SYNTHESIS OF HETEROCYCLES USING THIOAMIDE GROUPS

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Abstract——The utilities of thioamide groups as synthetic intermediates to heterocycles are presented.

CONTENTS:

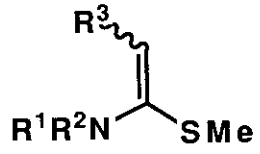
1. INTRODUCTION

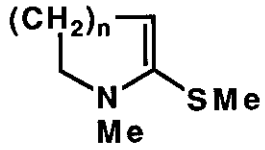
The thioamide group has increasingly been recognized as a useful synthon in organic syntheses[1] and has been shown to be easily convertible to a variety types of functional groups (amines,[2] enamines,[3] ketene S,N-acetals,[4] ketene S,S-acetals,[5] α-cyanoenamines,[6] thioimidates,[7] amides,[8] ketones,[9] esters,[9] etc.) and fully proved to be synthetically potential already in the total syntheses of vitamin B_{12}[10] (sulfide contraction), indole alkaloids[11] (thio-Claisen rearrangement) and other bioactive natural products.[12] In addition, characteristic reactions of thioamides (aldol condensation,[13] Michael addition,[14] and carbophilic addition[15]) with organometallics have been explored. We focus on the use of thioamides as versatile functional groups in the field of heterocyclic synthesis. In this review, our studies using thioamides as synthetic intermediates to heterocycles are presented.

2. SYNTHESIS OF HETEROCYCLES USING KETENE S,N-ACETALS

Ketene S,N-acetals (KSNA) derived from tertiary thioamides are regarded as

interesting α-alkylthio enamines. KSNA 1-8 are prepared from the corresponding tertiary thioamides according to the method of Gompper.[4]

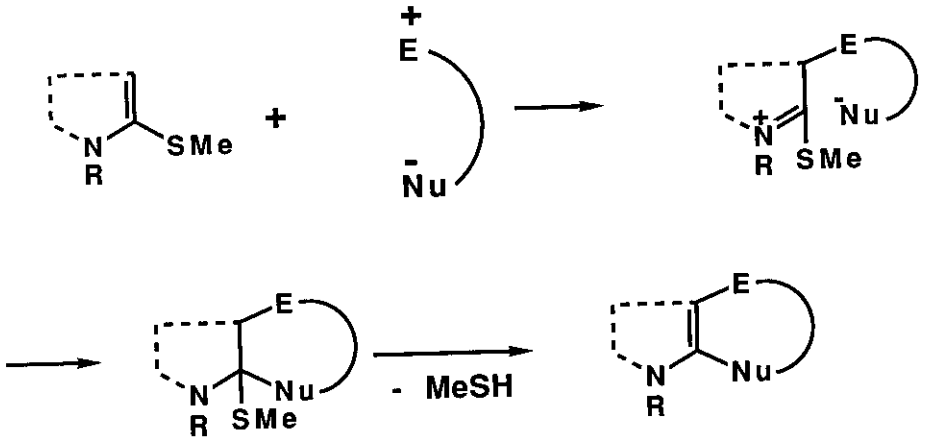




1 $R^1=R^2=Me$, $R^3=H$
2 $R^1=R^2=Me$, $R^3=Me$
3 $R^1=R^2=Me$, $R^3=Et$
4 $R^1=Me$, $R^2=Ph$, $R^3=H$
5 $R^1=Me$, $R^2=Ph$, $R^3=Me$

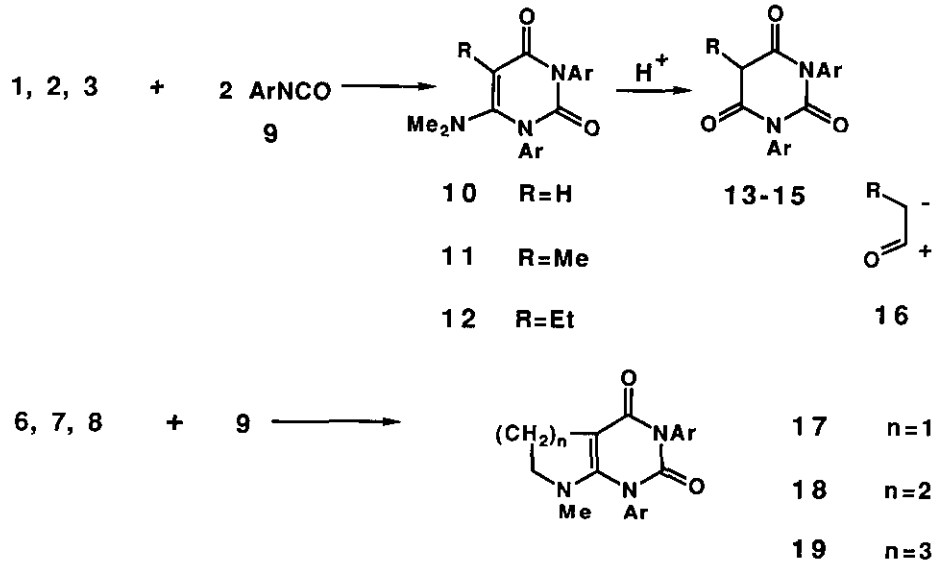
6 n=1
7 n=2
8 n=3

KSNA are allowed to react with a variety of electrophiles to form carbon-carbon bond at the β-position. The intermediate so formed is susceptible to an attack by nucleophiles at the α position. Subsequent selective elimination of alkanethiol group regenerates enamine available for further manipulation (Scheme 1).

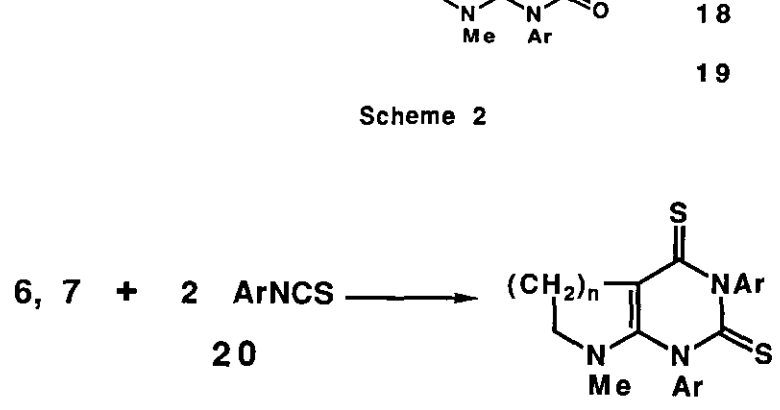


Scheme 1

Cycloaddition of KSNA **1-3** to aryl isocyanates is investigated.[16] Annelation of **1-3** with 2 equiv. aryl isocyanates **9** under reflux in toluene proceeds to give pyrimidine-2,4-diones **10-12**, respectively, in good yields.[17] Hydrolysis of the enamine moiety of **10-12** with 10% hydrochloric acid easily provides barbituric acids **13-15**. In this reaction, **1-3** are synthetically equivalent to **16** (Scheme 2). In a similar manner, the addition of cyclic KSNA **6-8** to 2 equiv. of **9** gave azacycloalka[2,3-d]pyrimidines **17-19**.[18] KSNA **6** and **7** are also reactive toward aryl isothiocyanates **20** and afford azacycloalka[2,3-d]pyrimidinedithiones **21** and **22**.[19] No pyrimidinedithiones are produced from the reaction of **1-3** and **8** with isothiocyanate (Scheme 3).

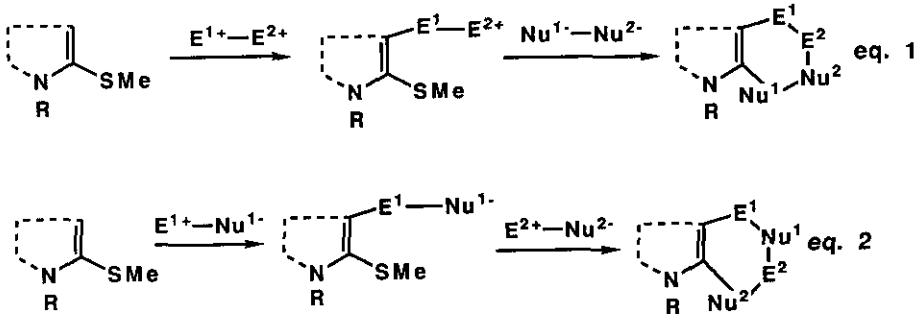


Scheme 2



Scheme 3

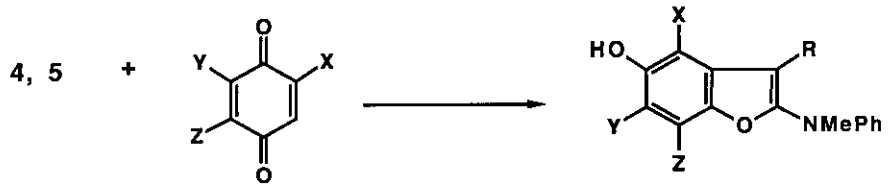
Next, cycloaddition of KSNA **4** and **5** with 1,4-quinones is carried out.[20] Annelation of **4** with benzoquinones **23**-**25** and naphthoquinones **26** and **27** under reflux in tetrahydrofuran (THF) or toluene as a solvent gives 2-aminobenzofurans **28**-**30** and naphtho[1,2-b]furans **31** and **32**, respectively, which are formed by selective cycloaddition and demethanethiolation. Treatment of **5** with **23**, **24**, and **26** in boiling toluene provides 3-methylbenzofuranes **33** and **34** and 3-methylnaphtho[1,2-b]furan **35**. We next turn our attention to further role of the enamine component of the furans products. Ring-expansion of 3-unsubstituted furans **28**, **29**, and **31** with dimethyl acetylenedicarboxylate in boiling dioxane gives rise to the ring enlarged oxepines **36**-**38**, respectively. Next the utility of **28** as Michael donor is tried. Addition of **28** to Michael acceptors **39** provides 3-substituted benzofurans **40** as expected, which are transformed into the biologically interesting benzofuran-2-ones **41** by hydrolysis with 10% hydrochloric acid. In these reactions, **4** may be regarded as a synthetic equivalent of **42** (Scheme 4).
It is possible that the addition of electrophiles at the β-position of KSNA under mild condition gives β-substituted KSNA, which have high potentiality to be transformed with elaboration into heterocycles as formulated in Scheme 5 (eq. 1 and 2).



Scheme 5

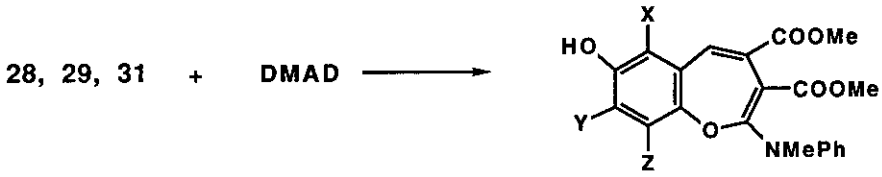
First the examples of eq.1 are described. Reaction of KSNA **1**,**6**, and **7** with aryl isothiocyanates **20** at room temperature in ether gave β-aminothiocarbonyl-α-methylthioenamines **43**, **44**, and **45**, respectively, which appear to be an attractive new synthetic equivalent of 1,3-dicarbonyl compounds.[21] However, the corresponding 1:1 adducts from **2**,**3**, and **8** are not obtained. The interesting

enamines **43**, **44**, and **45** undergo condensation with guanidine, acetamidine, and

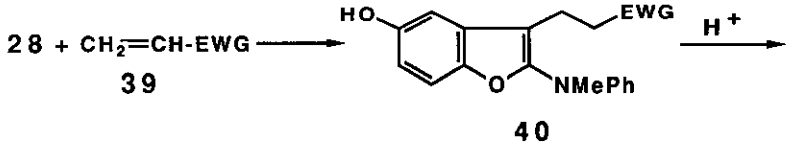


23 X=Y=Z=H
24 X=Y=Cl, Z=H
25 X=H, Y=Z=CN
26 X=H, Y=Z= 
27 X=Cl, Y=Z= 

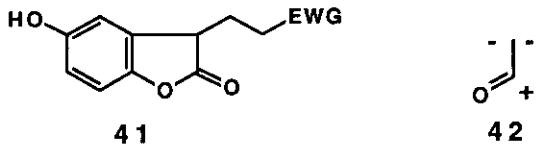
28 R=H **33** R=Me
29 R=H **34** R=Me
30 R=H
31 R=H **35** R=Me
32 R=H



36 X=Y=Z=H
37 X=Cl, Y=Z=H
38 X=H, Y=Z= 



40



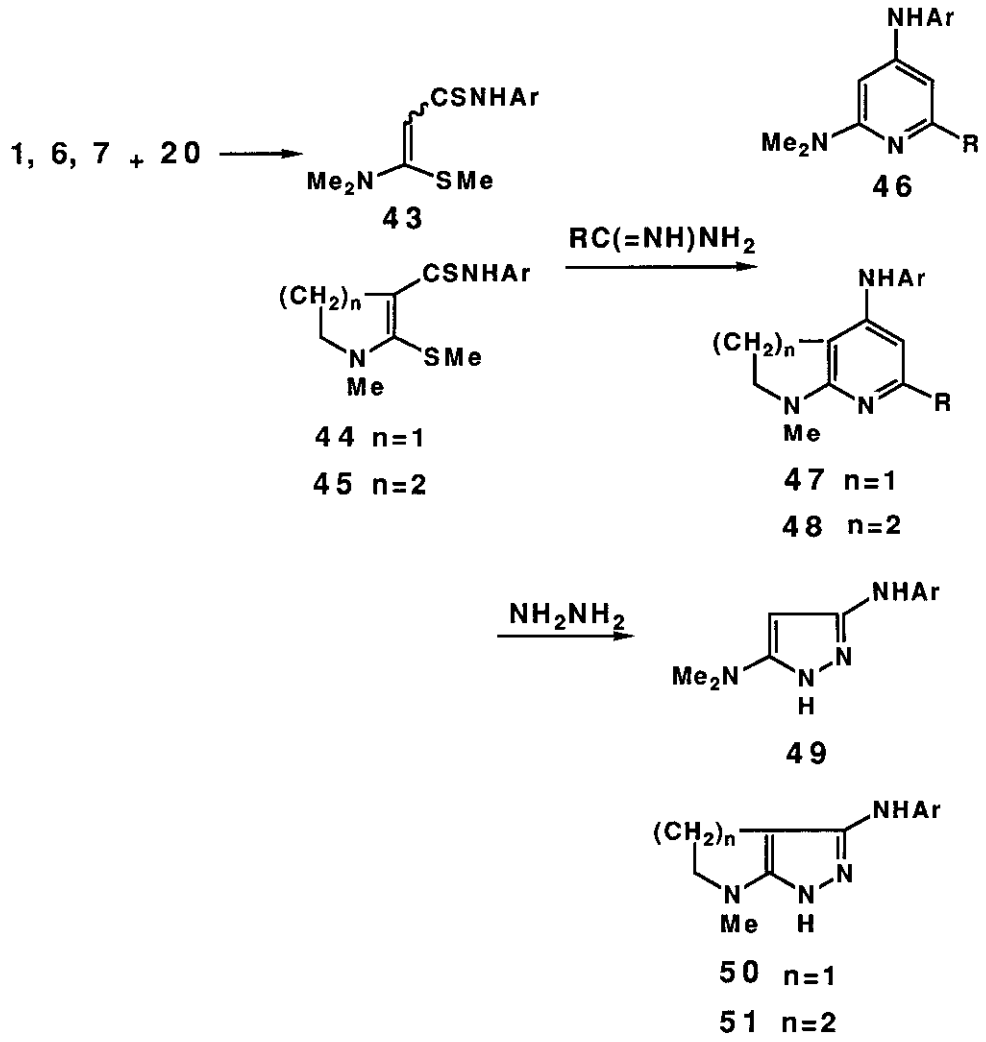
41

42

Scheme 4

benzamidine as bisnucleophiles in the presence of sodium ethoxide in boiling ethanol to provide pyrimidines **46**, **47**, and **48**, respectively. Similarly, the

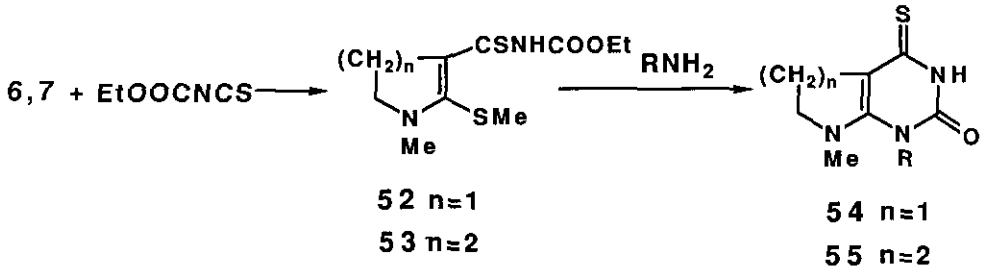
use of hydrazine affords the corresponding pyrazoles **49**, **50**, and **51** (Scheme 6).



Scheme 6

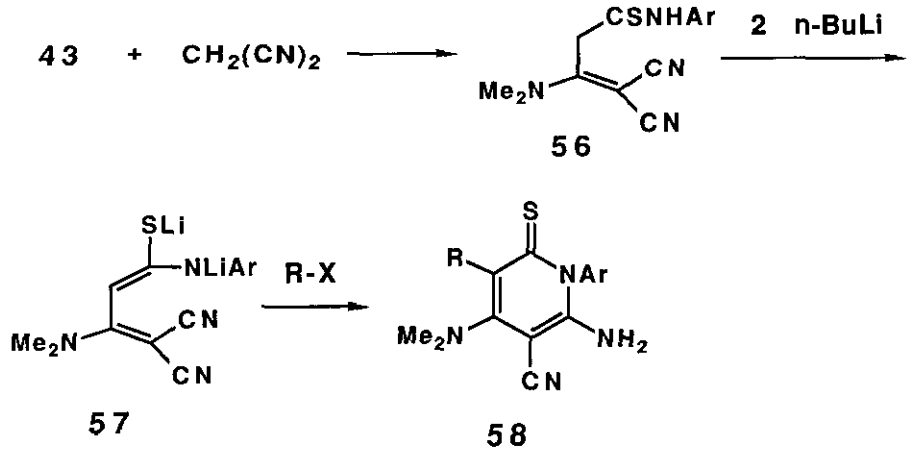
Addition of ethoxycarbonyl isothiocyanate to ether solutions of KSNA **6** and **7** gives 3-ethoxycarbonylaminothiocarbonyl-2-methylthioenamines **52** and **53**, which appear to be attractive new synthetic equivalents of 1,5-dicarbonyl compounds.[22] Compounds **52** and **53** are cyclized by reaction with primary amines as bisnucleophiles in boiling ethanol affording monothiouracil derivatives **54** and **55**, re-

spectively (Scheme 7).



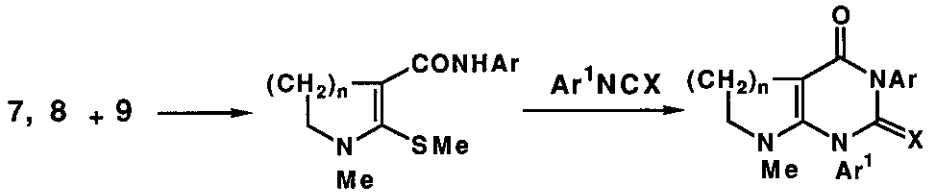
Scheme 7

Next, the examples of eq. 2 are described. The 1:1 adduct **43** shown above undergoes the addition-elimination reaction with malononitrile as carbon nucleophile to afford the enaminonitrile **56**. As described later, bis-lithio-ketene S,N-acetals derived from secondary thioamides are regarded as interesting metalloenamines and have been used as synthetic intermediates for heterocycles. Carbon-carbon bond-forming reaction of the bis-lithio-KSNA **57** [generated from **56** with 2 eq. of n-buthyllithium (n-BuLi)] with alkyl halides as electrophiles followed by cyclization yields 3-alkylpyridine-2-thiones **58** (Scheme 8).[23]



Scheme 8

Addition of aryl isocyanates **9** to KSNA **7** and **8** at ambient temperature in ether gave 1:1 adducts **59** and **60**, which are allowed to react with alternative aryl isocyanate to yield uracil derivatives **61** and **62**, respectively (Scheme 9).[24]



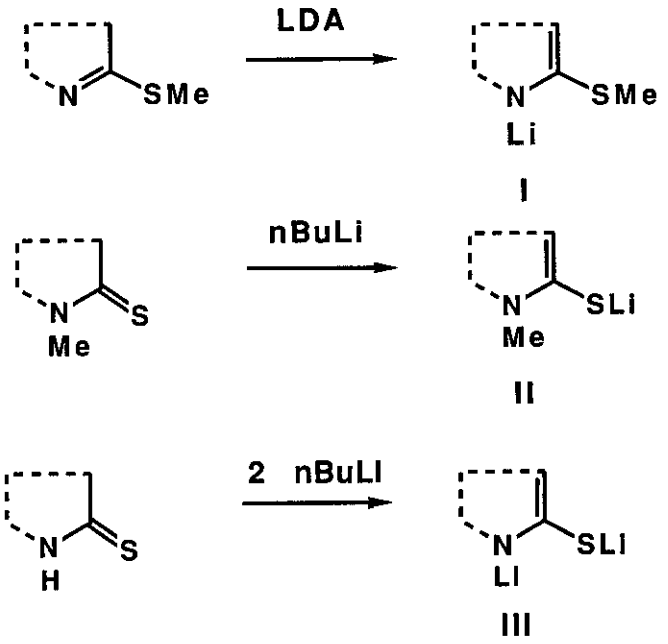
59 n=2
60 n=3

61 n=2
62 n=3

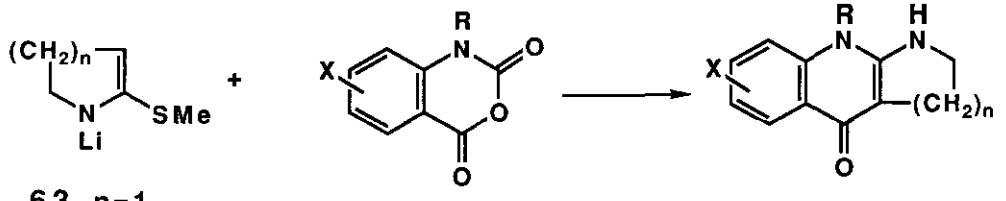
Scheme 9

3. SYNTHESIS OF HETEROCYCLES USING METALLOENAMINES

Three kinds of metallo-KSNA (I,II, and III) derived from thioamide groups belong to the interesting class of metalloenamines that react with many kinds of carbon electrophiles to form carbon-carbon bonds.



We embark on studies to apply the reaction employing metalloenamines to heterocyclic synthesis. Although metallo-KSNA derived from thioimidates may be regarded as interesting metalloenamines, their chemistry has scarcely been studied.[25] Metalloenamines **63-65**, generated from cyclic thioimidates by treatment with lithium diisopropylamide (LDA), react with N-alkylisatoic anhydrides to afford azacycloalka[2,3-b]quinolin-4-ones **66-68**, respectively (Scheme 10).[26]



63 n=1
64 n=2
65 n=3

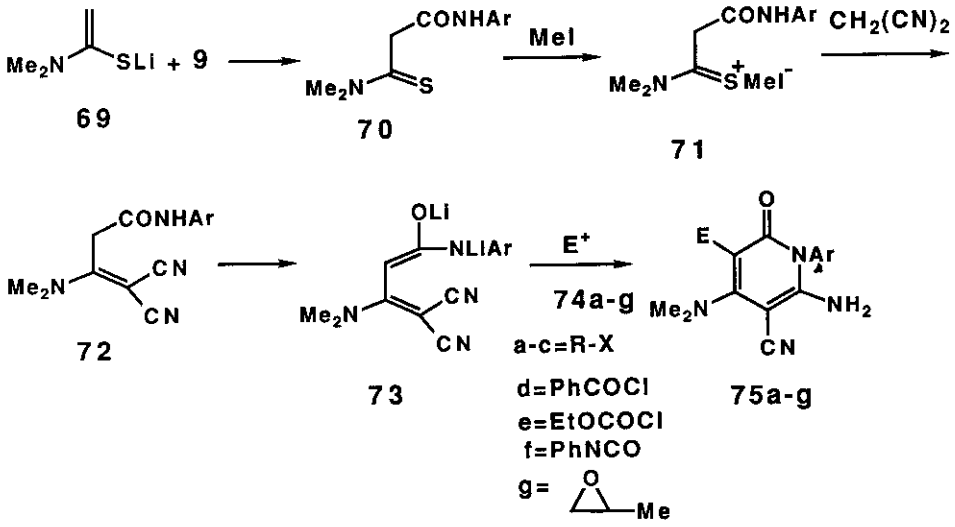
66 n=1
67 n=2
68 n=3

Scheme 10

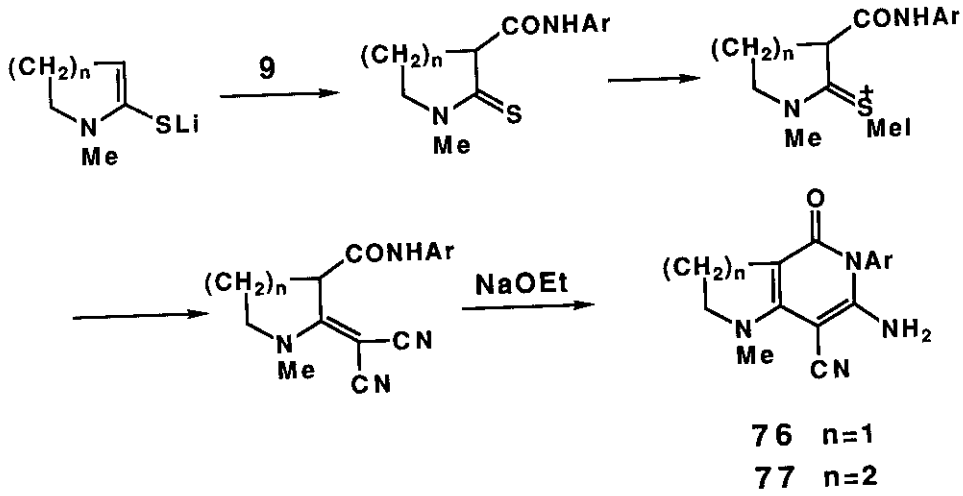
S-Lithio-KSNA **69**, generated from N,N-dimethylacetothioamide as tertiary thioamide with n-BuLi, reacts with aryl isocyanates **9** at -78°C to 0°C to afford the monothiodiamides **70**. Formation of thioiminium salts **71** with methyl iodide, followed by nucleophilic attack with malononitrile in the presence of 18-crown-6 as a catalyst and potassium fluoride as a base gives enaminonitriles **72**. The carbon-carbon bond-forming reaction of bislithioketene O,N-acetals **73**, generated from **72** with two equiv. n-BuLi, with a variety of electrophiles **74a-g** followed by cyclization with work-up yield multifunctionalized 2-pyridones **75a-g** (Scheme 11).[27] Reaction using **74g** is accelerated by the addition of boron trifluoride-ether.[28] Similarly, azacycloalka[3,2-c]pyridin-2-ones **76** and **77** are synthesized from N-methylthiolactames as shown in Scheme 12.[29]

Bis-Lithio-KSNA **78** and **79**, generated from secondary thiolactams by treatment of two equiv. n-BuLi (0°C), react with aryl isothiocyanates to afford the dithioamides **80** and **81**, respectively. Bismethylation of **80** and **81** with methyl iodide in the presence of potassium carbonate gives the dithioimidates **82** and **83** as 1,3-bis-electrophilic reagents, which are allowed to react with benzamidine as bis-nucleophile in the presence of sodium hydride to provide azacycloalka[2,3-

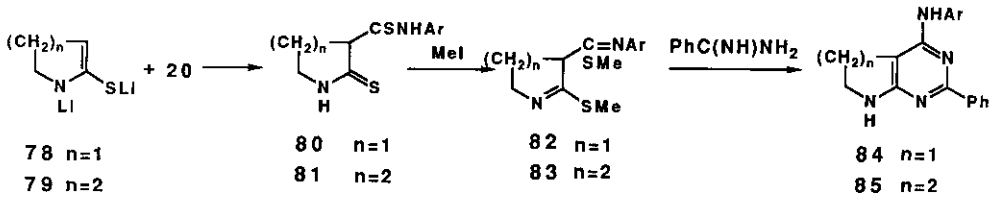
d]pyrimidines **84** and **85**, respectively (Scheme 13).[30]



Scheme 11



Scheme 12



78 n=1
79 n=2

80 n=1
81 n=2

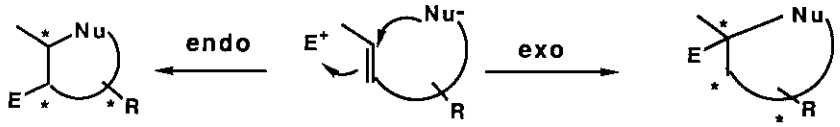
82 n=1
83 n=2

84 n=1
85 n=2

Scheme 13

4. ELECTROPHILIC OLEFIN HETEROCYCLIZATION

Electrophilic alkene cyclization processes that form carbon-heteroatom bonds are of growing importance, particularly in the regio- and stereoselective synthesis of heterocycles leading to bioactive natural products (Scheme 14).[31]

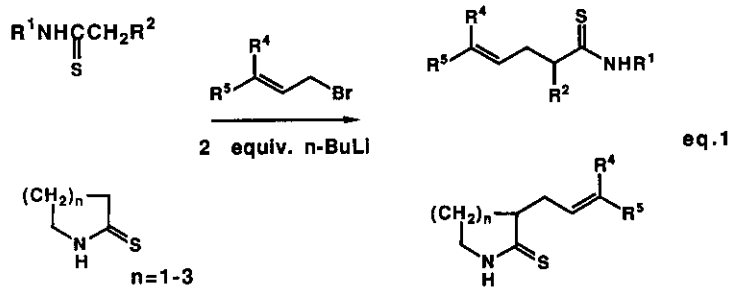


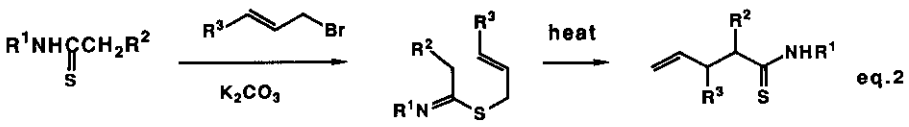
Nu=Heteroatom

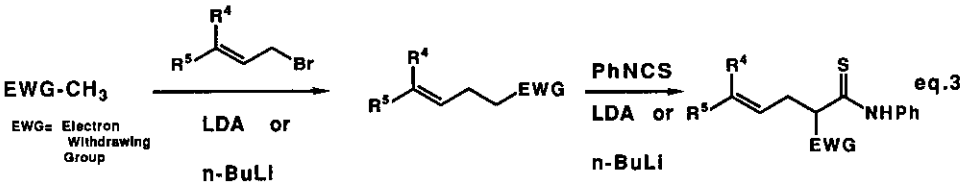
Scheme 14

Although halogenolactonization is a well-established important synthetic tool,[32] the analogous thiolactonization[33] and lactamization[34] have been less investigated. First we describe novel syntheses of 2-aminothiophenes via iodoiminothiolactonization of γ,δ-unsaturated secondary thioamides.[35] γ,δ-Unsaturated secondary thioamides are readily accessible by three procedures (1. allylation of dianions generated from secondary thioamides; 2. thio-Claisen rearrangement;[36] 3. allylation of active methyl groups followed by thioamidation with isothiocyanate) shown in Scheme 15. The γ,δ-unsaturated secondary thioamides **86a-y** with iodine in THF undergo iodoiminothiolactonization to give the iminothiolactones **87a-y**, which without isolation are converted by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the same flask into exo-olefins **88a-y**. N-Acetylation of **88a-y** with acetyl chloride in the presence of DBU as a base and 4-dimethylaminopyridine (DMAP) as a catalyst followed by spontaneous aromatization gave 2-aminothiophenes **89a-y** (Scheme 16). This iodine-induced cyclization proceeded regio- (5-exo-trigonal)[37] and chemo-selectively (sulfur-carbon bond

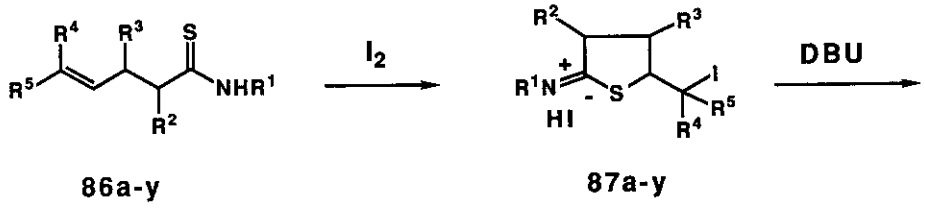
formation).



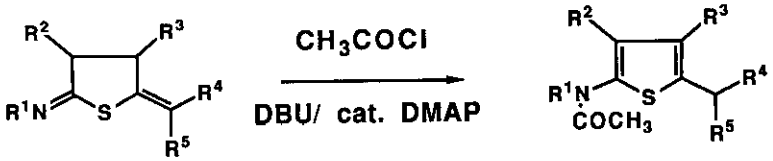




Scheme 15



86a-y 87a-y



88a-y 89a-y

Scheme 16

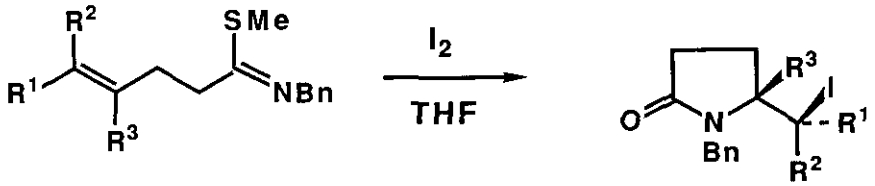
Table. Preparation of 2-Aminothiophenes 89a-y from γ,δ-Unsaturated Secondary Thioamides 86a-y

run	product	R^1	R^2	R^3	R^4	R^5	yield, %[a]	method[b]
1	**89a**	Bn	H	H	H	H	57	A
2	**89b**	Ph	H	H	H	H	53	A
3	**89c**	Bn	H	H	H	Me	25	A
4	**89d**	Bn	H	H	H	Ph	50	A
5	**89e**	Bn	H	H	Me	Me	47	A
6	**89f**	Ph	Me	H	H	H	23	A
6	**89g**	$-(CH_2)_3-$		H	H	H	36	A
7	**89h**	$-(CH_2)_3-$		H	H	Me	13	A
8	**89i**	$-(CH_2)_3-$		H	Me	Me	20	A
9	**89j**	$-(CH_2)_4-$		H	H	H	64	A
10	**89k**	$-(CH_2)_4-$		H	H	Me	54	A
11	**89l**	$-(CH_2)_4-$		H	Me	Me	85	A
12	**89m**	$-(CH_2)_5-$		H	H	H	83	A
13	**89n**	$-(CH_2)_5-$		H	H	Me	82	A
14	**89o**	$-(CH_2)_5-$		H	Me	Me	86	A
16	**89p**	Bn	cyclohexyl	H	H	H	25	B
17	**89q**	Bn	Ph	H	H	H	23	B
18	**89r**	Bn	H	Me	H	H	49	B
19	**89s**	Bn	Me	Me	H	H	37	B
20	**89t**	Bn	$PhSO_2$	Me	H	H	19	B
21	**89u**	Bn	Ph	Me	H	H	35	B
22	**89v**	Ph	$PhSO_2$	H	H	H	38	C
23	**89w**	Ph	$PhSO_2$	H	H	Me	35	C
24	**89x**	Ph	$PhSO_2$	H	Me	Me	18	C
25	**89y**	Ph	PhNHCO	H	H	H	12	C

a Overall yields of three-step sequences are shown.

b Procedures of preparation for **86a-y** (A=eq. 1), (B=eq. 2), and (C=eq. 3).

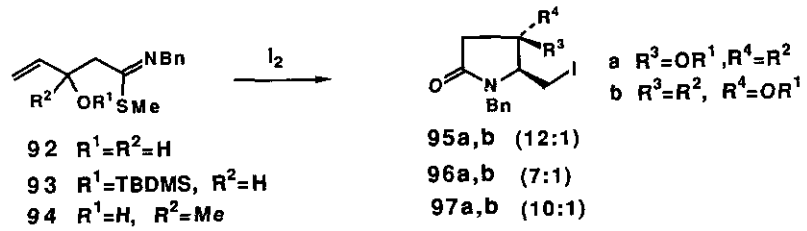
Iodine-induced cyclization of γ,δ-unsaturated thioimidates is performed.[38] γ,δ-Unsaturated thioimidates **90a-d** undergo regio- and diastereoselective iodine-induced cyclization to afford γ-lactams **91a-d** (Scheme 17).

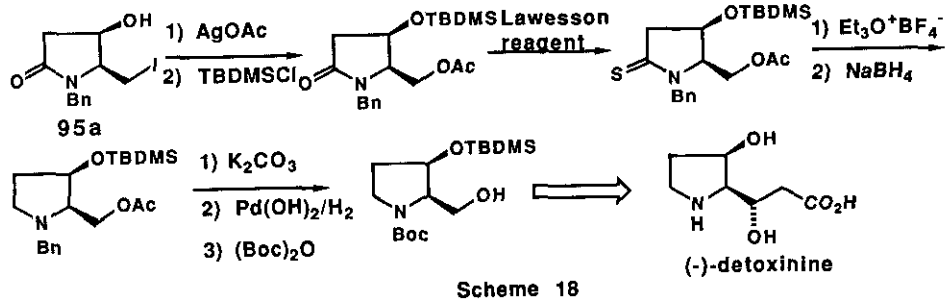


90a-d **91a-d**

Scheme 17

Iodolactamization of γ,δ-unsaturated β-hydroxythioimidates **92-94** is carried out to afford 4-hydroxy-γ-lactams **95a,b-97a,b**, respectively. It is predicted that the configuration of the major diasteromer **95a** would be 4,5-cis owing to the 1,2-cis directing ability of the iodonium ion and the hydroxy group in the transition state of this cyclization.[39] Its stereochemistry is determined by a stereocontrolled transformation of **95a** into the key intermediate to (-)-detoxinine (Scheme 18).[40]





Scheme 18

A high 1,3-trans selectivity in the iodolactamization of γ,δ-unsaturated α-

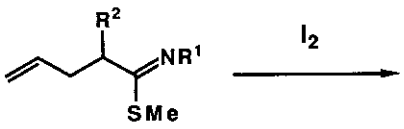
alkyl thioimidates **98-101** is observed. In view of the conformational flexibility of the five-membered ring transition state, the stereocontrol due to the homoallylic substituent is not expected to be high in contrast to the control shown by the allylic substituent. This interesting trans-stereoselectivity may be rationalized as follows. Among possible cyclic transition states, the most likely one, the 1,3-di-quasi-equatorial transition state **106b**, may be discounted owing to A(1,2) strain[41] between R^2 and the methylthio group. The strain forces the substituent R^2 to take a quasi-axial orientaion and hence the iodomethyl group a quasi-equatorial orientation as transition state **106a**. The structure of **102a** is confirmed by X-ray crystallographic analysis and **104a** is converted into the racemic intermediate to trans-4-cyclohexyl-L-proline,[42] which is a constituent of fosenopril (Andiotensin converting enzyme inhibitor) (Scheme 19).[43]

Next iodolactamization in δ,ε-unsaturated thioimidates is tried. Allylation of dianions of 3-benzenesulfonylpropionamides as homoenolates[44] give δ,ε-unsaturated secondary amides, which are transformed by successive desulfonylation, thionation, and methylation into the corresponding δ,ε-unsaturated thioimidates **107**. Iodolactamization of **107** proceeds regioselectively to provide δ-lactames **108** (Scheme 20).[45]

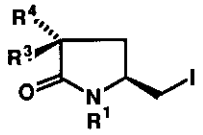
5. MISCELLANEOUS

Cyclic thioimidates are important building blocks for the synthesis of N-heterocycles such as alkaloids.[7] We are interested in exploring the utilization of cyclic thioimidates in a heterocyclic synthesis.[46] A common intermediate, the quinolizidine **109** obtained by annelation of a cyclic thioimidate with Nazarov's reagent[47] in the presence of mercuric chloride, is stereospecifically transformed into (±)-epilupinine and (±)-lupinine as shown in Scheme 21.[48] Stereospecific reduction of **109** with diisobutylaluminum hydride in the presence of triethylamine gives the trans-saturated β-ketoester, which is transformed by successive thioketalization, desulfurization, and reduction into (±)-epilupinine. Chemoselective thionation of **109** with Lawesson's reagent[49] provids the enaminothioketone, which is converted by desurfurization followed by stereospecific reduction with sodium borohydride into (±)-lupinine.

As azacycloalkanes such as pyrrolidines, piperidines, and perhydroazepines are

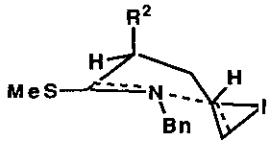


98 R^1=Ph, R^2=Me
99 R^1=Bn, R^2=Me
100 R^1=Bn, R^2=c.hexyl
101 R^1=Bn, R^2=Ph



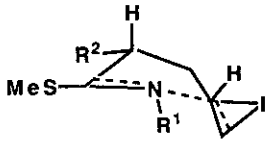
102a,b (6:1)
103a,b (12:1)
104a,b (13:1)
105a,b (14:1)

a R^3=H, R^4=R^2
b R^3=R^2, R^4=H



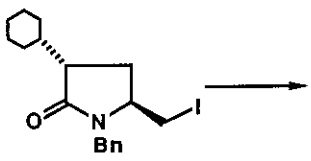
106a

102a-105a

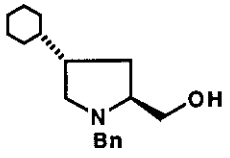


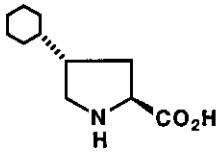
106b

102b-105b

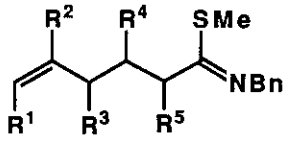


104a



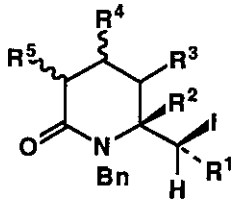


Scheme 19



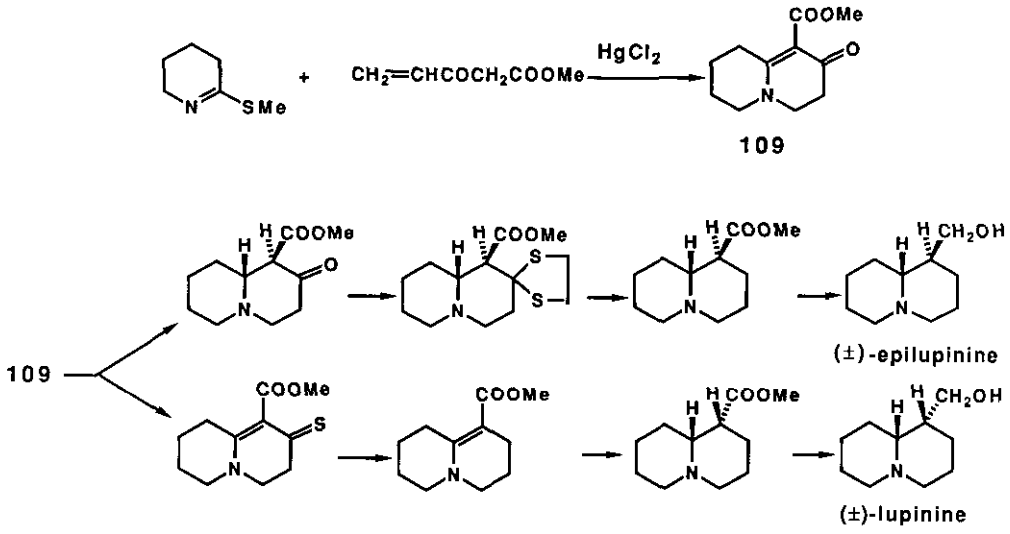
107

I_2



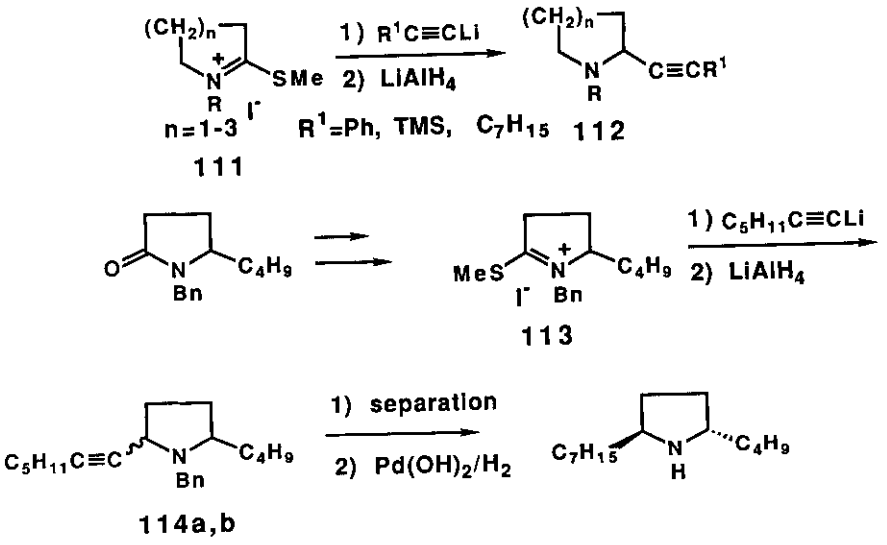
108

Scheme 20



Scheme 21

integral features of naturally occurring alkaloids, the development of functionalization methods for these ring systems is an important synthetic problem. One of the synthetic attempts in this direction has involved the nucleophilic addition of organometals to the carbonyl moiety of the corresponding lactams. Alkynyl azacycloalkanes **112** are synthesized by the addition reaction of lithium acetylides to S-methylamidinium salts **111** of thiolactams followed by a lithium aluminum hydride reduction of the adducts. This alkynylation is applied to a synthesis of trans-2-butyl-5-heptylpyrrolidine, a constituent of ant venom.[50] Thionation of 5-butylpyrrolidin-2-one prepared by our new method[51] followed by methylation yields amidinium salt **113**. Alkynylation of **113** with lithium heptylide followed by reduction gives a mixture of trans and cis compounds **114a,b**. After separation, **114a** (trans) undergoes both reduction and hydrogenolysis with palladium hydroxide to afford trans-2-butyl-5-heptylpyrrolidine (Scheme 22).[52]



Scheme 22

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