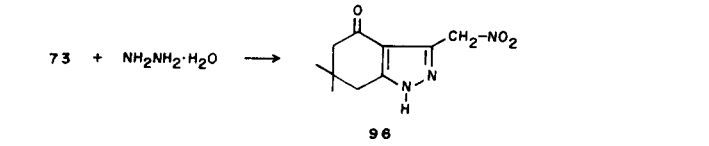
Ethylenediamine reacts with **73** or **76** to yield imidazolidene derivatives **92**, **93** [153]. Compound **73** reacts with *o*-phenylenediamine to give the benzimidazole derivative **94** [153].

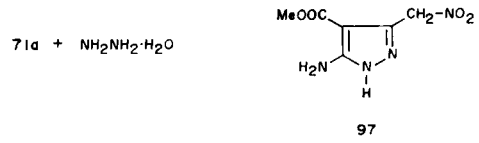


Mono-replacement products which are prepared by the reaction of **3** with active methylene compounds having a carbonyl group are masked 1,3-dicarbonyl compounds containing a thioether and a carbonyl group. It is well-known that 1,3-dicarbonyl compounds are very useful for the synthesis of heterocyclic compounds such as pyrazole or pyrimidine.

Reaction of **71d**, **e**, or **f** with hydrazine hydrate gives 3-nitromethylpyrazole derivatives **95a**,**b**,**c** in good yields [157]. Similarly, fused pyrazole **96** is prepared from **73** and hydrazine hydrate [99]. Schäfer has reported the synthesis of **97** from **71a** and hydrazine hydrate [158].

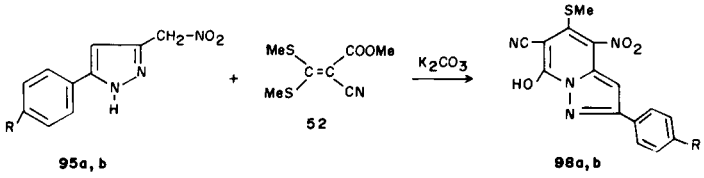






97

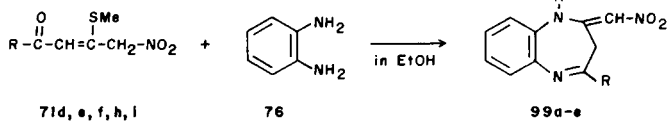
These nitromethylpyrazole derivatives have been shown to be useful in the synthesis pyrazolo[1,5-*a*]pyridine derivatives **98a,b** by the reaction of **95a** and **b** with ketene dithioacetal, **52** [157].



95a, b 52 98a, b

a, R = H, 91%
b, R = Cl, 87%

A variety of 1,3-dicarbonyl compounds react with *o*-phenylenediamines to give 2,3-dihydro-1*H*benzo[1,5]-diazepines which have varied biological activity. Reaction of **71d,e,f,h,** and **i** with *o*-phenylenediamine to give benzo[1,5]diazepine derivatives **99a,b,c,d,e** in good yields has also been reported [157].

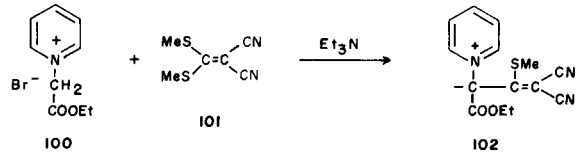


71d, e, f, h, i 76 99a-e

	R	Yield
99a,	Ph	95%
b,	Ph-OM(p)	78%
c,	Ph-Cl(p)	82%
d,		69%
e,		50%

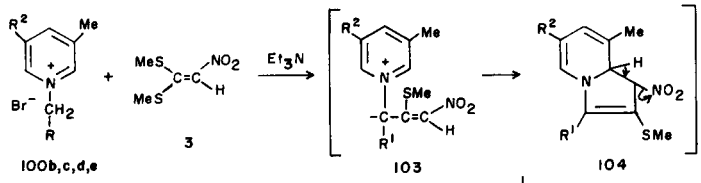
5) Reaction of **3** with *N*-Ylides or *N*-Imines.

We have recently reported the synthesis of indolizine derivatives of pyridinium *N*-ylides **100** with ketene dithioacetals [104-118]. Nitro ketene dithioacetal **3** has shown great utility in the synthesis of indolizine derivatives. Generally, pyridinium *N*-ylides react with ketene dithioacetals as 2-cyano-2,2-bis(methylthio)acrylonitrile to produce the stable pyridinium *N*-allylide **102** in good yields.



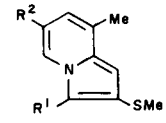
100 101 102

Although **102** appears to be stable, the same report discloses the instability (in refluxing ethanol) of the closely related *N*-allylide **103**, derived from **100** and **3**, with respect to their dihydroindolizine valence isomers **104**. Heterocycles **103** are not insoluble, however, since they undergo rapid denitration to provide indolizines **105a-d** *via* the 1,5-dipolar cyclization reaction in moderate yields [110]. Similarly, isoquiniline *N*-ylides (**106**) furnish pyrazolo[1,5-*a*]isoquinolines **107a,b,c**.

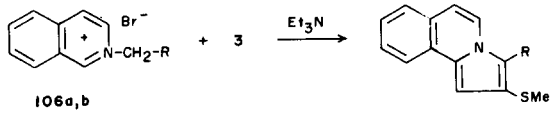


100b,c,d,e 3 103 104

	R1	R2	Yield
105a,	COPh	H	52%
b,	COOEt	H	82%
c,	COPh	Me	62%
d,	COOEt	Me	84%



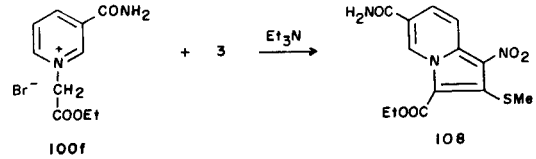
105a-d



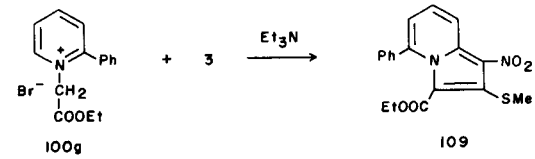
106a,b 107a,b,c

	R	Yield
107a,	COOEt	53%
b,	COOMe	16%
c,	COPh	22%

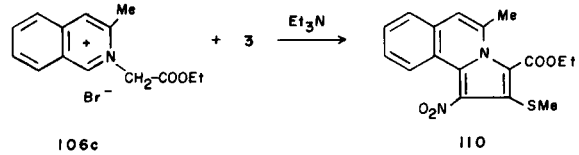
When the 3-carbamoylpyridinium salt **100f** is allowed to react with **3** in the presence of triethylamine in ethanol, the 1-nitro-6-carbamoylindolizine derivative (**108**) is obtained in 75% yield. Similarly, reaction of the 2-phenylpyridinium salt (**100g**) gives 1-nitro-5-phenylindolizine **109** in 27% yield. 1-Nitro-5-methylpyrrolo[1,5-*a*]isoquinoline **110** is prepared by the reaction of **106c** with **3** [156].



100f 108

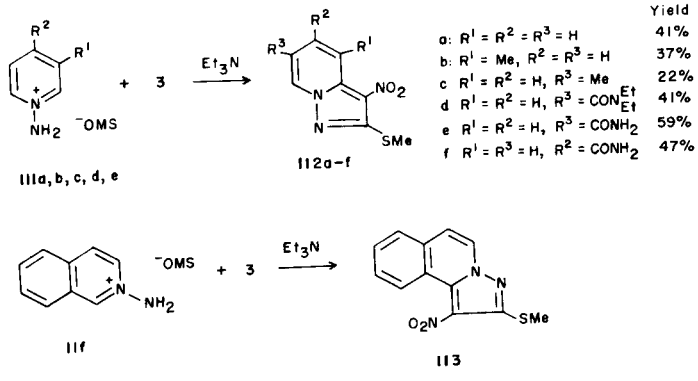


100g 109



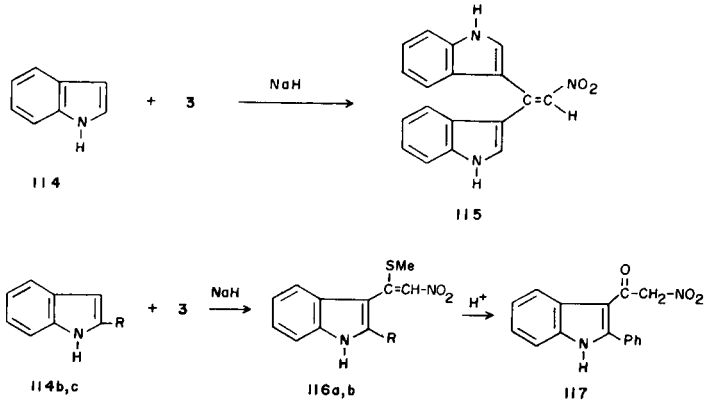
106c 110

Reaction of **3** with pyridinium *N*-imines **11a,b,c,d,e** in a 1,5-dipolar cyclization gives 2-methylthio-3-nitropyrazolo-[1,5-*a*]pyridines **112a-f** [130]. 1-Nitro-2-methylthiopyrazolo[5,1-*a*]isoquinoline **113** is synthesized by reaction of **3** with isoquinolinium *N*-imine **111f** [130].

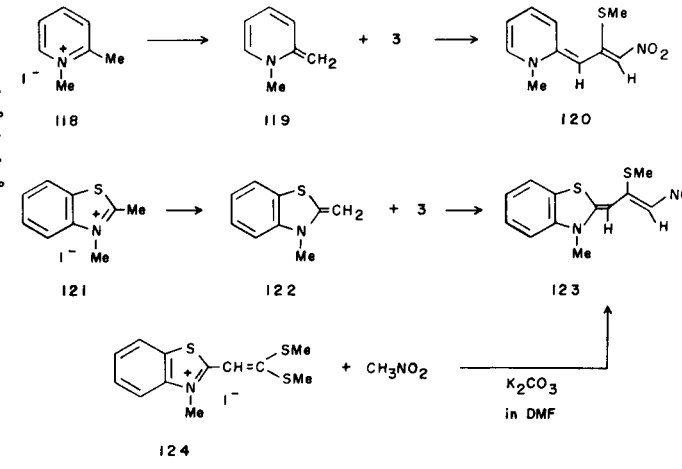


6) Reaction of **3** with Enamines and Imines.

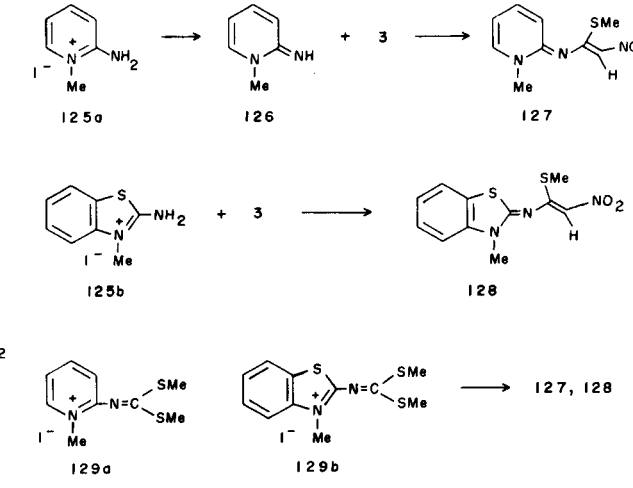
Despite numerous reports on the reaction of ketene dithioacetals with various nucleophilic reagents only a few examples of the reaction of ketene dithioacetal with enamines have been reported. We have reported the reaction of indole derivatives as aromatic enamines with **3**. Unsubstituted indole **114** reacts with **3** in the presence of sodium hydride in tetrahydrofuran to give the di(indol-3-yl)ethylene derivative **115** [153]. Reaction of 2-substituted indoles with **3** under the same conditions gives 3-(2-nitroethenyl)-indole derivatives **115a,b** which are easily converted to 3-nitroacyl compounds under acidic conditions.



A methylene base formed from 2-picoline methiodide (**118**), 1-methyl-2-methylene-1,2-dihydropyridine (**119**), exhibits a number of reactions characteristic of enamines. Reaction of **118** with **3** affords the corresponding 2-(nitroprop-2-enylidene)-1,2-dihydropyridine **120** in good yield. Similarly the 2-(nitroprop-2-enylidene)-3-methyl-2,3-dihydrobenzothiazole **123** is prepared from the corresponding 3-methyl-2-methylene-2,3-dihydrobenzothiazole (**122**) and **3** under the same conditions [156]. Compound **123** is obtained by the reaction of 3-methyl-2-[2-bis(methylthio)ethenyl]benzothiazolinium iodide (**124**) with nitromethane in the presence of potassium carbonate in dimethylformamide [156].



The heterocyclic imine 1-methyl-2-imino-1,2-dihydropyridine (**126**) derived from 2-amino-1-methylpyridinium iodide (**125a**) reacts with **3** to yield the 2-(*N*-nitroethenyl)-imino-1-methyl-1,2-dihydropyridine **127** which can also be prepared by the reaction of *N*-bis(methylthio)methyleneamino-1-methylpyridinium iodide (**129a**) with nitromethane. In the case of 2-amino-3-methylbenzothiazolium iodide (**125b**), the result is similar.

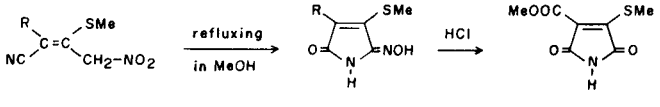


7) Treatment of Mono Substituted Products of **3** with Various Acids.

It is commonly known that nitro compounds are quite reactive. Primary or secondary aliphatic nitro compounds can by hydrolyzed, respectively, to aldehydes or ketones by treatment of their salts with sulfuric acid. This is called the Nef reaction [160-164]. When primary nitro compounds are treated with sulfuric acid without previous conversion to the salt form, they give carboxylic acids.

Hydroxamic acids are intermediates and can be isolated. Therefore this is also a method for their preparation. Both the Nef reaction and the hydroxamic acid process involve the aci form. The difference in products arises from higher acidity.

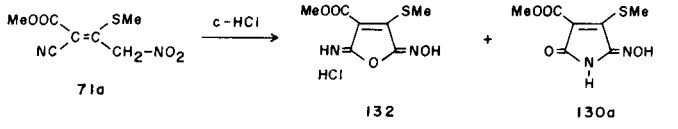
The products **71**, derived from **3** have a nitromethyl group and are useful for the synthesis of heterocyclic compounds. Compounds **71a,b**, and **c** are refluxed in methanol to give the corresponding maleimide derivatives **130a,b,c** in good yield [165]. These structures are confirmed by alkylation, hydrolysis and catalytic reduction. Hydrolysis of **130a** with hydrochloric acid solution in refluxing methylcellosolve gives 3-methylthio-4-methoxycarbonylmaleinimide (**131**) in 40% yield.



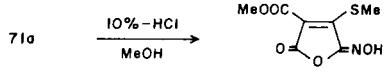
71a, b, c — 130a,b,c — 131

	Yield
a, COOMe	85%
b, $CONH_2$	50%
c, Ph	51%

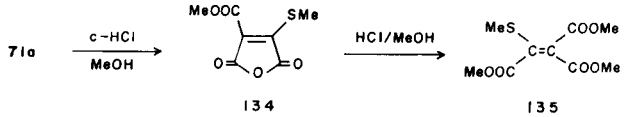
Treatment of **71a** with concentrated hydrochloric acid at 70° gives **130a** and 2-hydroxyimino-5-imino-4-methoxycarbonyl-3-methylthio-2,5-dihydrofuran hydrochloride (**132**) which is refluxed in methanol to yield **130a**. When **71a** is refluxed in a mixture of methanol and 10% hydrochloric acid solution, two products, **130a** and 2-hydroxyimino-4-methoxycarbonyl-3-methylthio-2,5-dihydrofuran-5-one (**133**), are formed. The latter is readily converted to the maleic anhydride derivative **134** by hydrolysis with concentrated hydrochloric acid in dioxane. Compound **134** is directly prepared from **71a** treatment with concentrated hydrochloric acid in dioxane. The ring opened product, trimethoxycarbonyl-1-methylthioethylene (**135**), is obtained by the introduction of hydrogen chloride gas in methanol. Hydrolysis of **71a** with sulfuric acid at 0° yields the butenolide derivative **136**, which is easily converted to cyanobutenolide (**137**) by treatment with phosphorus oxychloride.



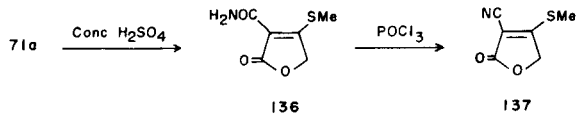
71a — 132 — 130a



71a — 133 — 130a

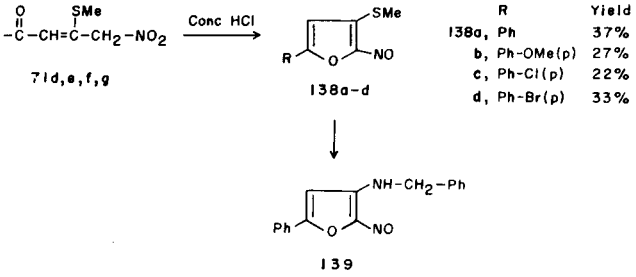


71a — 134 — 135



71a — 136 — 137

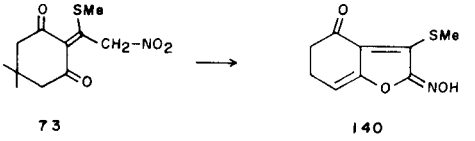
Treatment of **71d,e,f**, and **g** with concentrated hydrochloric acid at room temperature yields the 2-nitrosofuran derivatives **138a,b,c,d** [157]. Similar fused furan derivatives **140** and **141** are synthesized from the corresponding nitro ethylidene compounds. The methylthio group in **138a** and **141** can be replaced with amines to give the amino derivatives **139**, **142a**, and **b** [156].



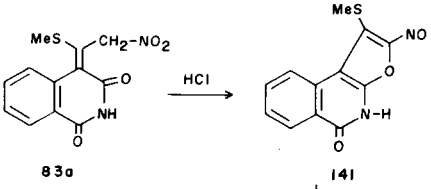
71d,e,f,g — 138a-d

R	Yield
138a, Ph	37%
b, Ph-OMe(p)	27%
c, Ph-Cl(p)	22%
d, Ph-Br(p)	33%

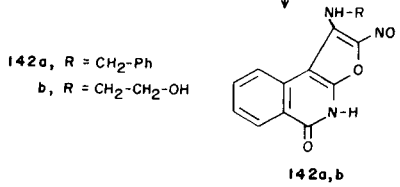
139



73 — 140



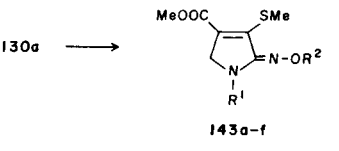
83a — 141



142a, R = CH_2-Ph
b, R = CH_2-CH_2-OH

142a,b

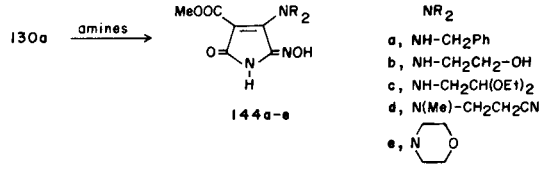
The products that are prepared by treatment with acids have an active methylthio group which can be displaced with nucleophiles such as amines or active methylene compounds. Compound **131a** is protected with various alkyl reagents because of its poor solubility in solvents such as methanol or benzene [165].



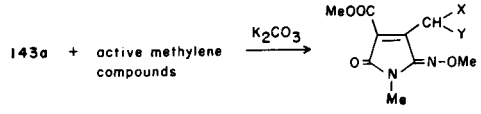
130a — 143a-f

	R^1	R^2	Yield
a,	Me	Me	70%
b,	Ts	H	20%
c,	Ms	H	20%
d,	CH_2-Ph	H	25%
e,	CH_2-Ph	CH_2-Ph	30%
f,	CH_2COOEt	H	72%

Nucleophilic substitution of the 4-methylthio group in **130a** with the appropriate amines gives the desired compounds **144a-e** in good yields [165].

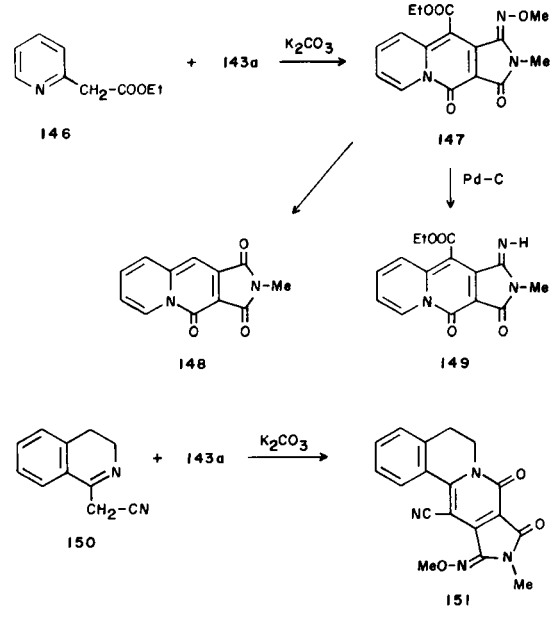


Compounds **145a,b**, and **c** are efficiently synthesized by the reaction of **143a** with active methylene compouds [165].

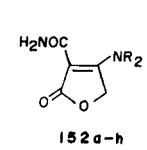


	Yield
a, X = Y = CN	80%
b, X = CN, Y = COOMe	70%
c, X = COMe, Y = COOEt	80%

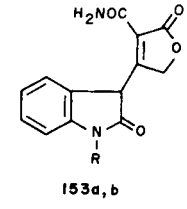
Ethyl 2-pyridylacetate (**146**) is reacted with **143a** in the presence of potassium carbonate at 100° in DMF to give pyrrolo[3,4-*b*]quinolizin-4-one **147** which is hydrolysized with hydrochloric acid to yield **148**. Reaction of **147** with palladium on carbon results in N-O bond cleavage to afford the imine derivative (**149**). A similar reaction is demonstrated where 1-cyanomethyl-3,4-dihydroisoquinoline (**150**) is reacted with **143a** to yield **151** in 85% yield [165].



It has been shown that the butenolide **136** reacts with an amine to give the corresponding replacement products **152a-h** in good yield. In the same report, the reaction of **136** with oxindole as an active methylene compound is shown to give the corresponding products **153a,b** [167].

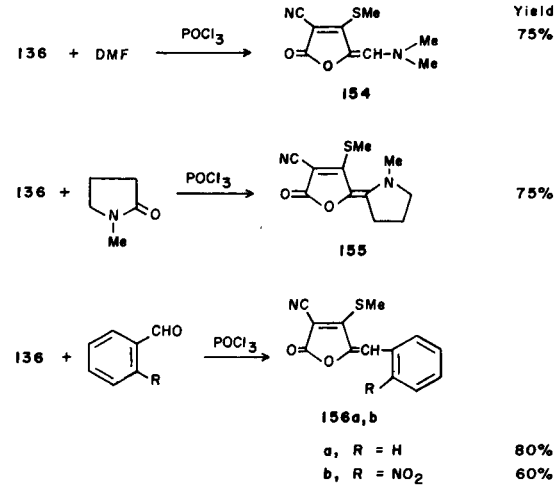


	NR2	Yield
152a,	NH-Ph	65%
b,	NH-CH2Ph	75%
c,	NH-CH2CH2-OH	70%
d,	NH-(H)	70%
e,	NH-CH2CH(OEt)2	80%
f,	NH-NH-Ph	65%
g,	N O	60%
h,	N	65%

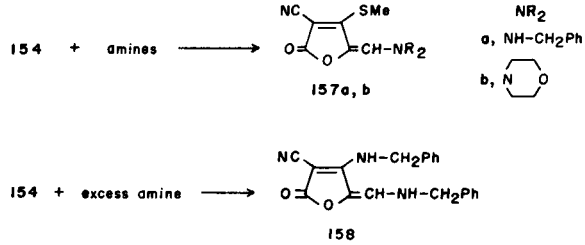


	Yield
153a, R = H	75%
b, R = Me	65%

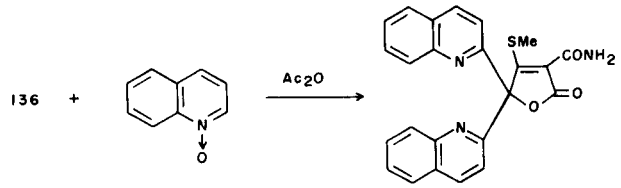
The methylene portion in butenolide **136** has shown nucleophilic character. Namely, aldehyde groups are introduced to the 5-position in the presence of phosphorus oxychloride at 100°.



The dimethylamino group of **154** is replaced with an amine to give the corresponding amino methylene derivatives **157a,b** in 30% and 70% yields, respectively. When excess amine is used, the replacement reaction of the methylthio group is carried out to give 4-amino-5-aminomethylenebutenolide **158** in 40% yield [167].



Quinoline *N*-oxide also reacts with **136** in the presence of acetic anhydride to give 5-di(quinolin-2-yl)butenolide **159** accompanied by the deoxygenation of the *N*-oxide function [167].



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REFERENCES AND NOTES

[1] J. D. Kendall and H. D. Edwards, British Patent 597,446 (1948); *Chem. Abstr.*, **42**, 4604a (1948).

[2] H. D. Edwards and J. D. Kendall, British Patent 620,800 (1949); *Chem. Abstr.*, **43**, 6650d (1949).

[3] H. D. Edwards and J. D. Kendall, U. S. Patent 2,533,233 (1950); *Chem. Abstr.*, **45**, 2804a (1951).

[4] W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2829 (1958).

[5] R. Gompper and W. Töpfl, *Chem. Ber.*, **95**, 2871 (1962).

[6] R. Gompper and W. Töpfl, *Chem. Ber.*, **95**, 2881 (1962).

[7] A. Thuillier and J. Vialle, *Bull. Soc. Chim. France*, 2187 (1962).

[8] A. Thuillier and J. Vialle, *Bull. Soc. Chim. France*, 2194 (1962).

[9] P. Rioult and J. Vialle, *Bull. Soc. Chim, France*, 3312 (1965).

[10] M. Saquet and A. Thuiller, *Bull. Soc. Chim. France*, 1582 (1966).

[11] A. Dornow and K. Dehmer, *Chem. Ber.*, **100**, 2577 (1967).

[12] P. Papini, G. Auzzi and M. Bambagiottl, *Gazz. Chim. Ital.*, **98**, 245 (1968).

[13]H. Graboyes, G. E. Jaffe, I. J. Pachter, J. P. Rosenbloom, A. J. Villani, J. W. Wilson, and J. Weinstoch, *J. Med. Chem.*, **11**, 568 (1968).

[14] R. Neidlein and H. Reuter, *Arch Pharm.*, **305**, 731 (1972).

[15] K. Hartke and S. Radau, *Ann. Chem.*, 2110 (1974).

[16] I. Shahak and Y. Sasson, *Tetrahedron Letters*, 4207 (1973).

[17] K. Peseke, *Pharmazie*, **30**, 258 (1975).

[18] R. R. Rastogi, H. Ila, and H. Junjappa, *J. Chem. Soc., Chem. Commun.*, 645 (1975).

[19] S. M. S. Chauhan and H. Junjappa, *Synthesis*, 798 (1975).

[20] M. Augustin and W. Dölling, *Z. Chem.*, **16**, 398 (1976).

[21] A. Kumar, H. Ila and H. Junjappa, *Synthesis*, 324 (1976).

[22] S. M. S. Chauhan and H. Junjappa, *Tetrahedron*, **32**, 1779 (1976).

[23] J. French, K. Peseke, and H. Kristen, *Pharmazie*, **31**, 851 (1976).

[24] P. Bocion, W. DeSilva, and P. Winternitz, German Patent 2,512,564 (1976); *Chem. Abstr.*, **84**, 59434g (1976).

[25] S. M. S. Chauhan and H. Junjappa, *Tetrahedron*, **32**, 1911 (1976).

[26] M. Watanabe, M. Minohara, K. Masuda, T. Kinoshita, and S. Furukawa, *Heterocycles*, **4**, 1875 (1976).

[27] A. Kumar, H. Ila, and H. Junjappa, *J. Chem. Soc., Chem. Commun.*, 592 (1976).

[28] A. Kumar, H. Ila, and H. Junjappa, *J. Chem. Soc., Chem. Commun.*, 593 (1976).

[29] S. M. S. Chauhan and H. Junjappa, *Synthesis*, 798 (1975).

[30] E. J. Corey, M. Shibasaki, J. Knolle, and T. Sugahara, *Tetrahedron Letters*, 785 (1977).

[31]M. Augustin, R. Schmidt and W. D. Rudorf, *Z. Chem.*, **17**, 289 (1977).

[32] M. Watanabe, K. Matsuno, T. Kinoshita and S. Furukawa, *Heterocycles*, **6**, 1781 (1977).

[33] W. D. Rudorf and M. Augustin, *J. Prakt, Chem.*, **319**, 545 (1977).

[34] A. Percival and P. N. Judson, German Patent 2,720,442 (1977); *Chem. Abstr.*, **88**, P136651n (1978).

[35] L. K. Gibhons, U. S. Patent 4,075,001 (1977); *Chem. Abstr.*, **88**, P170,135g (1978).

[36] W. D. Rudorf and M. Augustin, *J. Prakt. Chem.*, **320**, 576 (1978).

[37] R. R. Rastogi, A. Kumar, H. Ila and H. Junjappa, *J. Chem. Soc., Perkin Trans I*, 554 (1978).

[38] W. D. Rudorf and M. Augustin, *J. Prakt. Chem.*, **320**, 585 (1978).

[39] P. Bocion, W. DeSilva and P. Winternitz, Swiss Patent 601,984 (1978); *Chem. Abstr.*, **84**, 59434g (1978).

[40] A. Kumar, H. Ila and H. Junjappa, *J. Chem. Soc., Perkin Trans I*, 857 (1978).

[41] R. R. Rastogi, A. Kumar, H. Ila and H. Junjappa, *J. Chem. Soc., Perkin Trans I*, 549 (1978).

[42] A. Kakehi, S. Ito, T. Maeda, R. Takeda, M. Nishimura, M. Tamashima and T. Yamaguchi, *J. Org. Chem.*, **43**, 4837 (1978).

[43] W. D. Rudorf, *Tetrahedron*, **34**, 725 (1978).

[44] V. J. Ram and H. Pandeny, *Arch Pharm.* (Weinheim), **312**, 703 (1979).

[45] F. Eiden and F. Meinel, *Arch. Pharm.* (Weinheim), **312**, 302 (1979).

[46] J. P. Marino and J. L. Kostusyk, *Tetrahedron Letters*, 2489 (1979).

[47] J. P. Marino and J. L. Kostusyk, *Tetrahedron Letters*, 2493 (1979).

[48] M. Augustin, C. Groth, H. Kristen, K. Peseke and C. Wiechman, *J. Prakt. Chem.*, **321**, 205 (1979).

[49] M. Augustin and C. Groth, *J. Prakt Chem.*, **321**, 215 (1979).

[50] V. J. Ram, H. N. Pandey and L. Mishra, *Arch. Pharm.* (Weinheim), **312**, 586 (1979).

[51] M. Augustin and G. Jahreis, *J. Prakt, Chem.*, **321**, 699 (1979).

[52] A. Percival and P. N. Judson, Austrian Patent 354,186 (1979); *Chem. Abstr.*, **95**, P105,846h (1979).

[53] R. Everse, *Z. Chem.*, **19**, 250 (1979).

[54] H. Bohne and R. Malcherek, *Arch. Pharm.* (Weinheim), **313**, 81 (1980).

[55] V. J. Ram and H. K. Pandey, *Arch. Pharm.* (Weinheim), **313**, 465 (1980).

[56] V. J. Ram. *Arch. Pharm.* (Weiheim), **313**, 471 (1980).

[57] A. Kumar, V. Aggarwal, H. Ila and H. Junjappa, *Synthesis*, 748,(1980).

[58] W. D. Rudorf and M. Augustin, *Synthesis*, 1022 (1980).

[59] A. Kakehi, S. Ito, K. Nakanish, K. Watanabe and M. Kitagawa, *Bull. Chem. Soc. Japan*, **53**, 1115 (1980).

[60] K. Peseke and U. Schoenhusen, East German Patent 150,894 (1981); *Chem. Abstr.*, **97**, 162831b (1982).

[61] K. T. Potts, M. J. Cipullo, P. Ralli and G. Theodoridis, *J. Am. Chem. Soc.*, **103**, 3584 (1981).

[62] S. Apparao, A. Rahman, H. Ila and H. Junjappa, *Tetrahedron Letters*, 971 (1982).

[63] K. Peseke and U. Schoenhusen, East German Patent 156,807 (1982); *Chem. Abstr.*, **98**, P89,189n (1982).

[64] K. T. Potts, M. J. Cipullo, P. Ralli and G. Theodordis, *J. Org. Chem.*, **48**, 4841 (1983).

[65] H. Kristen, S. Georges and K. Peseke, East German Patent 203,546 (1983); *Chem. Abstr.*, **100**, 156,642e (1984).

[66] S. Apparao, H. Ila and H. Junjappa, *J. Chem. Soc., Perkin Trans I*, 2837 (1983).

[67] R. K. Dieter and J. R. Fishpaugh, *J. Org. Chem.*, **48**, 4439 (1983).

[68] A. Kakehi, S. Ito and B. Wada, *Bull. Chem. Soc. Japan*, **57**, 893 (1984).

[69] R. K. Dieter, Y. J. Lin and J. W. Dieter, *J. Org. Chem.*, **49**, 3183 (1984).

[70] H. B. Cottam, C. R. Petrie, P. A. McKernan, R. J. Goebel, N. K. Dalley, R. B. Davidson, R. K. Robins and G. R. Revankar, *J. Med. Chem.*, **27** 1119 (1984).

[71] S. Apparao, A. Datta, H. Ila and H. Junjappa, *J. Chem. Soc., Perkin Trans I*, 921 (1984).

[72] R. Okazaki, Y. Negishi and N. Inamoto, *J. Org. Chem.*, **49**, 3819 (1984).

[73] G. Kobayashi, S. Furukawa and Y. Matsuda, *Yakugaku Zasshi*, **86**, 1152 (1966).

[74] G. Kobayashi, S. Furukawa and Y. Matsuda, *Yakugaku Zasshi*, **86**, 1156 (1966).
[75] G. Kobayashi, S. Furukawa, Y. Matsuda and Y. Washida, *Chem. Pharm. Bull.*, **15**, 1871 (1967).
[76] G. Kobayashi, S. Furukawa, Y. Matsuda, S. Nakamura and R. Natsuki, *Yakugaku Zasshi*, **87**, 1044 (1967).
[77] G. Kobayashi, S. Furukawa, Y. Matsuda and Y. Washida, *Yakugaku Zasshi*, **87**, 857 (1967).
[78] G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki and S. Matsunaga, *Yakugaku Zasshi*, **90**, 127 (1970).
[79] G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki and S. Matsunaga, *Chem. Pharm. Bull.*, **18**, 124 (1970).
[80] G. Kobayashi, Y. Matsuda, R. Natsuki and M. Sone, *Chem. Pharm. Bull.*, **20**, 657 (1972).
[81] G. Kobayashi, Y. Matsuda and R. Natsuki, *Chem. Pharm. Bull.*, **21**, 921 (1973).
[82] G. Kobayashi, Y. Matsuda, R. Natsuki and Y. Tominaga, *Yakugaku Zasshi*, **92**, 713 (1972).
[83] G. Kobayashi, Y. Matsuda, R. Matsuki and Y. Tominaga, *Yakugaku Zasshi*, **92**, 1468 (1972).
[84] Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **21**, 1658 (1973).
[85] Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **93**, 1520 (1973).
[86] G. Kobayashi, Y. Tominaga, S. Kisaki, M. Sone and S. Ueno, *Chem. Pharm. Bull.*, **21**, 2344 (1973).
[87] G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga and C. Maseda, *Yakugaku Zasshi*, **94**, 44 (1974).
[88] G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, C. Maseda and H. Awaya, *Yakugaku Zasshi*, **94**, 50 (1974).
[89] S. Ueno, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **94**, 607 (1974).
[90] K. Mizuyama, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **94**, 702 (1974).
[91] H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **22**, 1424 (1974).
[92] C. Maseda, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **94**, 839 (1974).
[93] S. Kisaki, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **22**, 2246 (1974).
[94] M. Matsuo, H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **22**, 2765 (1974).
[95] S. Ueno, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **22**, 2624 (1974).
[96] H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **95**, 13 (1975).
[97] K. Mizuyama, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **95**, 290 (1975).
[98] Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **95**, 378 (1975).
[99] T. Hatada, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **95**, 623 (1975).
[100] K. Kurata, M. Matsuo, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **23**, 1629 (1975).
[101] Y. Tominaga, K. Mizuyama, Y. Miyake, H. Fujito, Y. Matsuda and G. Kobayashi, *Heterocycles*, **3**, 793 (1975).
[102] G. Kobayashi, Y. Matsuda, Y. Tominaga, C. Maseda, H. Awaya and K. Kurata, *Chem. Pharm. Bull.*, **23**, 2759 (1975).
[103] K. Kurata, H. Awaya, C. Maseda, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **95**, 1431 (1975).
[104] H. Fujito, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Heterocycles*, **4**, 939 (1976).
[105] Y. Tominaga, M. Sone, K. Mizuyama, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **24**, 1671 (1976).
[106] K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **24**, 2270 (1976).
[107] Y. Tominaga, Y. Matsuda and G. Kobayashi, *Heterocylces*, **4**, 1493 (1976).
[108] Y. Tominaga, Y. Miyake, H. Fujito, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **97**, 927 (1977).
[109] Y. Tominaga, H. Fujito, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **25**, 1519 (1977).
[110] Y. Tominaga, Y. Miyake, H. Fujito, K. Kurata, H. Awaya, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **25**, 1528 (1977).
[111] H. Fujito, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Heterocycles*, **6**, 379 (1977).
[112] K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Heterocycles*, **8**, 293 (1977).
[113] Y. Tominaga, A. Ushirogochi, Y. Matsuda and G. Kobayashi, *Heterocycles*, **8**, 193 (1977).
[114] H. Fujito, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **97**, 1316 (1977).
[115] M. Kuya, K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **26**, 680 (1978).
[116] K. Kurata, M. Yamada, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **98**, 623 (1978).
[117] K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **98**, 631 (1978).
[118] H. Fujito, Y. Tominaga, H. Awaya, K. Kurata, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **98**, 1412 (1978).
[119] K. Kashima, S. Hidaki, Y. Tominaga, Y. Matsuda, G. Kobayashi and K. Sakemi, *Yakugaku Zasshi*, **99**, 38 (1979).
[120] Y. Tominaga, H. Okuda, Y. Mitsutomi, Y. Matsuda and G. Kobayashi, *Heterocycles*, **12**, 503 (1979).
[121] Y. Tominaga, S. Hidaki, Y. Matsuda, G. Kobayashi and K. Sakemi, *Yakugaku Zasshi*, **99**, 540 (1979).
[122] S. Hidaki, Y. Tominaga, Y. Matsuda, G. Kobayashi and K. Sakemi, *Yakugaku Zasshi*, **99**, 1234 (1979).
[123] A. Ushirogochi, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Heterocycles*, **14**, 7 (1980).
[124] Y. Tominaga, S. Hidaki, Y. Matsuda, G. Kobayashi and K. Sakemi, *Yakugaku Zasshi*, **100**, 556 (1980).
[125] K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **101**, 980 (1981).
[126] K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **101**, 991 (1981).
[127] Y. Tominaga, S. Hidaki, Y. Matsuda, G. Kobayashi and K. Sakemi, *Yakugaku Zasshi*, **104**, 134 (1984).
[128] Y. Tominaga, H. Norisue, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **104**, 127 (1984).
[129] Y. Tominaga, H. Norisue, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **32**, 2910 (1984).
[130] Y. Tominaga, S. Hidaki, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **104**, 440 (1984).
[131] Y. Tominaga, A. Ushirogochi, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **32**, 3384 (1984).
[132] Y. Tominaga, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **32**, 1665 (1984).
[133] Y. Tominaga, A. Ushirogochi, Y. Matsuda and G. Kobayashi, *Heterocycles*, **21**, 636 (1984).
[134] E. Freund, *Chem. Ber.*, **52**, 542 (1919).
[135] R. Gompper and H. Schaefer, *Chem. Ber.*, **100**, 591 (1967).
[136] M. Sone, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **97**, 262 (1977).
[137] H. Schäfer, B. Bartho and K. Gewald, *J. Prakt Chem.*, **319**, 149 (1977).
[138] H. Schäfer and K. Gewald, *Z. Chem.*, **16**, 272 (1976).
[139] H. Schäfer, K. Gewald and M. Seifert, *J. Prakt. Chem.*, **318**, 39 (1976).
[140] H. Schäfer, B. Bartho and K. Gewald, *Z. Chem.*, **13**, 294 (1973).
[141] A. Kumar. H. Ila and H. Junjappa, *J. Chem. Soc., Chem. Commun.*, 593 (1976).
[142] H. Hamberger, H. Reinshagen, G. Schulz and G. Sigmund, *Tetrahedron Letters*, 3619 (1977).
[143] A. G. Cook, ed, "Enamines: Synthesis, Structure, and

Reactions'', Marcel Dekker Inc., New York, 1969.

[144] G. Kobayashi, Y. Matsuda, R. Natsuki and Y. Tominaga, *Yakugaku Zasshi*, **90**, 1251 (1970).

[145] Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **21**, 2770 (1973).

[146] G. Kobayashi, Y. Matsuda, Y. Tominaga and K. Mizuyama, *Chem. Pharm. Bull.*, **23**, 2749 (1975).

[147] H. Okuda, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **99**, 989 (1979).

[148] Y. Tominaga, H. Okuda, M. Tochiki, Y. Matsuda and G. Kobayashi, *Heterocycles*, **15**, 679 (1981).

[149] S. Rajappa, B. G. Advani and R. Sreenivasen, *Indian J. Chem.*, **15B**, 886 (1977).

[150] H. Schäfer and K. Gewald, *Z. Chem.*, **15**, 100 (1975).

[151] S. Rajappa and R. Sreenivasan, *Indian J. Chem.*, **15B**, 301 (1977).

[152] S. Rajappa, B. G. Advani and R. Sreenivasan, *Synthesis*, 656 (1974).

[153] G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga and M. Sone, *Yakugaku Zasshi*, **93**, 612 (1973).

[154] Y. Tominaga, Y. Morita, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **23**, 2390 (1975).

[155] Y. Tominaga, K. Kurata, H. Awaya, Y. Matsuda and G. Kobayashi, *Heterocycles*, **9**, 399 (1978).

[156] Author's unpublished results.

[157] Abstracts of the 129th Kyushu Branch Meeting of the Pharmaceutical Society of Japan, Fukuoka, Japan, p 7, 1983.

[158] H. Schäfer and K. Gewald, *J. Prakt. Chem.*, **325**, 41 (1983).

[159] K. Mizuyama, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **27**, 2879 (1979).

[160] W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

[161] P. Salomaa, in the Chemistry of the Carbonyl Group, S. Patai ed, Interscience, New York, 1966, P 177.

[162] S. F. Sun and J. T. Folliard, *Tetrahedron*, **27**, 323 (1971).

[163] T. Severin and D. König, *Chem. Ber.*, **107**, 1499 (1974).

[164] G. J. P. Becket and G. P. Ellis, *Tetrahedron Letters*, 719 (1976).

[165] M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **21**, 1667 (1973).

[166] M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **93**, 1008 (1973).

[167] M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **22**, 617 (1974).