# Recent Advances in the Chemistry of Ethoxycarbonyl Isothiocyanate and Related Compounds



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## Introduction.

Ethoxycarbonyl isothiocyanate (ECIT), the main representative of alkoxycarbonyl isothiocyanates, has proved a very useful synthetic reagent which is particularly suited for the construction of heterocyclic compounds. The chemistry of ECIT and related compounds up to 1973 was the subject of an earlier review [1]. The present paper covers mainly the literature of the period 1973-1981 (through volume 96 of Chemical Abstracts) and places emphasis on cyclization reactions. Simple, straightforward additions of nucleophilic reagents to ECIT are not reviewed, unless they possess some further point of interest.

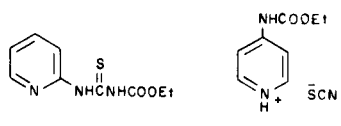
## Preparation.

Although commercially available [2], ECIT is more often than not prepared as needed from ethyl chloroformate and potassium thiocyanate following well established procedures [3,4]. The use of tetrahydrofuran as the solvent and a 3-fold excess of potassium thiocyanate affords ECIT in 65% yield [5], whereas a modification of Lamon's procedure [3] has improved the yield to 73% [6].

Phenoxycarbonyl isothiocyanate has been prepared in 60-80% yield from phenyl chloroformate and potassium thiocyanate in ethyl acetate [7].

## Acylating Activity.

Although ECIT reacts with most nucleophilic compounds at the isothiocyanate group to form products incorporating the thioamido group, in some cases a generally undesired reaction occurs at the ester carbonyl resulting in ethoxycarbonylation of the nucleophile and elimination of thiocyanic acid. Typically, whereas 2-aminopyridine reacts with ECIT to form the expected thiourea **1**, 4-aminopyridine yields instead 4-(*N*-ethoxycarbonylamino)pyridinium thiocyanate (**2**) [8].

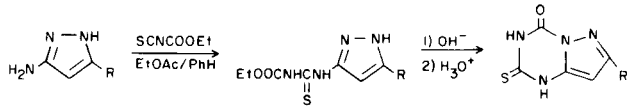


**1** **2**

To account for an analogous dual reactivity of acyl isothiocyanates, it has been proposed that greater basicity of the nucleophile and greater electrophilicity of the isothiocyanate carbonyl favor the acylation reaction [9]. However, a correlation between basicity of nucleophile and ethoxycarbonylating activity of ECIT has not been observed [4,8]. An attempt has been made to account for the dual reactivity of ECIT by making use of the concept of charge and frontier controlled interactions [10]. According to this principle, soft nucleophiles tend to attack the isothiocyanate group, whereas hard nucleophiles attack the carbonyl group of ECIT [10,11].

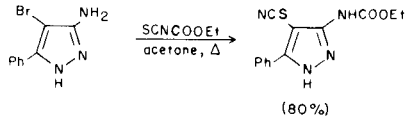
## Reactions With Aminoazoles and Other Aminoheterocycles.

Aminoazoles react with ECIT at the exocyclic amino group, or a ring nitrogen atom, or sometimes both. When the amino group is *alpha* to a ring nitrogen, the initial reaction which yields an *N*-ethoxycarbonylthiourea is often followed, either spontaneously or in a second step, by a cyclization resulting in the formation of a 1,3,5-triazine ring fused to the original azole ring. Thus, 3-aminopyrazole and 3-amino-5-phenylpyrazole react with ECIT at the exocyclic nitrogen atom and the resulting thioureas **3**, **4** are cyclized by alkali to pyrazolo[1,5-*a*]-1,3,5-triazines **5**, **6** [12,13,14]. However, the isolation of the 1,3-dithiourea

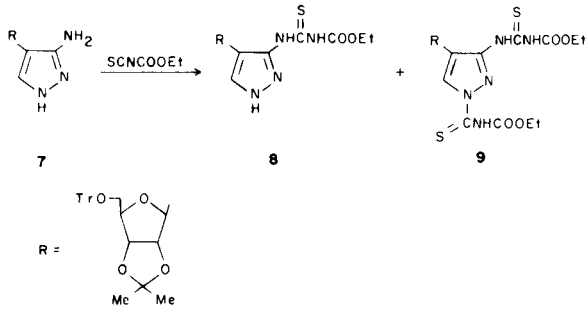


**3**, R = H (59%) **5**, R = H (96%)
**4**, R = Ph (86%) **6**, R = Ph (79%)

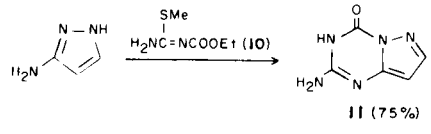
(15%) in addition to **3** from the reaction with 3-aminopyrazole shows that, even though to a smaller extent, reaction in that case also occurs at a ring nitrogen atom [12]. Formation of a thiourea involving the exocyclic amino group is also observed in the case of 5-amino-1,3-diphenylpyrazole, but for 3-amino-4-bromo-5-phenylpyrazole the reaction with ECIT results in ethoxycarbonylation of the amino group and replacement of the bromine atom by a thiocyanate group [15].



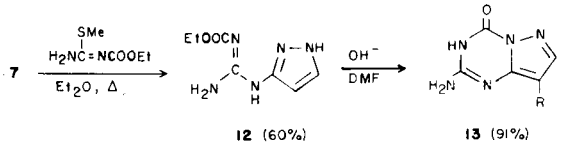

Treatment of the β-D-ribofuranosyl derivative **7** of 3-aminopyrazole with ECIT affords the thiourea at the amino group **8** as well as the 1,3-dithiourea **9**. The latter compound is easily converted into the former by boiling in




ethanol. On the other hand, 3-aminopyrazole itself reacts with *N*-ethoxycarbonyl-*S*-methylisothiourea (**10**, prepared in 86% yield by methylation of *N*-ethoxycarbonyl thiourea, which is readily available from ECIT and ethanolic ammonia) to form the pyrazolo[1,5-*a*]-1,3,5-triazine **11**. On

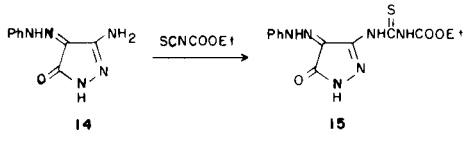



this basis, conditions have been found for the reaction of aminopyrazole **7** with isothiourea **10** to yield essentially pure monoadduct **12** (contaminated with only traces of a diadduct corresponding to **9**). Upon treatment with a base, or simply by heating in dimethylformamide, compound **12**

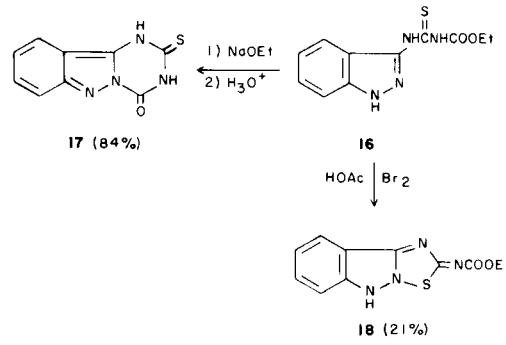



cyclizes to pyrazolotriazine *C*-nucleoside **13** [16].

The thiourea **15** obtained from 3-amino-4-phenylhydrazino-2-pyrazolone (**14**) resists cyclization by the action of

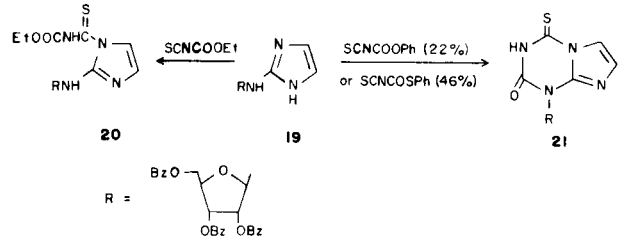



sodium ethoxide, hydrazine, phenylhydrazine, or concentrated sulfuric acid [17]. Reaction with ECIT occurs again at the exocyclic nitrogen of 3-aminoindazole, but the resulting thiourea **16** cyclizes to an 1,3,5-triazino[1,2-*b*]indazole



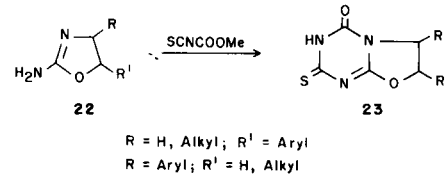

(**17**), upon treatment with base [18], and to an 1,2,4-thiadiazolo[2,3-*b*]indazole **18**, by the action of bromine or lead tetraacetate in acetic acid [19].

When treated with ethoxycarbonyl, phenoxycarbonyl, and *S*-phenylthiocarbonyl isothiocyanate, the β-D-ribofuranosyl derivative **19** of 2-aminoimidazole reacts at an imidazole ring nitrogen to yield the thiourea **20**, in the first case, but the cyclized imidazo[1,2-*a*]-1,3,5-triazine **21** in the latter two cases. Compound **20** does not cyclize into **21**

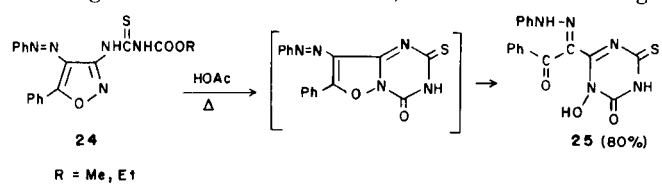



when heated in a solvent either alone, or in the presence of triethylamine [20].

The formation of oxazolo[3,2-*a*]-1,3,5-triazines **23** from 2-amino-4,5-dihydrooxazoles **22** and methoxycarbonyl isothiocyanate indicates that initial reaction occurs at the

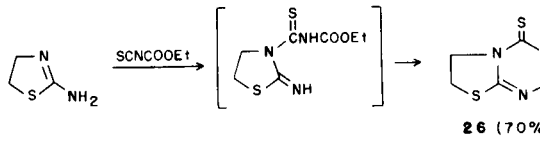



exocyclic nitrogen atom [21]. The thiourea **24** obtained from 3-amino-5-phenyl-4-phenylazoisoxazole and ECIT or methoxycarbonyl isothiocyanate does not cyclize upon heating or treatment with alkali, whereas in refluxing

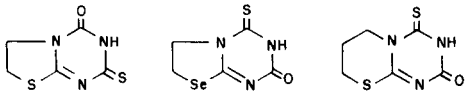



acetic acid cyclization appears to occur as anticipated, but the isoxazole ring is cleaved to yield a product assigned structure **25** [22].

In contrast to 2-aminothiazole which reacts with ECIT at both amino group and ring nitrogen atom to yield a mixture of products [23], 2-amino-2-thiazoline gives only one product. Its structure has been unequivocally established as that of thiazolo[3,2-*a*]-1,3,5-triazine **26**, which results by cyclization of the initially formed thiourea at the ring nitrogen [24], rather than that of the isomeric triazolotriazine **27**, as originally reported [25]. In an analogous manner, the reactions of ECIT with 2-amino-2-selenazoline and 2-amino-5,6-dihydro-4*H*-1,3-thiazine afford the

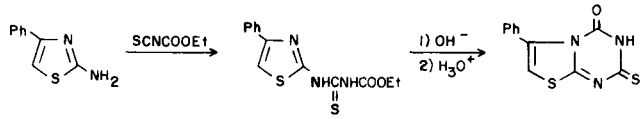



**26** (70%)



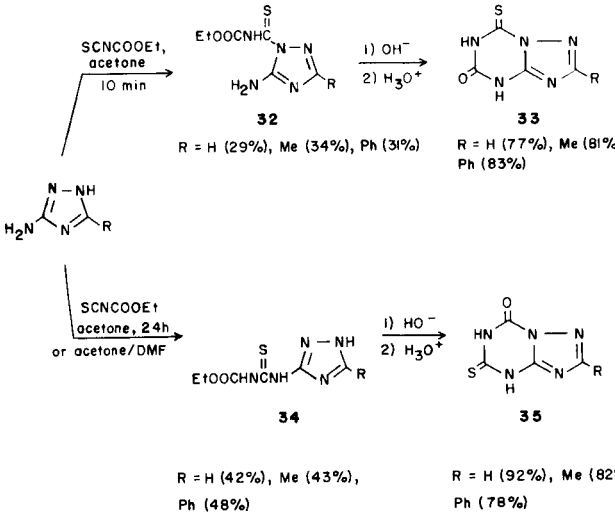
**27** **28** (83%) **29** (55%)

corresponding heterobicycles **28** and **29** [24]. In contrast, 2-amino-4-phenylthiazole reacts with ECIT at the amino group [15,26] to form a thiourea **30**, which cyclizes by the action of alkali to thiazolo[3,2-*a*]-1,3,5-triazine **31** [15].




**30** (75%) **31** (58%)

Upon brief treatment with ECIT in acetone, 3-amino-1,2,4-triazoles react at a ring nitrogen atom and the resulting thioureas **32** are cyclized by base to 1,2,4-triazolo-[1,5-*a*]-1,3,5-triazines **33**. A prolonged interaction in acetone, however, and reactions run in acetone-dimethylformamide mixtures regardless of duration, yield the thioureas



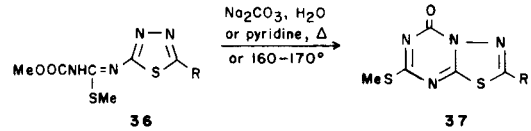

**32** R = H (29%), Me (34%), Ph (31%)

**33** R = H (77%), Me (81%), Ph (83%)

**34** R = H (42%), Me (43%), Ph (48%)

**35** R = H (92%), Me (82%) Ph (78%)

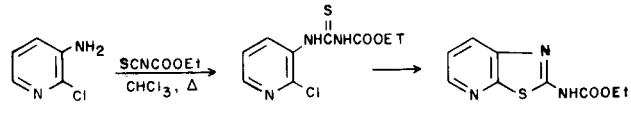
**34** at the amino group which cyclize by the action of alkali to the isomeric triazolotriazines **35** [27]. In the case of 2-amino-1,3,4-thiadiazoles, reaction with methoxycarbonyl isothiocyanate at the amino group yields thioureas, the *S*-methyl derivatives **36** which cyclize to 1,3,4-thiadiazolo-[3,2-*a*]-1,3,5-triazines **37**, possibly through the intermediacy of an imidoyl isocyanate resulting from **36** by loss of methanol [28,29].




**36** **37**

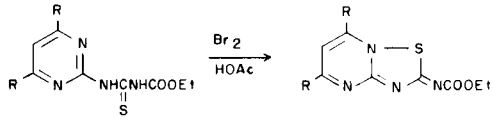
R = H, Me, Et, MeS, EtS, Ph, 2-EtOC$_6$H$_4$

In refluxing chloroform, 3-amino-2-chloropyridine reacts with ECIT to yield a thiazolo[5,4-*b*]pyridine **38**, presumably through the thiourea resulting from reaction



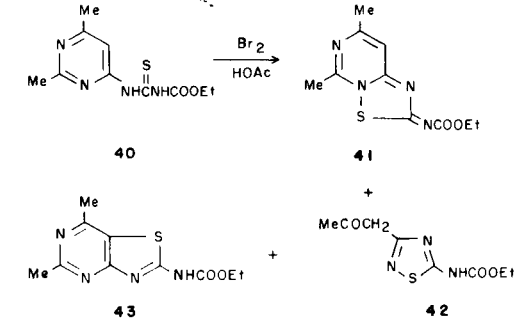

**38**

at the amino group [30]. The thiourea obtained from 2-aminopyrimidine, or 2-amino-4,6-dimethylpyrimidine undergoes oxidative cyclization upon treatment with bromine to yield a 1,2,4-thiadiazolo[2,3-*a*]pyrimidine **39** [18]. However, the reaction with bromine of the thiourea from 6-amino-2,4-dimethylpyrimidine **40** is more complex and yields a mixture of three products, **41**, **42**, **43**, of which **42**



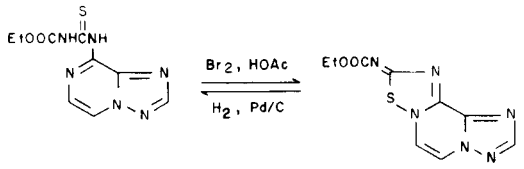

**39**

R = H (63%), Me (32%)



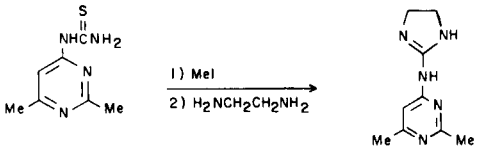

**40** **41** + **43** + **42**

results from **41** by cleavage of the pyrimidine ring. Overall, these results show that the main cyclization reaction of **40** involves a nitrogen atom [18], and not the C-5 of the pyrimidine ring as postulated earlier [31]. Reaction at the amino group of 8-amino-1,2,4-triazolo[1,5-*a*]pyrazine gives a thiourea **44**, which undergoes oxidative cyclization to the tricyclic product **45**. Hydrogenolysis reverses the



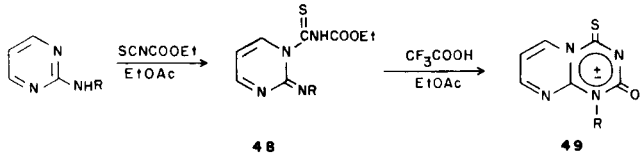

44 45 (77%)

reaction almost quantitatively [32]. Saponification of the adduct of 4-amino-2,6-dimethylpyrimidine and ECIT yields a thiourea **46**, the *S*-methyl derivative of which is converted into the 2-imidazolinyl derivative **47** by treatment with ethylenediamine [33]. In contrast to the previous reactions, that of 2-(*N*-alkylamino)pyrimidines




46 47

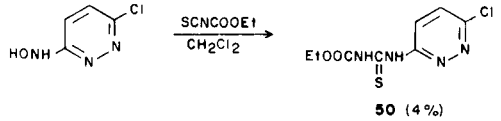
with ECIT occurs at a ring nitrogen atom and the resulting thioureas **48** cyclize to mesoionic compounds **49**




**48** R = Me (36%), Et (24%)

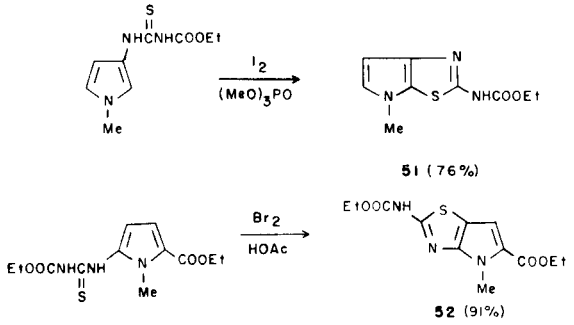
**49** R = Me (48%), Et (20%)

by the action of trifluoroacetic acid [34]. The formation in low yield of thiourea **50** together with sulfur by the reaction of 3-chloro-6-hydroxyaminopyrazine with ECIT indicates reduction of the hydroxyamino to an amino group by a redox process [34].



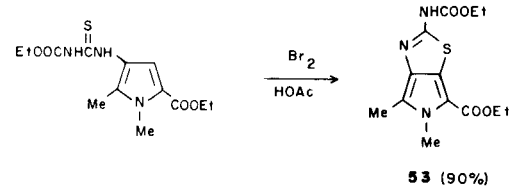

**50** (4%)

The thioureas obtained from 2- and 3-aminopyrroles and ECIT undergo oxidative cyclization to pyrrolo[3,2-*d*] **51**, [2,3-*d*] **52**, and [3,4-*d*]thiazoles **53** [35]. Analogous reactions lead to furo[2,3-*d*] **54** and thieno[3,2-*d*]thiazoles **55**



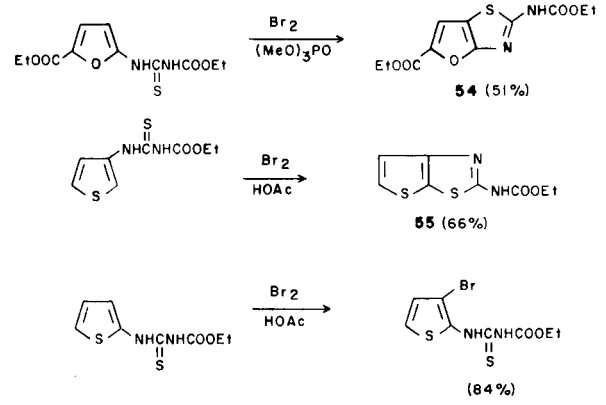

**51** (76%)

**52** (91%)




**53** (90%)

from aminofurans [36] and aminothiophenes [37], respectively, although the thiourea from 2-aminothiophene does

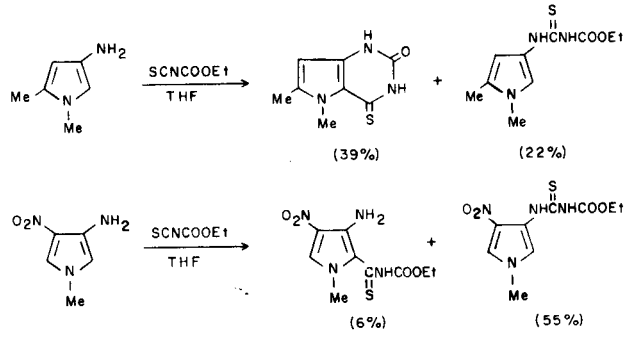



**54** (51%)

**55** (66%)

(84%)

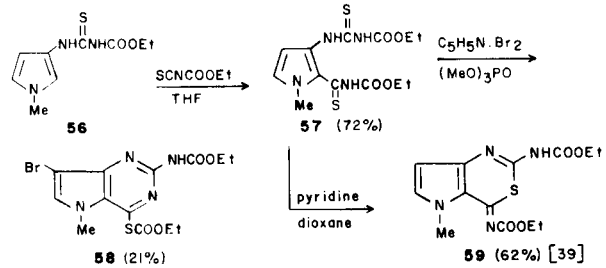
not yield a cyclic product under these conditions [37]. Whereas in 3-amino-1,5-dimethylpyrrole ring position 2 appears to be somewhat more reactive toward ECIT than the amino group [38], in 3-amino-1-methyl-4-nitropyrrole,




(39%) (22%)

(6%) (55%)

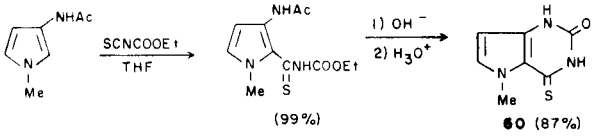
the order of reactivity is reversed [35]. The thiourea **56** obtained from 3-amino-1-methylpyrrole reacts further with ECIT at position 2 of the pyrrole ring and the resulting derivative **57** reacts with 2 equivalents of pyridinium perbromide to yield a brominated pyrrolo[3,2-*d*]pyrimidine




**56** **57** (72%)

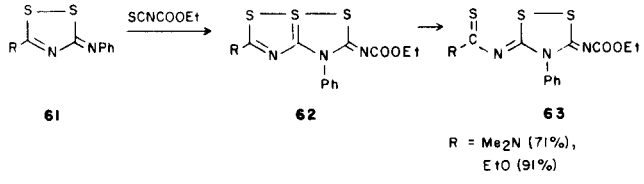
**58** (21%) **59** (62%) [39]

**58** [35]. On the other hand, treatment of diadduct **57** with pyridine causes a different cyclization resulting in a pyrrolo[3,2-*d*]-1,3-thiazine **59** [38]. An analogous sequence of reactions leads from 3-acetamido-1-methylpyrrole to a pyrrolo[3,2-*d*]pyrimidine **60** [38].

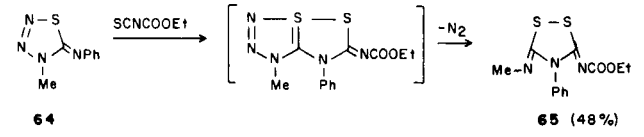



Reactions With Iminoheterocycles.

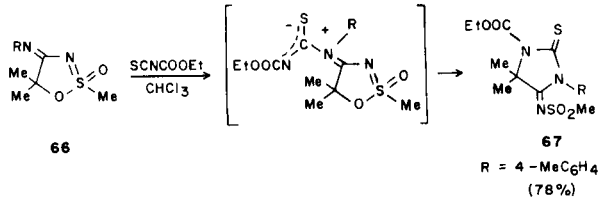
A 1,3-dipolar addition of ECIT to 3-substituted 5-phenylimino-1,2,4-thiadiazoles **61** is followed by (or proceeds simultaneously with) a bond reorganization to yield an adduct best represented by **63**, although structure **62** may be making a minor, no-bond resonance contribution [40,41]. A similar reaction of ECIT with 4-methyl-5-phenylimino-1,2,3,4-thiatriazoline (**64**) is accompanied by elimination of



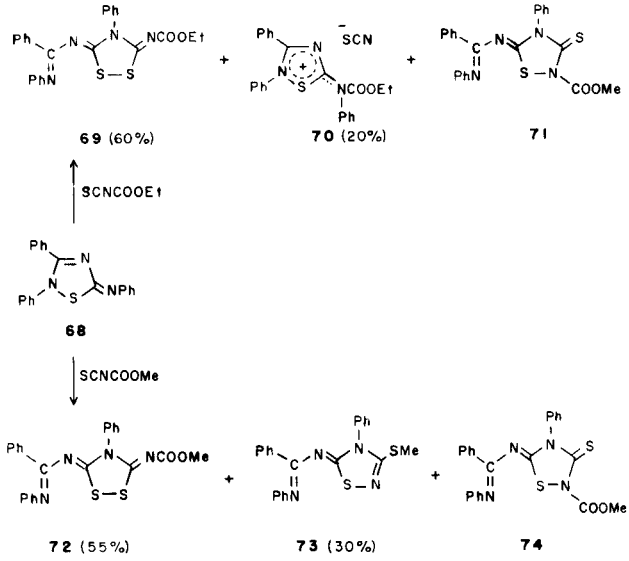

nitrogen and results in the formation of 1,2,4-dithiazolidine **65** [42]. Another cycloaddition reaction which is



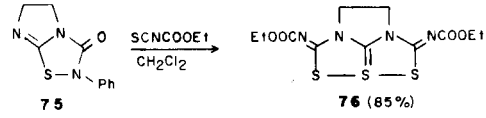

accompanied by ring opening and yields a new, equal size ring occurs when 4-imino-4,5-dihydro-1,2λ⁶,3-oxathiazol-2-one **66** is allowed to react with a tenfold excess of ECIT to



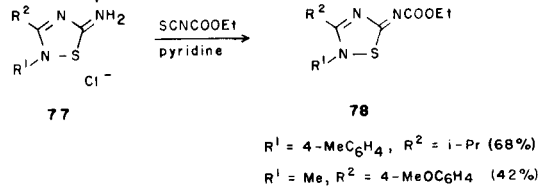

give **67** [43]. Analogous results are obtained when 2,3-diphenyl-5-phenylimino-Δ³-1,2,4-thiazoline (**68**) is treated with ECIT in benzene. The isolated products are **69** and **70**, but ¹H-nmr data indicate also the presence of a third product **71**, an isomer of **69**. When methoxycarbonyl isothiocyanate is used as reagent, **72** and **73** are isolated as products. The ¹H-nmr spectroscopy again shows the presence of a third product **74**, an isomer of **72** and possibly the precursor of **73**. As before, these cycloadditions result in ring opening and new, equal size ring formation, but in contrast to the earlier reactions [40,41,42,43] which all involve addition across the C=S bond, in this case addition occurs to some extent also across the C=N bond of the isothiocyanate [44].




The reaction of ECIT with biheterocycle **75** proceeds with loss of phenyl isocyanate and results in the formation

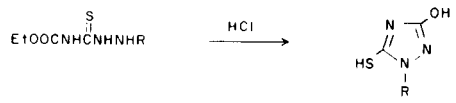



of heteropentalene **76** [45]. On the other hand, treatment of 5-imino-Δ³-1,2,4-thiadiazolines **77** causes ethoxycarbonylation of the exocyclic nitrogen atom and yields **78** [46].




Reactions With Hydrazines, Amidines, Amidrazones and Related Compounds.

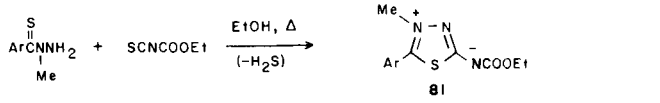
The adducts **79** of ECIT and phenyl- or alkylhydrazines cyclize upon treatment with hydrochloric acid to form 1-substituted 3-hydroxy-1*H*-1,2,4-triazolylthiols **80** [47,48].



79 80

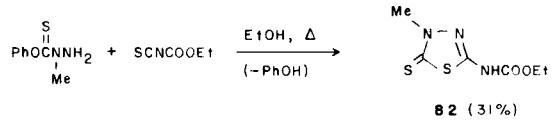
R = Me, Et, Pr, i-Pr, Bu, n-$C_{12}H_{25}$, Ph

*N*-Methylthiobenzhydrazides react with ECIT to form mesoionic 1,3,4-thiadiazoles **81**, but when a good leaving group is attached to the hydrazide thiocarbonyl, cyclization occurs in a different manner to yield a 1,3,4-thiadiazolidine-2-thione **82** [49,50].



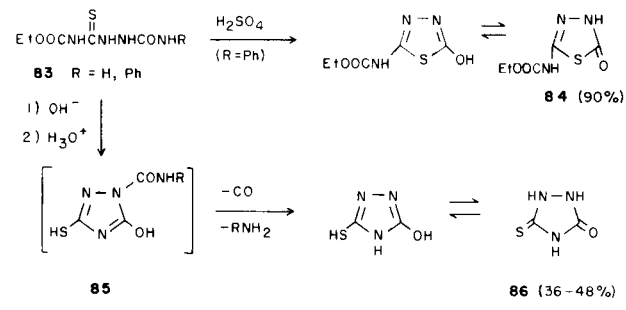
81

Ar = Ph (56%), 4-$ClC_6H_4$ (38%), 4-$EtOC_6H_4$ (43%)



82 (31%)

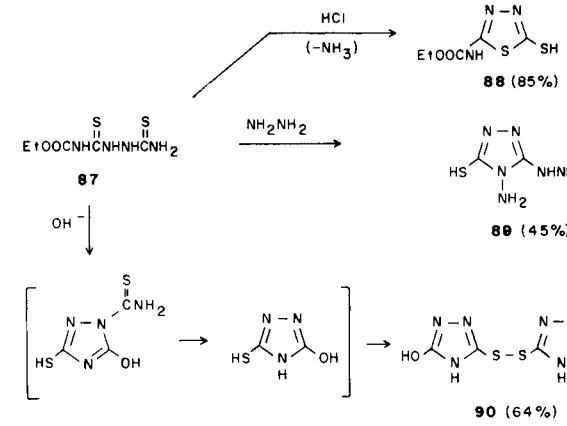
The reactions of ECIT with semicarbazides and thiosemicarbazides in dimethylformamide produce 1-ethoxycarbonyl-2-thiobiureas **83** (56-85%), or -bithioureas **87** (75-85%), respectively [51]. The former compounds are cyclized to 2-(*N*-ethoxycarbonylamino)-5-hydroxy-1,3,4-thiadiazole (**84**), by the action of concentrated sulfuric acid, and to 3-hydroxy-5-mercapto-1,2,4-triazole (**86**) (*via* the *N*-carbamoyl derivative **85**), by aqueous alkali. It thus appears that the electrophilic center of **83**, at which nucleophilic attack occurs, is the urea carbonyl carbon in acid media and the ester carbonyl carbon in alkaline media. The ring closure of 1-ethoxycarbonylbithioureas **87** and **91** proceeds similarly to afford 1,3,4-thiadiazoles under the influence of acids. Hydrochloric acid converts the parent linear adduct **87** to 2-(*N*-ethoxycarbonylamino)-5-mercapto-1,3,4-thiadiazole (**88**), with loss of ammonia, but the 6-aryl substituted bithioureas **91** to 2-arylamino-5-(*N*-ethoxycarbonylamino)-1,3,4-thiadiazoles (**92**), with loss of



83 R = H, Ph

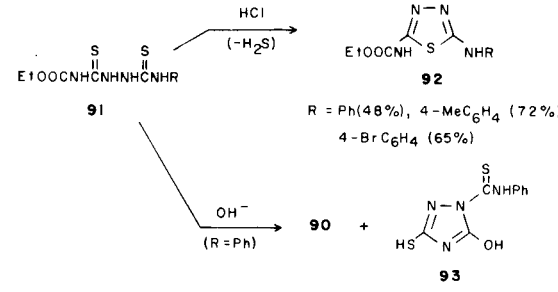
84 (90%)

85 86 (36-48%)



87 88 (85%) 89 (45%) 90 (64%)

hydrogen sulfide. The relative basicities of the RNH and SH groups seem to determine which of the two is lost upon cyclization. Hydrazinolysis of the parent bithiourea **87** yields 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (**89**),

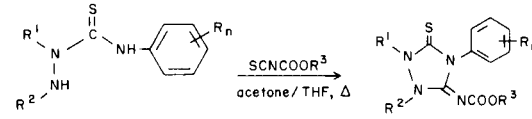


91 92 93

R = Ph(48%), 4-$MeC_6H_4$ (72%), 4-$BrC_6H_4$ (65%)

whereas the action of alkali on it leads to disulfide **90** presumably by oxidation of the initially formed 3-hydroxy-5-mercapto-1,2,4-triazole. In the case of the phenyl derivative **91** (R = Ph), both the primary cyclization product **93** and disulfide **90** are isolated following treatment with alkali. The relative amounts of the two products depend upon the duration of the treatment, the disulfide being favored by a more prolonged interaction [51].

Derivatives of 1,2,4-triazolidine-3-thione **95** are formed when 1,3,4-trisubstituted thiosemicarbazides **94** react with alkoxycarbonyl isothiocyanates [52,53].



94 95

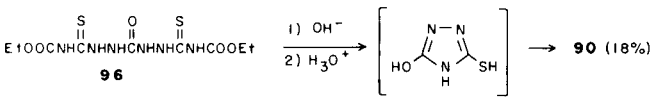
R = Me, MeO, halo, $F_3C$, 4-$ClC_6H_4CH_2O$

n = 0, 1, 2

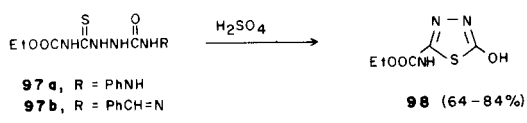
$R^1$, $R^2$ = Me, $(CH_2)_3$, $(CH_2)_4$

$R^3$ = alkyl

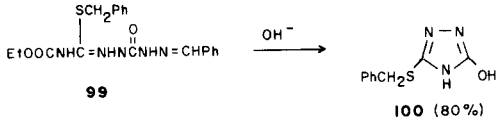
Carbonohydrazide undergoes diaddition with ECIT, unless one of the hydrazino groups is blocked [54]. The diadduct **96** is stable toward acids, but yields disulfide **90** upon treatment with aqueous alkali.



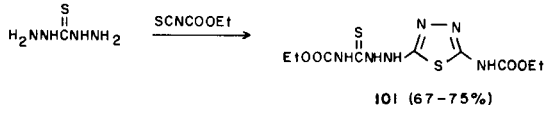
Monoadducts **97a** and **b** are cyclized by concentrated sulfuric acid to 2-(*N*-ethoxycarbonylamino)-5-hydroxy-1,3,4-thiadiazole (**98**) with loss of the corresponding



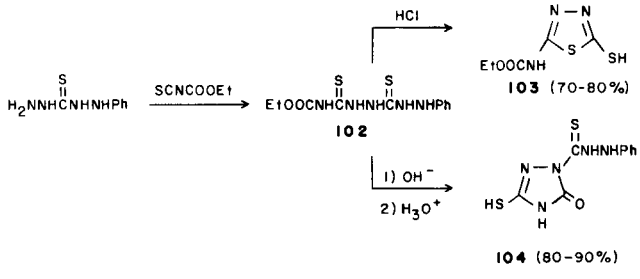
substituted hydrazine. Upon treatment with alkali, the *S*-benzyl derivative **99** of monoadduct **97b** furnished 3-benzylthio-5-hydroxy-1,2,4-triazole (**100**). In the case of thiocarbonohydrazide, diaddition of ECIT is accompanied by



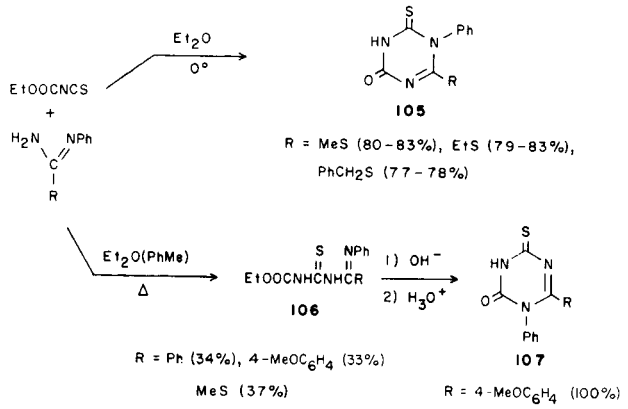
ring closure with loss of hydrogen sulfide to form 1,3,4-thiadiazole **101**.

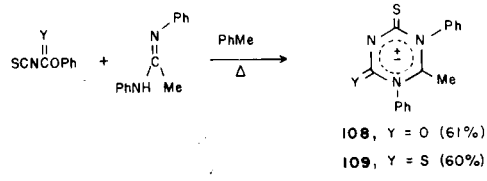


Monoadduct **102** follows the established cyclization pattern of such compounds being converted into a 2-amino-1,3,4-thiadiazole **103** by acids and into a 3-mercapto-1,2,4-triazole **104** by alkalies [54].

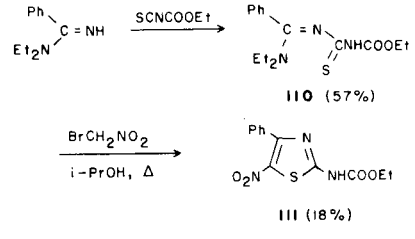


The reactions of *N*-phenylamidines with ECIT lead to 4-thioxo-1,3,5-triazin-2-ones **105**, or *N*-imidoyl-*N'*-ethoxycarbonylthioureas **106**, or mixtures of the two, depending upon the type of amidine and the reaction temperature [55]. It appears that the triazines result from the reaction of the substituted nitrogen, whereas the thioureas from the reaction of the unsubstituted amino group of the amidines with the isothiocyanate group of ECIT. The linear adducts do not cyclize spontaneously or thermally, but in some cases do so by the action of alkali to form thioxotriazinones **107** [55]. *N,N'*-Diphenylacetamidine reacts with phenoxycarbonyl and phenoxythiocarbonyl isothiocyanate to form the mesoionic monothione **108** and dithione **109**,

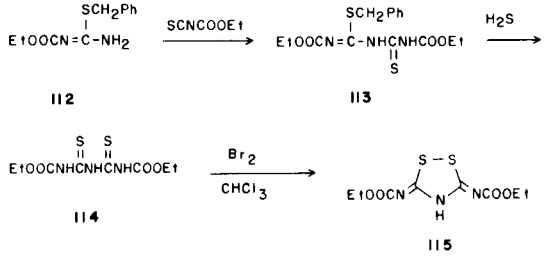




respectively [56]. The 1:1 adduct **110** from *N,N*-diethylbenzamidine and ECIT undergoes a cyclization reaction with bromonitromethane which yields a substituted thiazole **111** [57]. The thiourea **113** resulting from *S*-benzyl-*N*-

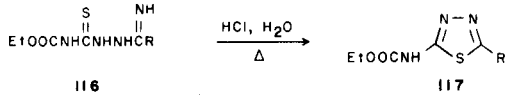


ethoxycarbonylisothiourea (**112**) and ECIT is debenzylated by hydrogen sulfide to **114**, which is cyclized to 1,2,4-dithiazolidine **115** upon treatment with bromine [58].



The results of the reactions between ECIT and amidrazone salts appear to depend on the structure of the amidrazone and the temperature. At room temperature and in the presence of triethylamine, unsubstituted amidrazone

hydroiodides react with ECIT in dimethylformamide to yield 1-imidoyl-4-ethoxycarbonyl-3-thiosemicarbazides **116** which cyclize to 1,3,4-thiadiazoles **117** upon treatment with acid, but fail to form the isomeric 1,2,4-triazoles under the influence of alkali.



**116** **117**

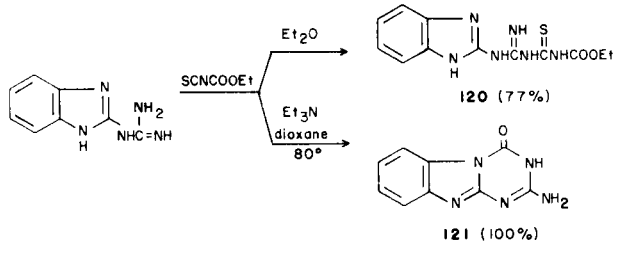
R = Ph (54%), $PhCH_2$ (48%) R = Ph (80%), $PhCH_2$ (56%)

In the case of acetamidrazone hydrochloride, the room temperature reaction with ECIT in dimethylformamide yields directly a 1,3,4-thiadiazole **117** (R = Me, 62%) [59]. At 95-100°, 1-substituted amidrazones yield 4-ethoxycarbonyl-1,2,4-triazolin-5-thiones **118**, as major, and 1,2,4-triazolin-5-thiones **119**, as minor products [60]. Unsubstituted amidrazone hydrochlorides, however, under the same

R, R' = H, Me, Ph **118** **119**

conditions lead not to 1,2,4-triazolin-5-thiones, as originally reported [60], but to 1,3,4-thiadiazoles, just as by the room temperature reaction [59].

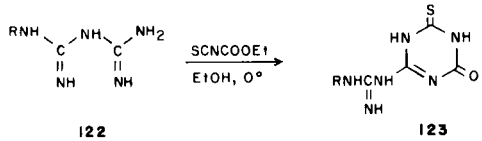
Under mild conditions, 2-guanidinobenzimidazole reacts with ECIT at the side chain to give the rather unstable thiourea **120**, but under somewhat more vigorous conditions ethoxycarbonylation of the side chain leads to a benzimidazo[1,2-*a*]-1,3,5-triazine **121** [61]. The cyclization



**120** (77%)

**121** (100%)

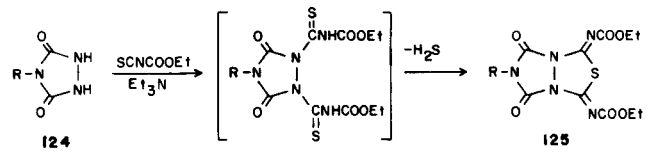
reactions of ECIT with arylbiguanides **122** proceed with elimination of ethanol and yield thioxo-1,3,5-triazinones **123** [62]. In the presence of triethylamine, 4-substituted



**122** **123**

R = 4-$MeC_6H_4$ (68%), 4-$ClC_6H_4$ (62%)

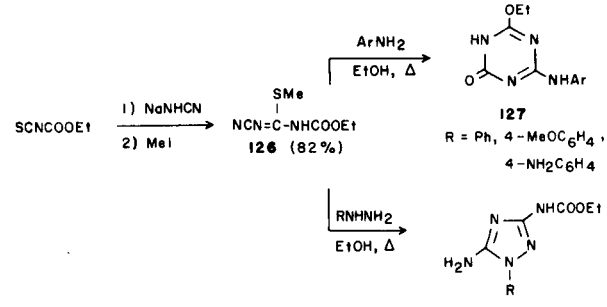
1,2,4-triazoline-3,5-diones **124** react with ECIT to form derivatives of 1,3,4-thiadiazolo[3,4-*a*]-1,2,4-triazole **125** [63].



**124** **125**

R = Me (43%), Ph (35%)

Upon treatment with aromatic amines, the *S*-methyl derivative of the adduct of ECIT and cyanamide **126** yields rather unexpectedly 2-arylamino-4-ethoxy-6-oxo-5,6-dihydro-1,3,5-triazines **127**. The formation of these compounds may be due to an intermediate formation of oxadiazines which undergo a Dimroth rearrangement. With



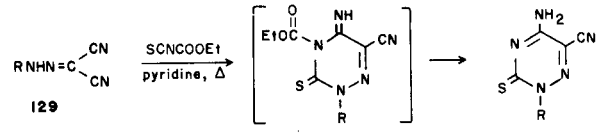
**126** (82%) **127**

R = Ph, 4-$MeOC_6H_4$, 4-$NH_2C_6H_4$

**128**

R = Ph, PhCO(50-60%)

hydrazines, **126** reacts in the expected manner to form substituted 1,2,4-triazoles **128** [64]. Arylhydrazonomesoxalonitriles **129** react with ECIT to yield derivatives of

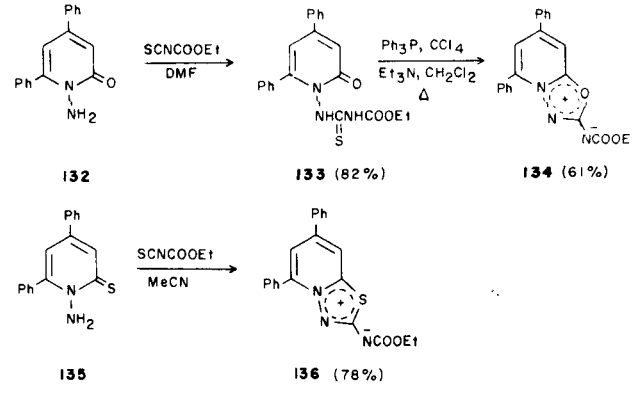


**129** **130** **131**

R = Ph, 4-$ClC_6H_4$ (80%)

1,2,4-triazine **131** presumably by loss of the ethoxycarbonyl group from the initial cyclization products **130** [65].

Mesoionic derivatives of 1,3,4-oxadiazolo[3,2-*a*]pyridine **134** and 1,3,4-thiadiazolo[3,2-*a*]pyridine **136** are prepared



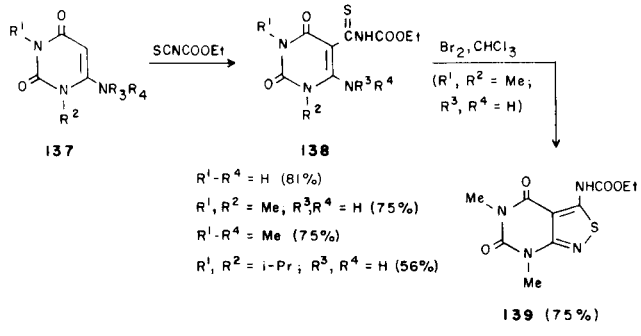
**132** **133** (82%) **134** (61%)

**135** **136** (78%)

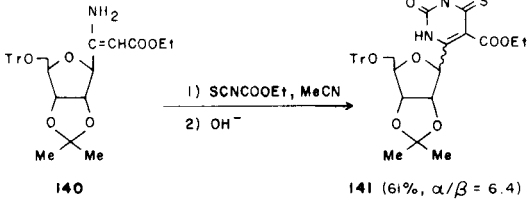
from ECIT and 1-amino-4,6-diphenyl-2-pyridone (**132**), or 1-amino-4,6-diphenyl-2-pyridinethione (**135**), respectively. The intermediate thiourea **133** is isolated in the first case, whereas it undergoes spontaneous cyclodehydrosulfurization in the second [66].

Reactions With Enamines and Related Compounds.

The reaction of 4-aminouracils **137** with ECIT yields 4-aminouracil-5-thiocarboxamides **138** which undergo oxidative cyclization to 3-aminoisothiazolo[3,4-*d*]pyrimidines **139** [67]. Compound **140** reacts with ECIT at the enamine β-carbon and the resulting thiourea cyclizes under the influence of alkali to a 5-ethoxycarbonyl-4-thiouracil-*C*-

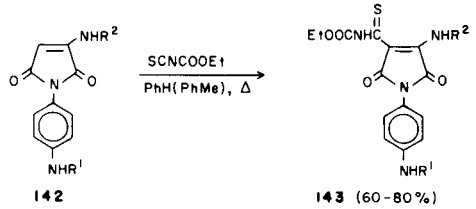



**137** **138** **139** (75%)




**140** **141** (61%, α/β = 6.4)

nucleoside **141** [68]. Similarly, 1-aminoaryl-3-alkylaminomaleimides **142** are thioacylated at position 4 to give *N*-ethoxycarbonylthioamides **143** [69].

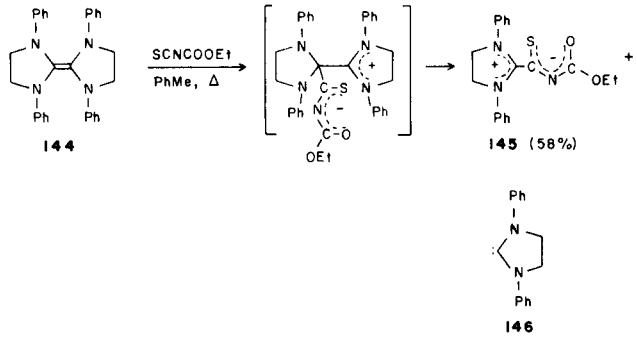



**142** **143** (60-80%)

$R^1$ = H, Me, MeO, Cl

$R^2$ = n-Bu, $O(CH_2)_4$

In refluxing toluene, ECIT reacts with the electron rich olefin **144** to form a zwitterionic product **145** with elimination of a carbene **146**. Dipole **145** enters into cycloaddition reactions with isocyanates and diacylacetylenes which

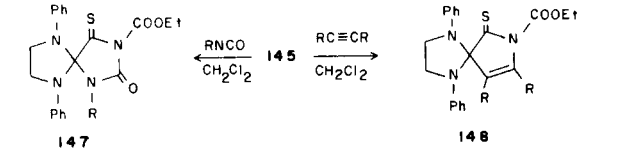



**144** **145** (58%)



**146**

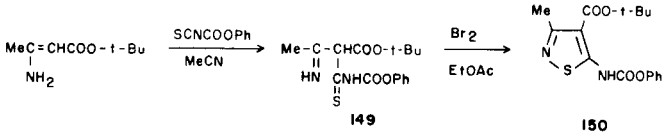
yield spiro compounds **147** and **148** [70]. Treatment of




**147** R = Ph (62%), cyclohexyl (63%)

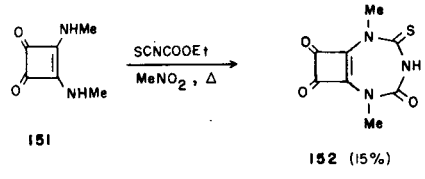
**148** R = COOMe (96%), PhCO (98%)

*t*-butyl 3-aminocrotonate with phenoxycarbonyl isothiocyanate gives the thioamide **149** which cyclizes by the action of bromine to an isothiazole **150** [71].



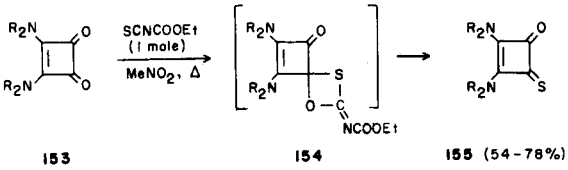

**149** **150**

Addition occurs across the C=N bond of ECIT when it reacts with the 1,2-bismethylamide of quadratic acid (**151**) to form the bicyclic product **152**. In contrast, addition occurs across the C=S bond of ECIT in its reactions with

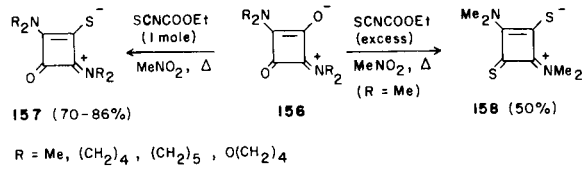



**151** **152** (15%)

tertiary diamides of quadratic acid **153** and **156** with the result that one or both carbonyls of the latter compounds are converted into thiocarbonyls to form **155, 157** and **158**. In these cases, it is probable that the O/S exchange occurs through an unstable intermediate **154** containing a spiro, 4-membered ring [72].

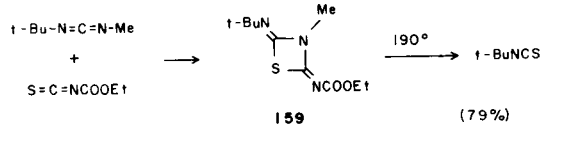



**153** **154** **155** (54-78%)

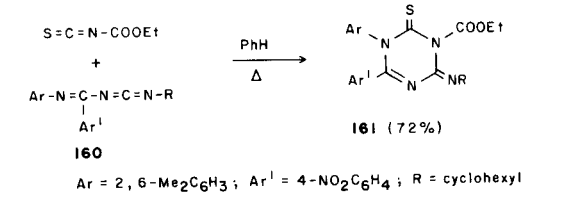



Reactions with Carbodiimides.

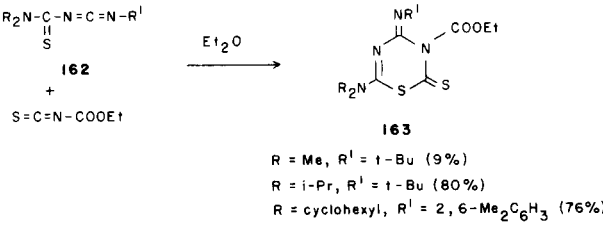
A 2+2 cycloaddition exclusively across the C=S bond of ECIT occurs when it reacts with methyl-*t*-butylcarbodiimide, as evidenced by the observation that the adduct **159** gives a negative Feigl test for thiocarbonyl and is




thermally decomposed to *t*-butyl isothiocyanate [73]. In contrast, 2+4 cycloadditions across the N=C bond of ECIT are observed in its reactions with imidoyl- **160** and thiocarbamoylcarbodiimides **162** to yield cycloadducts

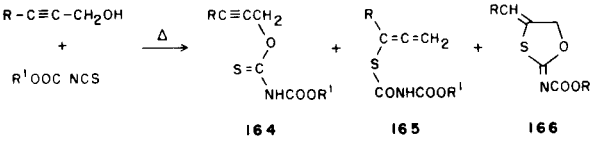



**161** [74] and **163** [75], respectively.



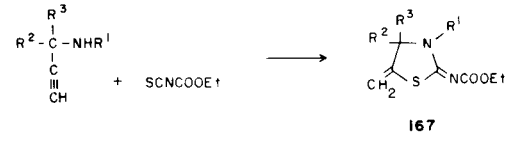

Reactions with Hydroxy- and Aminoacetylenes.

Alkynylmethanols react with alkoxycarbonyl isothiocyanates to form *O*-alkynylmethyl *N*-alkoxycarbonylthiocarbamates **164**, *S*-allenyl *N*-alkoxycarbonylthiocarbamates **165**, and 2-(*N*-alkoxycarbonylimino)-4-alkyliden-1,3-oxathiolanes **166**.

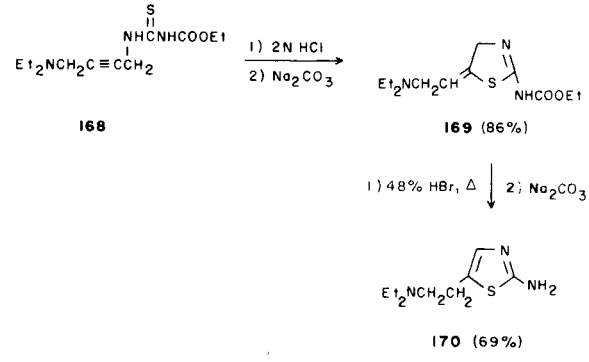



The overall yields become lower, the larger the alkyl groups of the isothiocyanates, whereas the relative amounts of the products depend on the groups at position 3 of the alcohols. Thus, with ECIT 2-propyn-1-ol yields all three products (R = H, R' = Et), but 2-butyn-1-ol gives only adduct **164** (R = Me, R' = Et), and 3-phenyl-2-propyn-1-ol affords **164** (R = Ph, R' = Et) and **166** (R = Ph, R' = Et). Heating and/or treatment with base converts adducts **164** to **165** and **166** [76]. A two-step sequence, reaction of an alkynylmethanol with an alkoxycarbonyl isothiocyanate and treatment of the product with aqueous sodium bicarbonate, has been developed into a general method of preparation of 1,3-oxathiolanes **166** [77].

Analogous reactions of 1-ethynylamines with ECIT have been used to prepare 2-(*N*-ethoxycarbonylimino)-5-methylenethiazolidines **167** [78,79,80]. The adduct **168** obtained



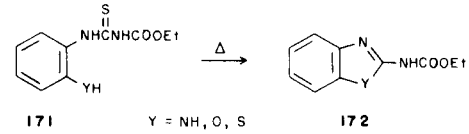

from *N,N*-diethyl-1,4-butynediamine and ECIT cyclizes by



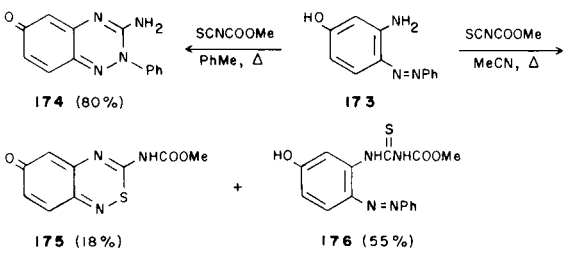

the action of dilute hydrochloric acid to a 2-thiazoline derivative **169**, which is converted into 2-amino-5-[2-(*N,N*-diethylamino)ethyl]thiazole (**170**) upon treatment with hot concentrated hydrobromic acid [81].

Miscellaneous Cyclization Reactions.

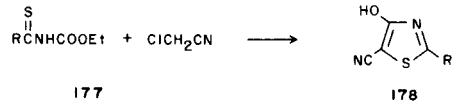
The adducts **171** obtained from ECIT and *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol cyclize upon heating with loss of hydrogen sulfide to form




2-(*N*-ethoxycarbonylamino)benzimidazole, -benzoxazole, and benzothiazole **172**, respectively [82]. Aminophenylazophenol **173** reacts with methoxycarbonyl isothiocyanate to yield, depending on the reaction conditions, either the

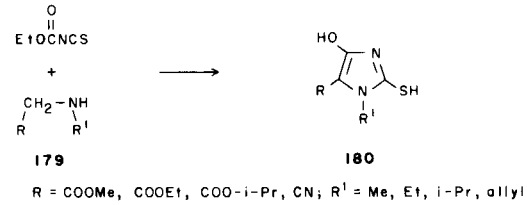



benzo-1,2,4-triazinone **174**, or a mixture of benzo-2,1,4-thiadiazinone **175** and the intermediate thiourea **176** [83]. Substituted thiazoles **178** are formed when the adducts from ECIT and alcohols or thiols **177** react with chloro-



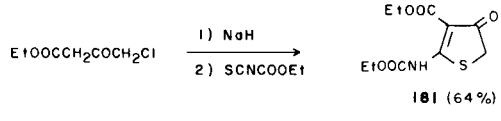

R = EtO, BuO, cyclohexyloxy, $PhCH_2O$, 4-$MeC_6H_4CH_2O$, 4-$ClC_6H_4CH_2O$, EtS, 4-$ClC_6H_4CH_2S$

acetonitrile [84]. The reaction of ECIT with *N*-alkylaminoacetates, or *N*-alkylaminoacetonitriles **179** yields 1,5-disubstituted-4-hydroxy-2-mercaptoimidazoles **180** [85].

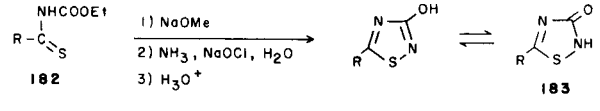



R = COOMe, COOEt, COO-i-Pr, CN; $R^1$ = Me, Et, i-Pr, allyl

The sodium salt of ethyl 4-chloroacetoacetate enters into a ring forming reaction involving the C=S bond of ECIT to yield a dihydrothiophene derivative **181** [86]. On

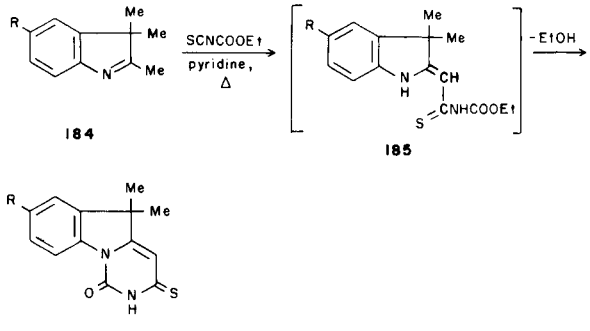



the other hand, the sodium salts of the adducts **182** of ECIT and ethanol, *p*-chlorobenzyl alcohol, or dimethylamine react with chloramine to form 3-hydroxy-1,2,4-thiadiazoles **183** [87].



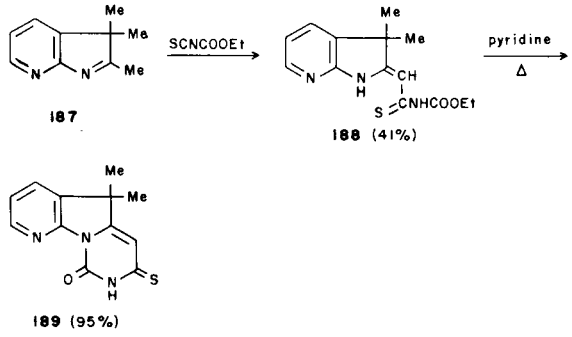

R = EtO (36%), 4-$ClC_6H_4CH_2O$ (50%), $Me_2N$ (57%)

In refluxing pyridine, or toluene with added triethylamine, 2,3,3-trimethylindolenines **184** react with ECIT to form tricyclic products **186**, presumably by cyclization of

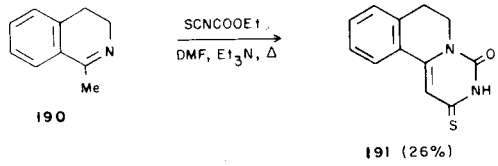



R = H, MeO (40%), $NO_2$ (42%)

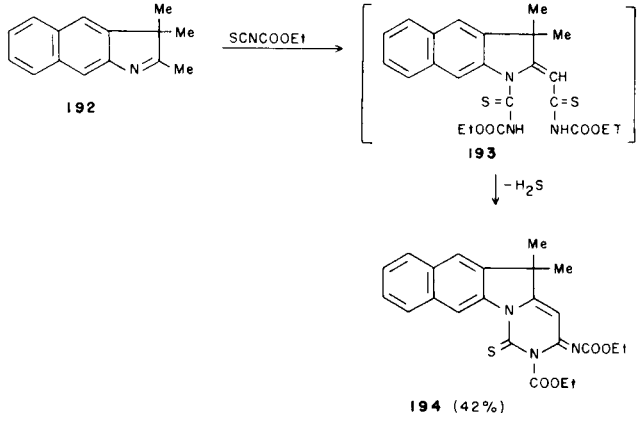
the intermediate 1:1 adducts **185** [88,90]. In the case of 2,3,3-trimethyl-3*H*-pyrrolo[2,3-*b*]pyridine (**187**), the 7-aza analog of **184** (R = H), the decreased nucleophilicity of the pyrrole nitrogen allows isolation of the 1:1 adduct **188**




which cyclizes to **189** in boiling pyridine [89]. A similar cyclization reaction occurs when 1-methyl-3,4-dihydroisoquinoline (**190**) is treated with ECIT in boiling dimethylformamide containing triethylamine to form **191** [90].

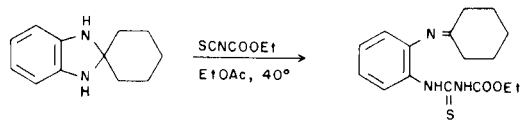



Finally, the product **194** of the room temperature treatment of 2,3,3-trimethyl-3*H*-benz[*f*]indole (**192**) with ECIT appears to result by cyclization of an initially formed diadduct **193** [89].



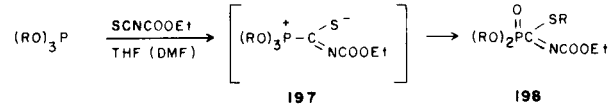
Miscellaneous Reactions.

The spiro compound **195** enters into a ring opening reaction with ECIT which yields the thiourea **196** [91]. When the vapor of ECIT is exposed to 350°, under a pressure of




**195** **196**

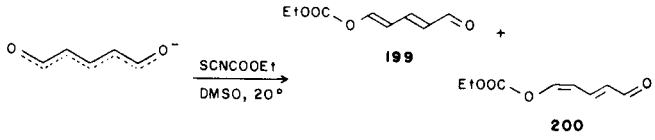
5 Torr, a mixture of ethyl thiocyanate (90%) and ethyl isothiocyanate (5%) is formed, the latter compound resulting secondarily by rearrangement of the thiocyanate. The formation of the same products in virtually the same ratio by an analogous pyrolysis of ethoxycarbonyl thiocyanate is taken to indicate a common intermediate [92]. In tetrahydrofuran or dimethoxyethane, at room temperature, ECIT reacts with trivalent phosphorus esters to form phos-




**197** **198**

R = Me (57%), Et (62%)

phonates **198**, probably through intermediate betaines **197** [93,94]. The reaction of ECIT with the potassium salt of glutacondialdehyde in dimethylsulfoxide results in eth-

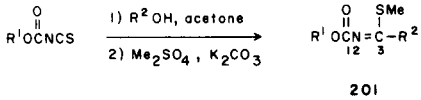



**199** **200**

oxycarbonylation of the anion and yields only the *trans* product **199** at 5°, but a 2.7:1 mixture of the *trans* and *cis* **200** isomers at 20° [95,96].

Reactions of *N*-Ethoxycarbonylthiocarbamates and *N*-Ethoxycarbonylthioureas.

The reactivity of these readily available derivatives of alkoxycarbonyl isothiocyanates toward nucleophilic attack at the thiocarbonyl is considerably enhanced by conversion into their *S*-methyl derivatives **201** and **202** [97]. With difunctional nucleophiles the esters **201** and **202** undergo cyclization in either the 1,3-, or the 3,3-sense. Thus 1,3-

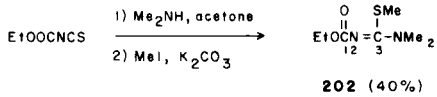



**201**

$R^1$ = Et, $R^2$ = Me (29%)

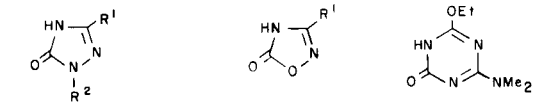
$R^1$ = $R^2$ = Et (35%)

$R^1$ = $Cl_3CCH_2$, $R^2$ = Me (44%)




**202** (40%)

cyclizations with hydrazine, hydroxylamine, and guanidines give 1,2,4-triazolones **203**, 1,2,4-oxadiazolones **204**, and 1,3,5-triazinones **205**, respectively. With 1,2-(aliphatic and aromatic) and 1,3-(aliphatic)diamines, the esters **201**

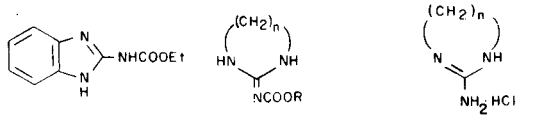


**203** **204** **205** (67%)

$R^1$ = MeO, $R^2$ = H (56%)
$R^1$ = MeO, $R^2$ = Ph (49%)
$R^1$ = $Me_2N$, $R^2$ = H (28%)

$R^1$ = MeO (42%),
$Me_2N$ (71%)

undergo 3,3-cyclization reactions providing a one-carbon unit in the formation of benzimidazole **206** and guanidines **207**. Although the ester group of **207** resists hyrolysis when R = Et, it is easily removed by treatment with zinc dust in aqueous acetic acid when R = $CCl_3CH_2$ thus allowing convenient preparation of cyclic guanidines **208** from aliphatic diamines [97].

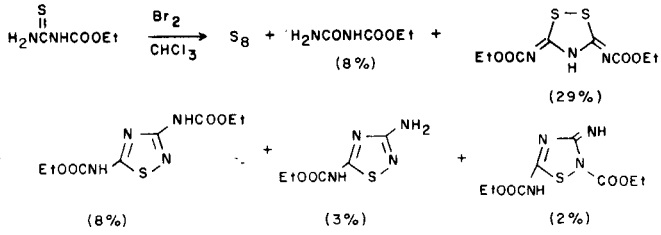


**206** (72%) **207** **208**

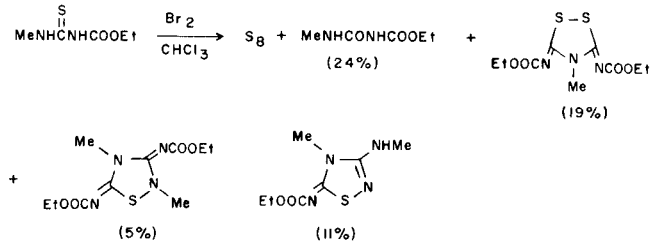
R = Et, n = 3 (43%)
R = $Cl_3CCH_2$, n = 3 (83%)
R = $Cl_3CCH_2$, n = 2 (84%)

n = 2 (83%)
n = 3 (98%)

*N*-Ethoxycarbonylthiourea, which is easily obtained from ECIT and alcoholic ammonia, reacts with bromine in chloroform to give a complex mixture of products.



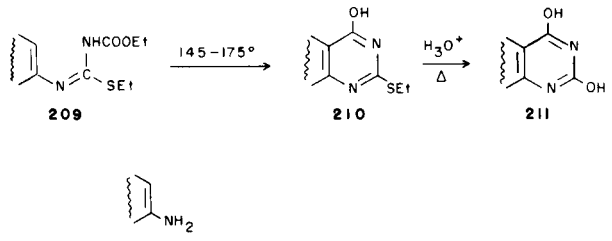

Under the same conditions, *N*-ethoxycarbonyl-*N'*-methylthiourea yields an analogous mixture, whereas *N*-ethoxy-




carbonyl-*N'*-phenylthiourea is simply oxidized to the corresponding urea [98].

The *S*-ethyl derivatives **209** of *N*-ethoxycarbonylthio-

ureas obtained from ECIT and aromatic or heteroaromatic amines lose ethanol upon heating and give rise to fused 2-ethylthio-4-hydroxypyrimidines **210**, which are easily



**209** **210** **211**

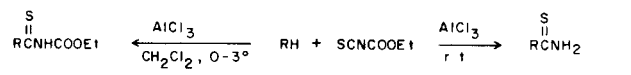


= aniline (36%)
4-amino-2-methylquinoline (88%)
4-amino-2-chloroquinoline (93%)
8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (80%)

hydrolyzed to the corresponding fused 2,4-dihydroxypyrimidines **211** [99].

Reactions of *N*-Ethoxycarbonylthioamides.

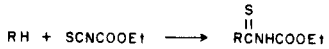
In the presence of anhydrous aluminum chloride, ECIT reacts with aromatic compounds to form *N*-ethoxycarbonylthioamides **212a**, when equivalent amounts of the two reagents are allowed to react in dichloromethane at 0-3°. The same reaction yields directly the corresponding thioamides **213**, when an excess of the aromatic compound is used at ambient, or higher temperature.



**212a** (17-90%) **213** (56-91%)

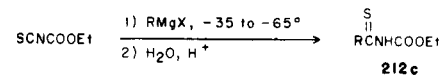
R = Ph, 4-$MeC_6H_4$, 4-$EtC_6H_4$, 4-*i*-$PrC_6H_4$, 4-*t*-$BuC_6H_4$, 2,5-$Me_2C_6H_3$, 2,4,6-$Me_3C_6H_2$, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$.

In the latter case, it appears that aluminum chloride catalyzes ethylation of unreacted aromatic compound by the initially formed **212a**, which is thereby transformed to a thiocarbamate complex later hydrolyzed and decarboxylated into a thioamide **213**. In the case of alkoxybenzenes, the reaction stops at the *N*-ethoxycarbonylthioamide stage under all conditions tested, presumably because of strong coordination of the catalyst with the ether oxygen atom [100]. ECIT reacts in a similar manner with thiophene, in the presence of anhydrous stannic chloride [101], and with more reactive heteroaromatic compounds, such as pyrrole [102], 1-methylpyrrole [35], and indole [103], in the absence of a catalyst, to yield the corresponding adducts **212b**. *N*-Ethoxycarbonyl aliphatic thioamides **212c** are accessible through the low-temperature reaction of ECIT with alkylmagnesium halides [103,104].



**212b**

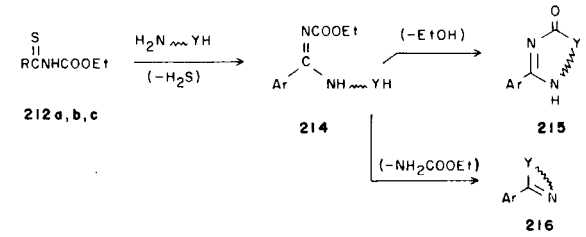
R = 2-pyrrolyl (93%), 2-thienyl (81%), 1-methyl-2-pyrrolyl (82%), 3-indolyl (59%)



**212c**

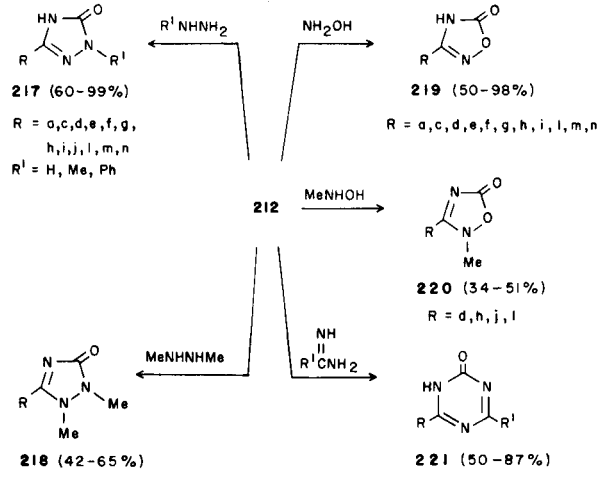
R = Me (74%), Et (72%), Pr (81%), Bu (86%), $PhCH_2$ (50%)

*N*-Ethoxycarbonylthioamides **212a,b,c** have proved to be versatile starting materials for the preparation of a wide variety of heterocyclic compounds. When treated with a dinucleophilic reagent possessing at least one primary or seondary amino group, **212a,b,c** react initially at the thiocarbonyl with elimination of hydrogen sulfide and formation of an *N*-ethoxycarbonylamidine (**214**). The



**212a,b,c** **214** **215** **216**

second nucleophilic group of the reagent then attacks the ester carbonyl of **214**, if it is possible for a 5- or 6-membered ring **215** to be formed. When this ring would be 7-membered, or larger, the second nucleophilic group reacts instead with the C=N bond of **214** to cause elimination of ethyl carbamate and formation of a ring **216** incorporating only the thiocarbonyl carbon of **212**. Thus the reactions of *N*-ethoxycarbonylthioamidies with hydrazines, hydroxylamines, and amidines follow the first route and lead to 1,2,4-triazolones **217, 218**, 1,2,4-oxadiazolones **219, 220**, and 1,3,5-triazinones **221**, respectively [103,105]. In contrast, the reactions of *N*-ethoxycarbonylthioamides **212** with 1,2-, 1,3-, and 1,4-dinucleophilic reagents follow the



**217** (60-99%) **219** (50-98%)
R = a,c,d,e,f,g, h,i,j,l,m,n
R' = H, Me, Ph
R = a,c,d,e,f,g,h,i,l,m,n

**212**

**220** (34-51%)
R = d,h,j,l

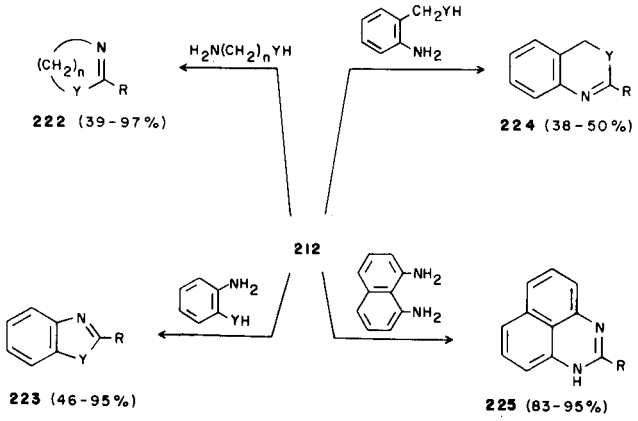
**218** (42-65%) **221** (50-87%)

R = c,d,e,f,g,h,i

R = a,d,i,j,l
R' = Ph, $PhCH_2S$

a = Et, b = $PhCH_2$, C = Ph, d = 4-$MeC_6H_4$, e = 4-$EtC_6H_4$, f = 4-*i*-$PrC_6H_4$, g = 4-*t*-$BuC_6H_4$, h = 4-$MeOC_6H_4$, i = 4-$EtOC_6H_4$, j = 4-$ClC_6H_4$, k = 4-$BrC_6H_4$, l = 2-pyrrolyl, m = 2-thienyl, n = 3-indolyl

second route shown earlier to form various other heterocyclic compounds: 4,5-dihydroimidazoles, -oxazoles, -thiazoles, 1,4,5,6-tetrahydropyrimidines, 5,6-dihydro-1*H*-oxazines, 4,5,6,7-tetrahydro-1*H*-1,3-diazepines **222**, benzimidazoles, benzoxazoles, benzothiazoles **223**, 3,4-dihydroquinazolines, 4*H*-1,3-benzoxazines **224**, and perimidines **225** [105,106].




n = 2, Y = NH, R = b,d,h,l,m
n = 2, Y = O, R = a,b,h,l,m
n = 2, Y = S, R = d, h, l, m
n = 3, Y = NH, R = d,h,l,m
n = 3, Y = O, R = a,d,k,l
n = 4, Y = NH, R = d,j,k,l

Y = NH, R = d,h
Y = O, R = d,h

Y = NH, R = b,d,h,l,m
Y = O, R = a,d,h,l,m
Y = S, R = d,h,l,m

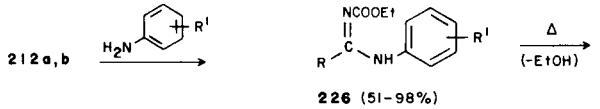
R = c,f,h,m

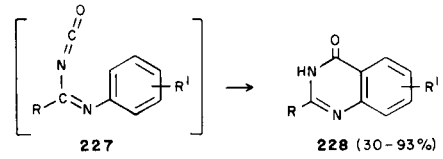
a-m: as in immediately preceding reaction scheme

A new method of preparation of β-ketoesters is based on the reaction of resonance stabilized Wittig reagents with *N*-ethoxycarbonylthioamides **212c** [104].


R = Me, Et, Pr, Bu

Treatment of **212a,b** with aromatic amines, under mild conditions, yields *N*-ethoxycarbonylamidines **226** which undergo thermal cyclization to quinazolinones **228**, very likely through an intermediate imidoyl isocyanate **227** [101,102,107]. Analogous reactions of **212a** with ethyl

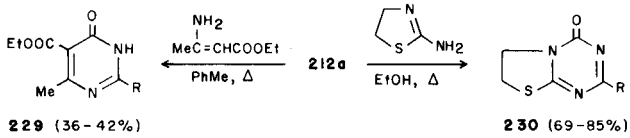



R = Ph, 4-$MeC_6H_4$, 4-$EtC_6H_4$, 4-*i*-$PrC_6H_4$, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 1-pyrrolyl, 2-pyrrolyl, 2-thienyl

R′ (in amine) = H, 3-Me, 4-Me, 2-MeO, 4-Cl, benzo[*c*]

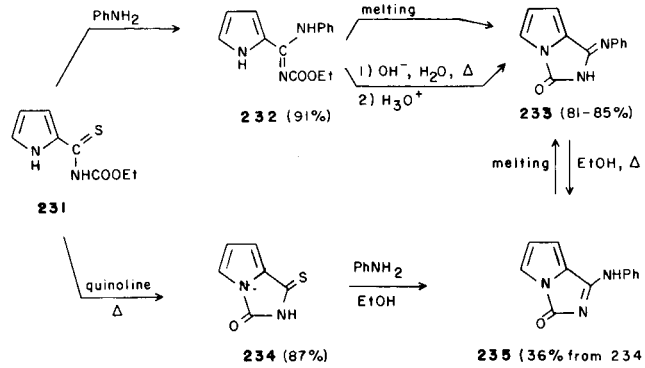
3-aminocrotonate and 2-amino-2-thiazoline yield substituted pyrimidinones **229** and thiazolo[3,2-*a*]-1,3,5-triazinones **230**, respectively [107].



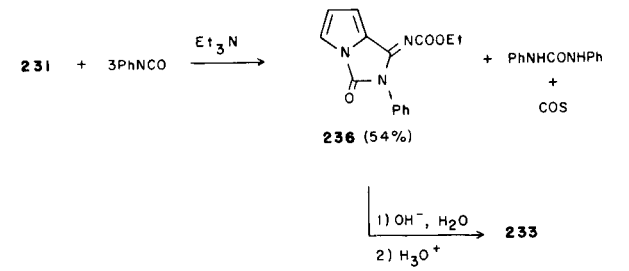

R = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$

R = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$

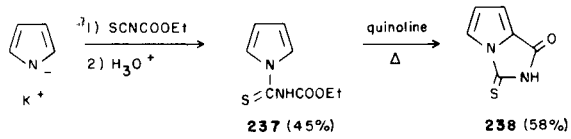
In the case of *N*-ethoxycarbonylpyrrole-2-thiocarboxamide (**231**), the potential nucleophilic character of the pyrrole nitrogen atom increases significantly the possibilities of cyclization reactions [102].



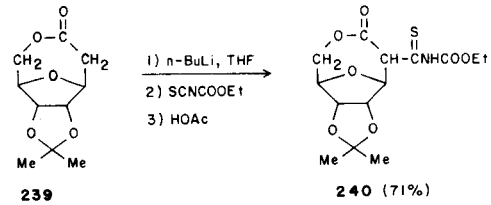

Thus, amidine **232**, which is formed from **231** and aniline under mild conditions, cyclizes upon melting or treatment with aqueous alkali to pyrrolo[1,2-*c*]imidazolone **233**. A tautomer (**235**) of this compound results from the action of aniline on 2-thiopyrrole-1,2-dicarboximide (**234**), which is obtained when **231** is heated briefly in quinoline.



When treated with an excess of phenyl isocyanate, in the presence of triethylamine, **231** enters into a different cyclization reaction which yields pyrrolo[1,2-*c*]imidazolone **236** together with *N,N'*-diphenylurea and carbonyl sulfide. Under the influence of aqueous alkali, **236** undergoes ring opening, loss of carbon dioxide, and new ring closure to form the phenylimino derivative **233**. Finally the potassium salt of pyrrole reacts with ECIT to form *N*-ethoxycarbonylpyrrole-1-thiocarboxamide (**237**), which cyclizes to 1-thiopyrrole-1,2-dicarboximide (**238**) upon heating in quinoline [102].




The conversion of lactone **239** into its derivative **240** exemplifies the use of an organolithium compound for the preparation of an *N*-ethoxycarbonylthioamide [6].

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