SYNTHESIS OF [2.2.3]CYCLAZINES, AZA[2.2.3]CYCLAZINES AND THEIR RELATED COMPOUNDS

Yoshinori Tominaga,* Yoshihide Shiroshita, and Akira Hosomi*
Faculty of Pharmaceutical Sciences, Nagasaki University,
1-14, Bunkyo-machi, Nagasaki 852, Japan

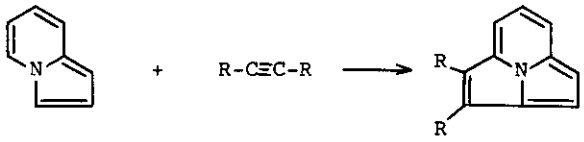
Abstract——Recent developments in the synthesis of [2.2.3]-cyclazines, benzo[g][2.2.3]cyclazines, benzo[a][2.2.3]cyclazines, dibenzo[a,h][2.2.3]cyclazines, dibenzo[a,g][2.2.3]-cyclazines, 1-aza[2.2.3]cyclazines, 5-aza[2.2.3]cyclazines, and 1-azabenzo[h][2.2.3]cyclazines by the [8 + 2] cycloaddition reaction of dimethyl acetylenedicarboxylate (DMAD) with the various type indolizines are summarized by major emphasis that is placed on the results obtained in our own laboratory. The synthesis of indolizines, imidazo[1,2-a]-pyridine, and their related compounds which are key intermediates for the synthesis of cyclazines is also described.

CONTENTS

1 INTRODUCTION

[2.2.3]Cyclazines, peripheral conjugate aromatic compounds with delocalized 10π electrons are interesting from both theoretical and practical standpoints. [1-4] Much attention has been recently directed to the synthesis and properties of a series of these derivatives, especially the parent one. When Beokelheide reported first the synthesis of [2.2.3]cyclazines in 1958, he coined the word "cyclazine" as a common name.[5] After that, the cyclazine refers to a fused planar conjugate ring system, a molecule with three rings, where the rings share a central nitrogen atom. According to the nomenclature of Chemical Abstracts, this is named as pyrrolo[2,1,5-cd]indolizine.

It has been known that the [8 + 2] cycloaddition reaction of indolizine derivatives with a suitable acetylenic compound is the most simple and general synthesis of [2.2.3]cyclazines.[1-4] However the synthesis of starting indolizines has not been always satisfactorily found.



In particular, in order to get a variety of functionalized [2.2.3]cyclazine derivatives, it is necessary to establish the convenient and effective synthetic method of the starting indolizine derivatives.[6,7] Introduction of functional groups onto the indolizine moiety in advance is most suitable for this purpose, since it is difficult to get the desired compounds by the regiospecific and electrophilic displacement reaction at cyclazine nucleus. However there are few

examples to investigate the cycloaddition reaction of indolizines bearing alkyl or aryl groups on the pyridine ring with acetylenic compounds, although numerous publications of the [8 + 2] cycloaddition reaction of indolizines with dienophiles have been appeared.[1-4] Polycyclic cyclazines,[8-11] especially, benzannelated cyclazines, were not so extensively studied before we had started the work. In this review article, one of the most useful and convenient synthetic methods of indolizine derivatives by use of ketene dithioacetals which are important for the starting compounds to cyclazines is described, and subsequent synthesis of the [2.2.3]cyclazines and benzannelated [2.2.3]cyclazines by the [8 + 2] cycloaddition reaction of the resulting indolizines with dimethyl acetylenedicarboxylate (DMAD) is reported along with the effect of benzannelation upon the physical properties.

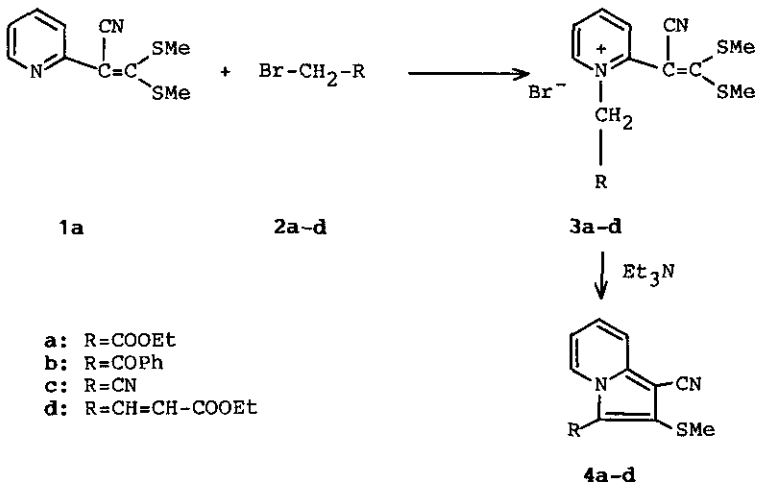
2 [2.2.3]CYCLAZINES

2.1 Synthesis of 2-methylthioindolizine-1-carbonitriles

3-Unsubstituted indolizine derivatives are key intermediates for the synthesis of [2.2.3]cyclazines.[1-4] At first, we attempted the preparation of 3-unsubstituted indolizines using the reaction of ketene dithioacetals, the valuable precursors to heterocyclic compounds.[6,11-17]

We have demonstrated that the reaction of active methylene compounds with carbon disulfide followed by methylation with alkyl reagents in the presence of a base gives the corresponding ketene dithioacetals.[6,11,12,14] 2-Cyano-3,3-bis(methylthio)-2-pyrid-2-ylacrylonitrile (**1a**) is prepared by the reaction of 2-pyridylacetonitrile with carbon disulfide in the presence of sodium hydride followed by methylation with dimethyl sulfate. This compound reveals high reactivity and reacts with amine or active methylene compounds to give the corresponding products replaced on the methylthio groups in good yields.[18]

When **1a** is allowed to react with ethyl bromoacetate (**2a**), followed by treatment with triethylamine or potassium carbonate, 3-ethoxycarbonyl-2-methylthioindolizine-1-carbonitrile (**4a**) is obtained in 85% yield.[19] Other indolizine derivatives (**4b-d**) are also prepared by the reaction of **1a** with bromomethyl compounds (**2b-d**) as shown in Scheme 1.[19] It is difficult to prepare indolizine derivatives substituted on the pyridine ring, because starting substituted 2-pyridylacetonitriles are inaccessible.

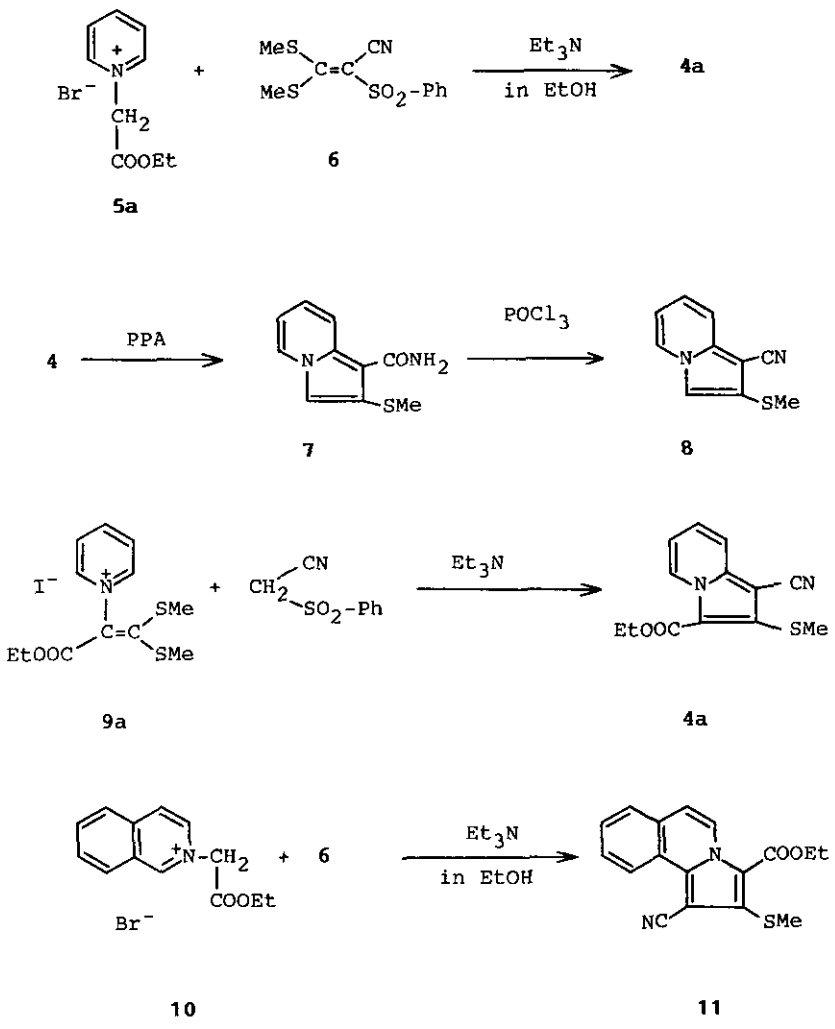


Scheme 1

The synthesis of indolizine derivatives by the 1,5-dipolar cyclization of pyridinium allylides, readily prepared by the reaction of pyridinium N-ylides with ethoxymethylene compounds, has been reported.[20-22] We now found that the preparation of indolizines was attained by a novel route using ketene dithioacetals. The reaction of sulfonyl ketene dithioacetal (**6**) with a pyridinium salt (**5a**) in the presence of triethylamine in ethanol gives the corresponding indolizine-1-carbonitriles (**4a**) which is also prepared by the reaction of pyridinium ketene dithioacetal (**9a**) with phenylsulfonylacetonitrile.[23] Thus sulfonyl ketene dithioacetal is also a useful electrophilic reagent for the synthesis of indolizine-1-carbonitriles.[23] The ester group in indolizines can be removed by treatment with polyphosphoric acid. This method is also applied for the preparation of pyrrolo[2,1-a]isoquinoline (**11**) from **10** (Scheme 2).[24]

2.2 Synthesis of 2-Methylthioindolizine-3-carbonitriles

A convenient and general method for preparing [2.2.3]cyclazines is the [8 + 2] cycloaddition reaction of 3-unsubstituted indolizines with suitable acetylenic compounds.[1-4] *It has recently been reported that the reaction of indolizines,* containing a leaving group in the 3-position, with dimethyl acetylenedicarboxy-



Scheme 2

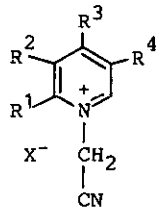
late (DMAD) gives the corresponding [2.2.3]cyclazine derivatives.[25, 26] Matsumoto et al. have reported that indolizine-3-carbonitrile derivatives are also useful starting materials for the synthesis of [2.2.3]cyclazine derivatives.[27] Indolizine-3-carbonitriles are prepared by cycloaddition-extrusion reactions of dicyanomethylides with phenyl vinyl sulfoxide[28] or 1,2-bis(trimethylsilyl)ethene.[29] However, 1,2-unsubstituted indolizine-3-carbonitriles are not so stable and turn dark brown on standing except derivatives bearing an electron-withdrawing group on the pyridine ring. Therefore, in an extension of the cycloaddition reaction on the studies of [2.2.3]cyclazines, appropriate 1,2-disubstituted indolizines whose substituents can be readily removed after the

cycloaddition reaction should be chosen. From this viewpoint, the methylthio and nitro group may be suitable as a leaving group after the cyclization reaction.

In this section, the synthesis of indolizine-3-carbonitrile derivatives by the reaction of N-cyanomethylpyridinium N-ylides (**11a-i**) with nitro ketene dithioacetal, 1,1-bis(methylthio)-2-nitroethene (**12**) will be described.[12] We reported the synthesis of ethyl indolizine-3-carboxylate, 3-aroylindolizines, and pyrazolo[1,5-a]pyridines by the 1,5-dipolar cyclization reaction of the corresponding pyridinium N-ylides or pyridinium N-imines with this ketene dithioacetal (**12**).[30-31] These procedures can be conveniently applied to the synthesis of indolizine-3-carbonitriles. The reaction of N-cyanomethylpyridinium chloride (**11a-i**) with **12** in the presence of triethylamine in ethanol gives 2-methylthioindolizines-3-carbonitrile (**13a-j**) and 2-methylthio-1-nitroindolizine-3-carbonitrile (**14a-k**) by the 1,5-cyclization reaction. The yields are shown in Scheme 3. These products, more stable than the corresponding 1,2-unsubstituted indolizine-3-carbonitrile, are readily separated by alumina column chromatography. This method is a facile synthesis of 8-alkylated indolizines and an example of the regiospecific 1,5-dipolar cyclization. Thus the reaction of pyridinium N-ylides bearing alkyl groups as well as the methyl group on the pyridine ring with **12** increases a ratio of the formation of 1-unsubstituted indolizine-3-carbonitriles (**13a-g**). When 4-benzyl or 4-phenyl pyridinium salts (**11f,g**) are allowed to react with **2** in the same condition, 1-nitroindolizine-3-carbonitriles (**14h,i**) are obtained in 29 and 33 % yields, respectively, along with **13h** and **13i** (45 and 61%). In the case of the reaction of 2-phenylpyridinium N-ylide (**11h**) with **12**, 3-methylthio-1-nitro-5-phenylindolizine (**14j**) is obtained as a major product in 41% yield. Yield of **13j** is 24%.

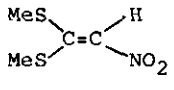
The reaction of **11i** bearing a N,N-diethylcarbamoyl group as the electron-withdrawing group with **12** in the same manner gives only 6-N,N-diethylaminocarbamoyl-2-methylthio-1-nitroindolizine-3-carbonitrile (**14k**) in 42% yield. In this case, the 1,5-dipolar cyclization reaction occurs only at the 5-position on pyridinium ring. This reaction is useful for the direct preparation of 1-nitroindolizines derivatives without nitration (Scheme 3).[33]

Desulfurization of **13a** with Raney-nickel in ethanol occurs smoothly to give a desired indolizine-3-carbonitrile (**15a**) in 77% yield.[29] 6,8-Dimethylindolizine-3-carbonitrile (**15b**) is also prepared from **13f** in good yield in a manner similar to that described for **15a** (Scheme 4).[29]



11a-i

a: $R^1=R^2=R^3=R^4=H$
b: $R^1=R^3=R^4=H$, $R^2=Me$
c: $R^1=R^3=R^4=H$, $R^2=Et$
d: $R^1=R^3=H$, $R^2=R^4=Me$
e: $R^1=R^2=R^4=H$, $R^3=Et$
f: $R^1=R^2=R^4=H$, $R^3=Bn$
g: $R^1=R^2=R^4=H$, $R^3=Ph$
h: $R^2=R^3=R^4=H$, $R^1=Ph$
i: $R^1=R^3=R^4=H$, $R^2=CONEt_2$



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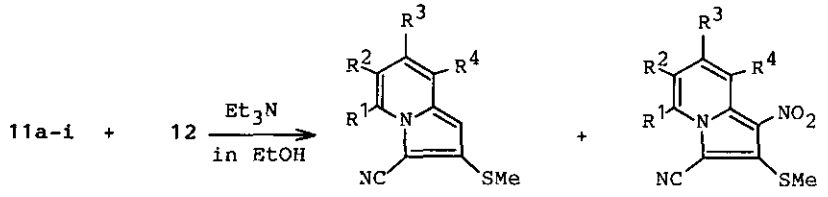
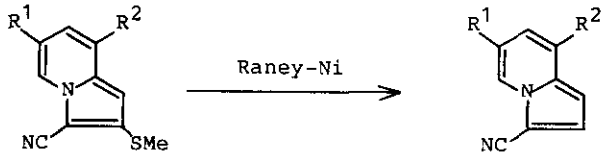


13a-k **14a-k**

No.	R^1	R^2	R^3	R^4	mp(°C)	Yield(%)[a]		No.	R^1	R^2	R^3	R^4	mp(°C)	Yield(%)[a]	
13a	H	H	H	H	41	43		**14a**	H	H	H	H	223	47	
b	H	Me	H	H	--	4	b)	**b**	H	Me	H	H	231	10	c)
c	H	H	H	Me	97	82		**c**	H	H	H	Me	---	--	
d	H	Et	H	H	--	3	b)	**d**	H	Et	H	H	205	14	c)
e	H	H	H	Et	67	64		**e**	H	H	H	Et	---	--	
f	H	Me	H	Me	105	90		**f**	H	Me	H	Me	162	4	
g	H	H	Et	H	36	24		**g**	H	H	Et	H	210	3	
h	H	H	Bn	H	95	45		**h**	H	H	Bn	H	189	29	
i	H	H	Ph	H	112	61		**i**	H	H	Ph	H	213	33	
j	Ph	H	H	H	135	24		**j**	Ph	H	H	H	208	41	
k	H	NEt	H	H	---	--	c)	**k**	H	NEt	H	H	136	42	

Me=methyl, Et=ethyl, Bn=benzyl, Ph=phenyl, NEt=N,N-diethylcarbamoyl
a)Isolated yield. b)Determined by NMR spectrum. c) Not detected in a reaction mixture.

Scheme 3



13a,f **15a,b**

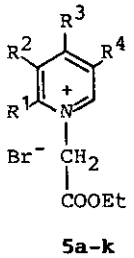
No.	R^1	R^2	mp(°C)	Yield(%)
15a:	H	H	48	77
b:	Me	Me	104	88

Scheme 4

2.3 Synthesis of 1,2,3-Unsubstituted Indolizines

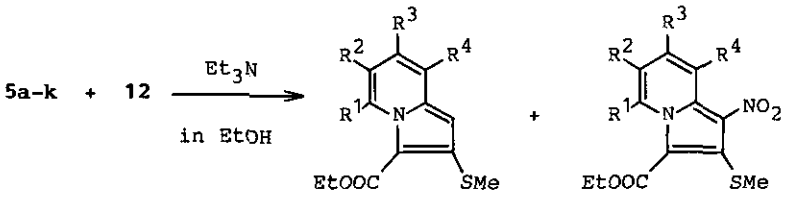
1,2,3-Unsubstituted indolizines are still now the most important key intermediates for the synthesis of [2.2.3]cyclazine.[1-4] At present the most general synthesis of indolizines is still conducted by the Tschitschibabin reaction because it can easily be modified for the synthesis of a variety of substituted indolizines.[7] However this method is inconvenient for the synthesis of 1,2,3-unsubstituted indolizines. We have solved this serious problem by use of ketene dithioacetals.

The reaction of 1-ethoxycarbonylmethylpyridinium bromide (**5a-k**) with **12** in the presence of triethylamine in ethanol gives the desired ethyl 2-methylthioindolizine-3-carboxylate (**16a-k**) in good yields, along with ethyl 2-methylthio-1-nitroindolizine-3-carboxylate (**17a-d**). The reaction of **5g**, bearing an electron-withdrawing carbamoyl group, with **12** under the similar conditions gives ethyl 6-carbamoyl-2-methylthio-1-nitroindolizine-3-carboxylate (**17b**) and ethyl 8-carbamoyl-2-methylthioindolizine-3-carboxylate (**16h**) in 73 and 8% yields, respectively. 3-N,N-Diethylcarbamoyl-1-ethoxycarbonylmethylpyridinium bromide (**5h**) reacts with **12** to give **16i** and **17c** in 4 and 45% yields, respectively. When 4-acetyl-1-ethoxycarbonylmethylpyridinium bromide (**5i**) reacts with **12** under the similar conditions, ethyl 7-acetyl-2-methylthio-1-nitroindolizine-3-carboxylate (**17d**) is obtained in only 21% yield. In these reactions, 1-nitroindolizine derivatives are obtained as major products (Scheme 5).[34]



5a-k

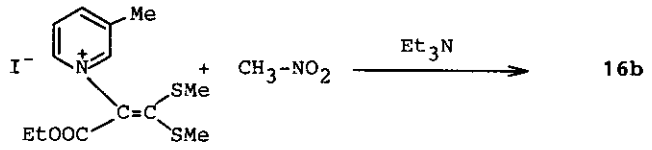
5a: $R^1=R^2=R^3=R^4=H$
b: $R^1=R^3=R^4=H$, $R^2=Me$
c: $R^1=R^3=R^4=H$, $R^2=Et$
d: $R^1=R^2=R^4=H$, $R^3=Et$
e: $R^1=R^2=R^4=H$, $R^3=Bn$
f: $R^1=R^3=H$, $R^2=R^4=Me$
g: $R^1=R^3=R^4=H$, $R^2=CONH_2$
h: $R^1=R^3=R^4=H$, $R^2=CONEt_2$
i: $R^1=R^2=R^4=H$, $R^3=COMe$
j: $R^1=R^2=R^4=H$, $R^3=Ph$
k: $R^2=R^3=R^4=H$, $R^1=Ph$



16a-k **17a-d**

No.	R^1	R^2	R^3	R^4	mp(°C)	Yield(%)
16a	H	H	H	H	46	93
b	H	H	H	Me	87	82
c	H	Me	H	H	38	5
d	H	H	H	Et	70	46
e	H	H	Et	H	58	28
f	H	H	Bn	H	75	48
g	H	Me	H	Me	97	84
h	H	H	H	Ca	238	8
i	H	NEt	H	H	111	4

No.	R^1	R^2	R^3	R^4	mp(°C)	Yield(%)
17a	H	H	H	H	105	5
b	H	Ca	H	H	222	73
c	H	NEt	H	H	111	45
d	H	H	Ac	H	159	21

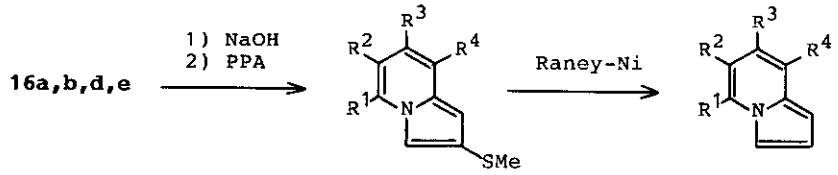


9b

Me=methyl, Et=ethyl, Bn=benzyl, Ph=phenyl, NEt=N,N-diethylcarbamoyl, Ca=carbamoyl, Ac=acetyl.

Scheme 5

Deesterification of **16a,b,d,e** using sodium hydroxide in methanol followed by treatment with polyphosphoric acid (PPA) gives the corresponding 2-methylthioindolizine (**18a-e**) in 93% yield. The desulfurization of **16a,b,e** with Raney-nickel in ethanol solution occurs smoothly to give the parent indolizine (**19a-c**) in good yields (Scheme 6).[34, 35]



18a-e 19a-c

No.	R^1	R^2	R^3	R^4	mp(°C)	Yield(%)
18a	H	H	H	H	67	92
b	H	H	H	Me	36	94
c	H	H	H	Et	oil	99
d	H	H	Bn	H	58	90
e	H	Me	H	Me	66	92

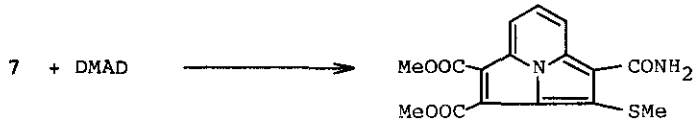
No.	R^1	R^2	R^3	R^4	mp(°C)	Yield(%)
19a	H	H	H	H	73	58
b	H	H	H	Me	oil	75
c	H	Me	H	Me	oil	90

Me=methyl, Et=ethyl, Bn=benzyl.

Scheme 6

2.4 Synthesis of Cycl[3.2.2]azine

We first found that the cycloaddition of indolizines bearing electron-withdrawing groups, e.g., cyano or carbamoyl group, with acetylenic compounds, namely, the reaction of 7 with DMAD giving the expected [2.2.3]cyclazine (**20**) in good yields.[19] Afterward it was reported that the [8 + 2] cycloaddition reaction of 2,3-unsubstituted indolizine-3-carbonitriles with DMAD occurs smoothly on heating in toluene to give the corresponding dimethyl [2.2.3]cyclazine-1,2-dicarboxylates in moderate yields.[27] 2-Methylthioindolizine-3-carbonitrile (**13a**) are also expected as a key intermediate for the synthesis of [2.2.3]cyclazine derivatives. The reaction of 2-methylthioindolizine-3-carbonitrile (**13a**) with DMAD in xylene gives a cyclized product, dimethyl 3-methylthio[2.2.3]cyclazine-1,2-dicarboxylate (**21a**) in 22% yield. In a similar manner, dimethyl 5,7-dimethyl-3-methylthio[2.2.3]cyclazine-1,2-dicarboxylate (**21b**) is obtained in 12% yield (Scheme 7).[34]



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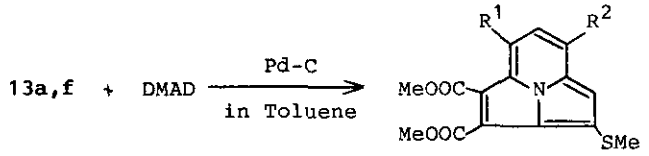


21a-b

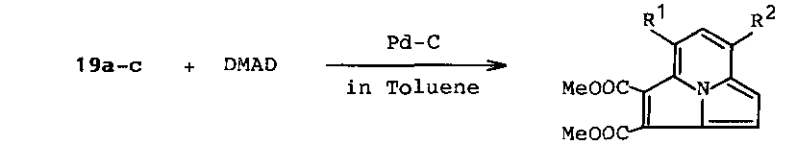
No.	R^1	R^2	mp(°C)	Yield(%)
21a	H	H	113	22
b	Me	Me	138	12

Scheme 7

In 1961, Boekelheide reported the synthesis of dimethyl [2.2.3]cyclazine-1,2-dicarboxylate (**21a**) from 1,3-unsubstituted indolizine (**19a**) with DMAD in good yield.[36] However alkyl- and aryl-substituted cyclazines on pyridine ring are not prepared because it is difficult to get starting alkylated indolizines.[37] 5,7-Dimethyl[2.2.3]cyclazine derivatives (**24b**) may be important precursor for

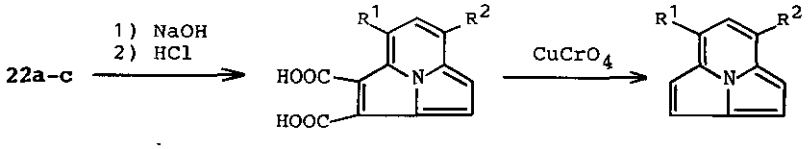
the synthesis of meta cyclophane derivatives containing cyclazine rings.[38] Therefore we attempted the synthesis of 5,7-dimethyl[2.2.3]cyclazine (**24b**). The reaction of 6,8-dimethylindolizine (**19c**) with DMAD in the presence of 5% palladium on charcoal in boiling toluene gives a desired cyclized product, dimethyl 5,7-dimethyl[2.2.3]cyclazine-1,2-dicarboxylate (**22c**) in 13% yield. 5-Methyl-[2.2.3]cyclazine-1,2-dicarboxylate (**22b**) is also prepared from **19b** in a manner similar to that described for **22c**.

Removal of the ester group of **22c** in general method as shown in Scheme 8 smoothly occurs to gives 5,7-dimethyl[2.2.3]cyclazine (**24b**) in good yield (Scheme 8).



22a-c

No.	R^1	R^2	mp(°C)	Yield(%)
22a	H	H	88	33
b	H	Me	93	34
c	Me	Me	60	25



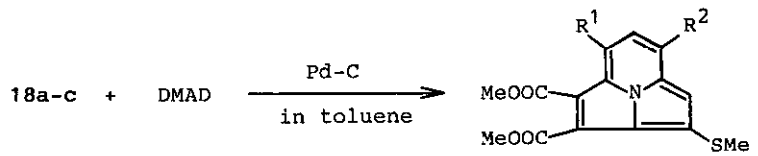
23a, b **24a, b**

No.	R^1	R^2	mp(°C)	Yield(%)
24a	H	H	64	30
b	Me	Me	48	27

Scheme 8

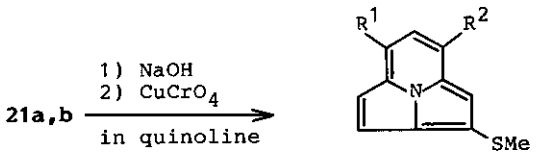
The [8 + 2] cycloaddition reaction of 2-methylthioindolizine (**18a**) with DMAD also proceeds smoothly to give the corresponding dimethyl 3-methylthio[2.2.3]-cyclazine-1,2-dicarboxylate (**21a**) in 38% yield. Dimethyl 5,7-dimethyl-3-methyl-

thio[2.2.3]cyclazine (**21b**) and dimethyl 7-methyl-3-methylthio[2.2.3]cyclazine (**21c**) are prepared in a manner similar to that described for **22a** in 49 and 40% yields, respectively. Hydrolysis of 21a,b using sodium hydroxide in methanol followed by acidification with 10% hydrogen chloride gives the corresponding diacid. Decarboxylation of the diacid with copper chromate is conducted in boiling quinoline to afford 2-methylthio[2.2.3]cyclazine (**25a,b**). The desulfurization of **25a,b** with Raney-nickel in ethanol occurs smoothly to give a desired parent [2.2.3]cyclazine (**24a**) in 25% yield (Scheme 9).[34]



21a-c

No.	R^1	R^2	mp(°C)	Yield(%)
21a	H	H	113	38
b	Me	Me	138	40
c	H	Me	131	49



25a,b

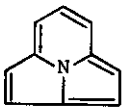
No.	R^1	R^2	mp(°C)	Yield(%)
25a	H	H	oil	56
b	Me	Me	oil	25

Scheme 9

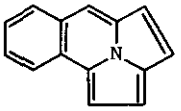
3 BENZO[g][2.2.3]CYCLAZINES

Considerable efforts have been recently devoted to investigate the effect of benzo-fusion on aromatic annulenes.[39-44] It is generally recognized that benzannelation reduces diatropicity of the macrocyclic system and this reason is explained by the increasing bond localization in the macrocyclic ring. There-

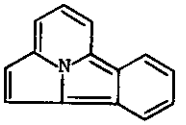
fore it seems worthwhile to prepare two possible benzo-fused [2.2.3]cyclazine isomers, benzo[g][2.2.3]cyclazine (**26**) and benzo[a][2.2.3]cyclazine (**27**) (Scheme 10).



24a



26

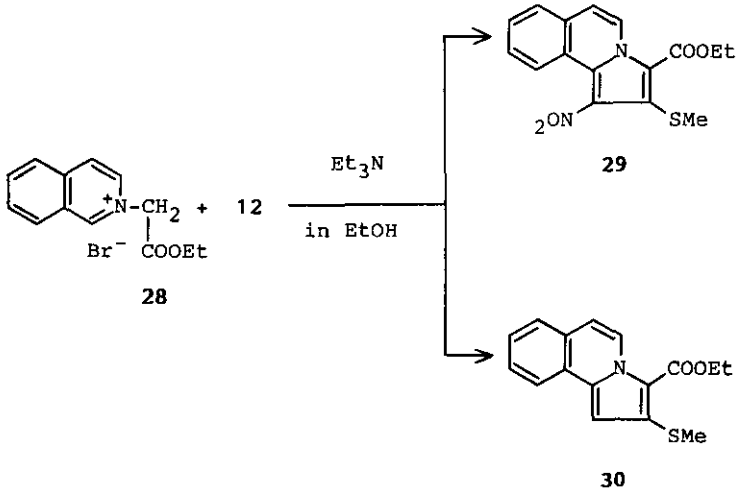


27

Scheme 10

3.1 Synthesis of Pyrrolo[2,1-a]isoquinolines

We have reported a facile synthesis of ethyl 1-cyano-2-methylthiopyrrolo- [2,1-a]isoquinoline-3-carboxylates by use of isoquinolinium N-ylides and sulfonyl ketene dithioacetals.[23] This method can be applied to the synthesis of parent pyrrolo[2,1-a]isoquinoline in a manner similar to that described for the synthesis of indolizine derivatives using nitro ketene dithioacetal.[12] At first, we attempted the reaction of 2-ethoxycarbonylmethylisoquinolinium bromide (**28**) with 1,1-bis(methylthio)-2-nitroethylene (**12**) in the presence of triethylamine in ethanol. However, unfortunately, this reaction gives a mixture of ethyl 2-methylthio-1-nitropyrrolo[2,1-a]isoquinoline-3-carboxylate (**29**) and ethyl 2-methylthiopyrrolo[2,1-a]isoquinoline-3-carboxylate (**30**) in a ratio of 1:1 in 94% yield (Scheme 11).[45]



28

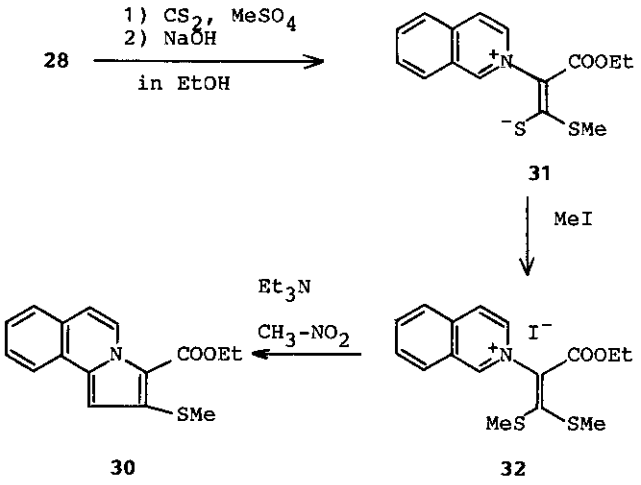
29

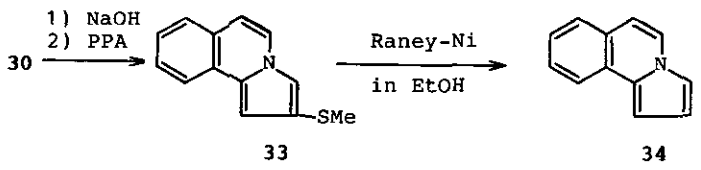
30

Scheme 11

It has been reported that pyridinium ketene dithioacetals react with active methylene compounds to yield the corresponding displacement product of the methylthio group of ketene dithioacetals in good yields.[31,46] We apply the above reaction to the synthesis of the parent pyrrolo[2,1-a]isoquinoline (**34**), otherwise inaccessible.[47] The starting isoquinolinium ketene dithioacetal, 2-[1-ethoxycarbonyl-2,2-bis(methylthio)vinyl]isoquinolinium iodide (**32**) is prepared as follows. An ethanol solution of sodium hydroxide is added portionwise to a solution of 2-ethoxycarbonylmethylisoquinolinium bromide (**28**), an excess of carbon disulfide, and dimethyl sulfate in ethanol at room temperature with stirring to afford the corresponding methyl dithiocarboxylate (**31**). The successive methylation of **31** with methyl iodide in ethanol gives the desired ketene dithioacetals (**32**) in 70% yield (from **28**).[48] The reaction of **32** with nitromethane in the presence of triethylamine in ethanol gives ethyl 2-methylthiopyrrolo[2,1-a]isoquinoline-3-carboxylate (**30**) in 56% yield. This method is much better than the reaction of **28** with **12**, since it is not necessary to separate **29** and **30**. Hydrolysis and subsequent decarboxylation of **30** occurs smoothly to give 2-methylthiopyrrolo[2,1-a]isoquinoline (**33**), a key intermediate for the synthesis of **40**, in 91% yield.

Desulfurization of **33** with Raney-nickel in ethanol gives a parent pyrrolo[2,1-a]isoquinoline (**34**)[47] in 88% yield. This solid compound (**34**) is not so stable and turned dark brown soon after isolation (Scheme 12).





Scheme 12

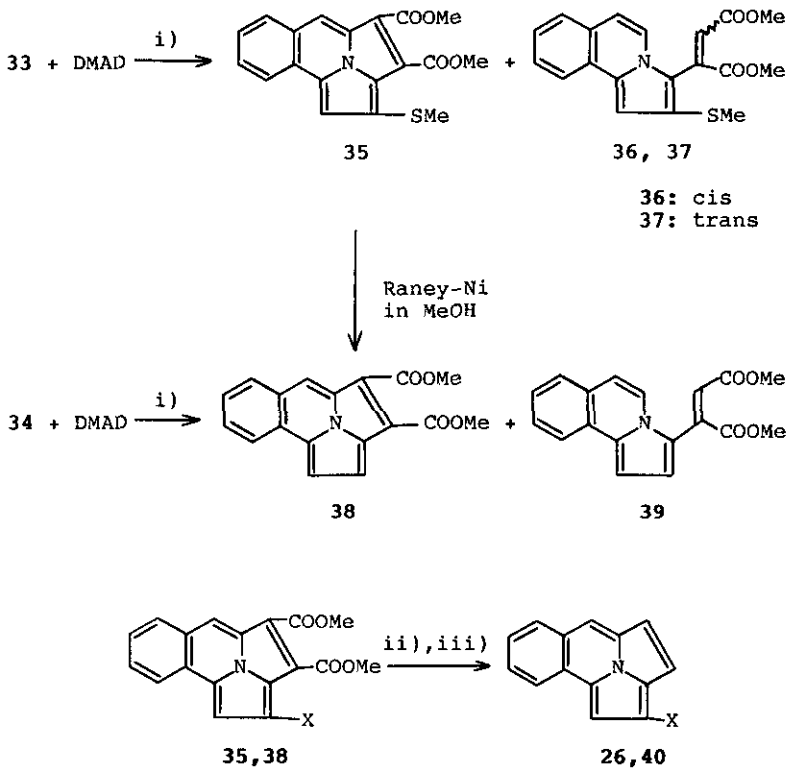
3.2 Synthesis of Benzo[g][2.2.3]cyclazine

The cycloaddition reaction of **33** with DMAD in the presence of 5% palladium on charcoal at reflux for 30 hours in toluene gives three products (**35-37**). Desulfurization of **35** with Raney-nickel occurs easily to give dimethyl benzo[g]-[2.2.3]cyclazine-3,4-dicarboxylate (**38**) in 44% yield. Hydrolysis of the diester (**38**) with 10% sodium hydroxide proceeds quantitatively to give the diacid. Finally, decarboxylation of the diacid by use of copper chromate in quinoline proceeds smoothly to give the desired benzo[g][2.2.3]cyclazine (**26**). The overall yield of **26** is 22% from **38**. Alternatively **38** is obtained from the parent pyrrolo[2,1-a]isoquinoline (**34**) by the reaction with DMAD in 33% yield, together with the Michael addition product (**39**) in 11% yield. 2-Methylthiobenzo[2.2.3]-cyclazine (**40**) is also prepared from **35** in 27% yield in a manner similar to that described for the synthesis of **26** (Scheme 12).[49]

The benzocyclazine (**26**) has a sweet odor like naphthalene and analytically pure sample was obtained as a stable crystalline solid of bright yellow leaflets (mp 141°) after recrystallization from methanol. In the ^{1}H-NMR spectrum the chemical shifts are shown in the range of δ 7.37-8.23 ppm for the peripheral protons of the cyclazine ring and 7.62-8.67 ppm for the benzene ring protons. Thus owing to the benzo-fusion, the peripheral protons displayed downfield shift relative to those of the [2.2.3]cyclazine (**24a**),[5] implying no reduction of the ring current.

4 BENZO[a][2.2.3]CYCLAZINES

In an extension of the previous work, we were successful in the synthesis of benzo[a][2.2.3]cyclazine(**27**).[50] The Wittig reaction of **42**, which is prepared



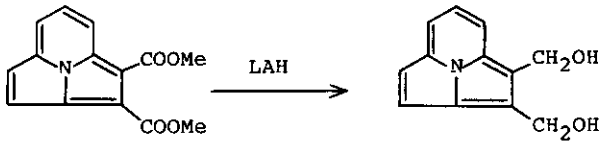
No.	X	mp(°C)	Yield(%)
40:	SMe	89	22(from **24**)
26:	H	141	27(from **27**)

i) Pd-C in toluene. ii) NaOH and then HCl.
iii) $CuCrO_4$ in quinoline.

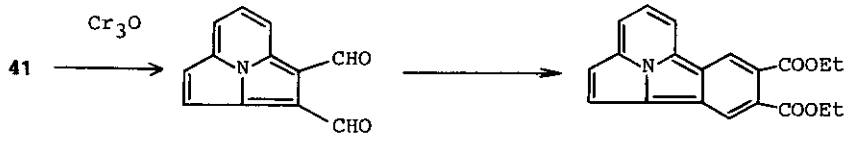
Scheme 13

by reduction of 22a with lithium aluminium hydride followed by oxidation with chrominium oxide-pyridine complex, with diethyl (diethylphosphinyl)succinate gives diethyl benzo[a][2.2.3]cyclazine-7,8-dicarboxylate (**43**) in poor yield (Scheme 14). So we attempted another synthesis of 27.

The [12 + 2] cycloaddition reaction of **44** with DMAD at reflux for 20 hours in toluene gives the expected dimethyl benzo[a][2.2.3]cyclazine-1,2-dicarboxylate (**45**) in 54% yield. Parent benzo[a][2.2.3]cyclazine (**27**) is prepared from **45** in a manner similar to that described for **26** in 49% yield (Scheme 15).[50]

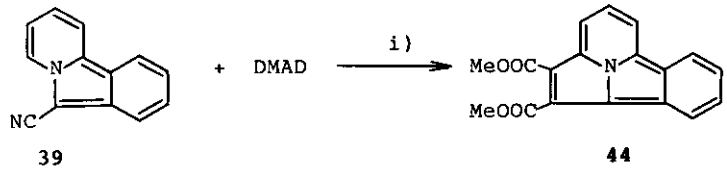


22a 41

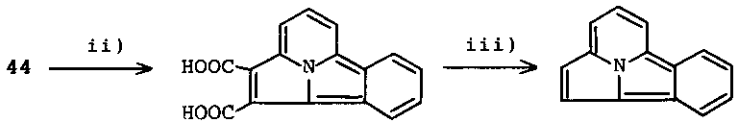


42 43

Scheme 14



39 44



45 27

No.	mp(°C)	Yield(%)
44	176	54
27	75	49

i) Reflux in toluene.
ii) NaOH and then HCl. iii) $CuCrO_4$ in quinoline.

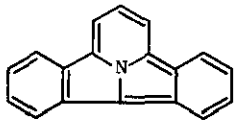
Scheme 15

The benzocyclazine (27) which had a sweet odor like **24a** and is a stable bright yellow leaflets, mp 75°C, was obtained by the recrystallization from methanol. The complex of this compound with 2,4,7-trinitro-9-fluorenone gave dark brown

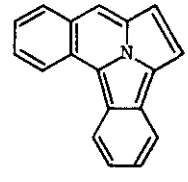
needles, mp 218°C. The major bands of **27** at λ max 260, 315, and 430 nm in the UV spectrum are bathochromically shifted from those of the parent **24a** at λ max 255, 308, and 390 nm, respectively. This may be consistent with the longer conjugated aromatic system in **27**. In **27**, a proton resonates at δ 7.17 ppm (J=3.7 Hz) which shows more upfield shift than that of the parent compound (**34a**) (7.40 ppm). The coupling constant of this proton with 1-position is recognized as a typical aromatic nature, and is smaller than that of benzo-[g][2.2.3]cyclazine (**27**).

5 DIBENZO[a,h]- AND DIBENZO[a,g][2.2.3]CYCLAZINES

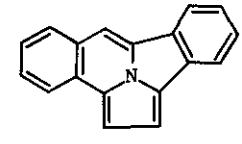
In the previous chapter, we described the synthesis and some physical properties of the monobenzo-annelated [2.2.3]cyclazines on the [a]- and [g]-ring, and their related compounds. Recently Mitchell and co-workers showed that the bond localization was caused by the fusion of benzene ring or other aromatic rings in the studies of benzannelated dihydropyrenes.[40-44] In these studies, they have also reported that the transoid fusion of the benzene rings perturbs slightly the diatropicity in the annulenes, whereas the cisoid fusion brings about strongly the bond localization on the macrocyclic annulene ring of dibenzo-annelated pyrene. Matsumoto and his co-workers have already reported the synthesis of a dibenzo-annelated [2.2.3]cyclazine (**46**) which is symmetrical, and also showed that **46** is viewed as the 18π-peripheral conjugate system in spite of expected large resonance stabilization owing to the benzene nucleus.[51, 52] In an extension of the studies on [2.2.3]cyclazine, we describe the synthesis of the dibenzo-annelated [2.2.3]cyclazine (**47**) which displays the largest bathochromic shift, comparing with other mono- and dibenzo-cyclazine and the parent [2.2.3]cyclazine (**24a**).



46



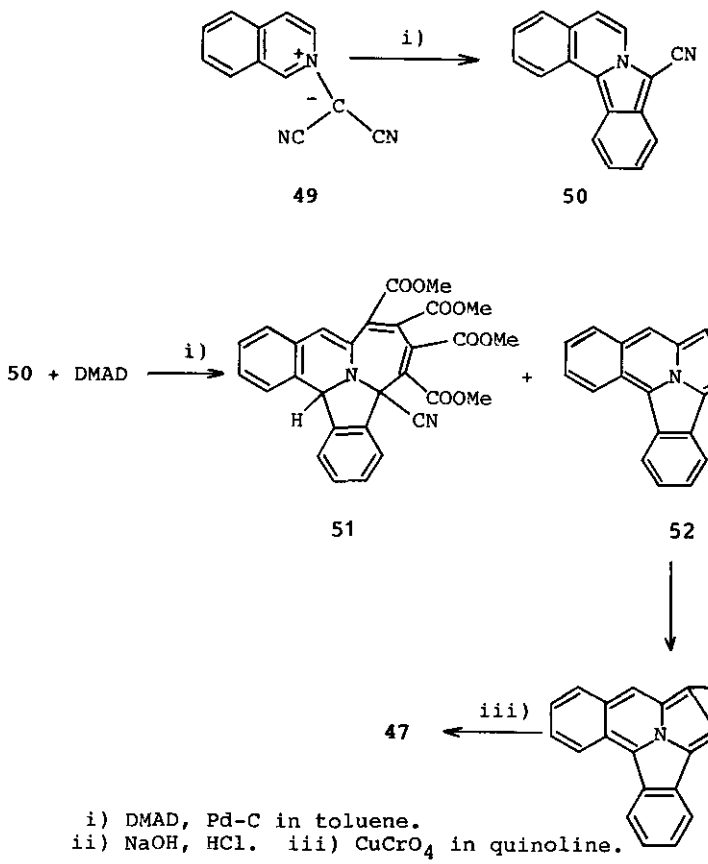
47



48

Scheme 16

The reaction of isoquinolinium dicyanomethylide (**49**), readily prepared from isoquinoline and tetracyanoethylene oxide,[53] with benzyne generated from anthranilic acid and isoamylnitrite gave 1-cyanoisoindolo[2,1-a]isoquinoline (**50**), mp 168°C, in 74% yield. Compound (**50**) was allowed to react with DMAD in the presence of a small amount of acetic acid at reflux for 20 hours in toluene to give the desired product, dimethyl dibenzo[a,h][2.2.3]cyclazine-1,2-dicarboxylate (**52**), mp 185°C, in 26% yield, along with dibenzo[f,i]cycl[4.3.2]azine derivative (**51**), mp 182°C, in 6% yield. The addition of a small amount of acetic acid was important for the improvement of the yield of **52**, though the yield was only 1% without acetic acid. The desired dibenzo[a,h][2.2.3]cyclazine (**34**) is synthesized from **52** in a manner similar to that described for **27** (Scheme 17).[54]

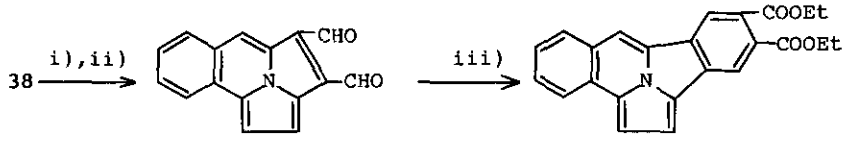


No.	mp(°C)	Yield(%)
47	139	32
51	182	6
52	185	26

Scheme 17

Dibenzo[a,h][2.2.3]cyclazine (**47**) is orange red needles. Its structure was confirmed by elemental analysis and by various spectroscopic data. The complex of this compound with 2,4,7-trinitro-9-fluorenone gives dark brown needles, mp 205°C. In its UV spectrum shown in Fig. 1, **47** shows much more bathochromic shift than absorption maxima of monobenzo-annelated [2.2.3]cyclazines (**26** and **27**) and the remarkable red shift in comparison with the parent [2.2.3]cyclazine (**24a**), respectively, consistent with the enlargement of the conjugation in poly-aromatic system in the former. The behaviors in the aromatic proton chemical shift (7.44-9.06 ppm) of **47** are similar to those of **46** (7.43-9.07 ppm). The vicinal coupling constant for C1-H and C2-H (7.44, 8.06 ppm, $J_{1,2}$=4.57 Hz) is similar to the corresponding value of [2.2.3]cyclazine (**24a**) ($J_{1,2}$=4.4 Hz). However this coupling constant is smaller than that of the corresponding C1-H and C2-H in **26** ($J_{1,2}$=4.9 Hz) and larger than that of C1-H and C2-H in **27** ($J_{1,2}$=3.7 Hz).

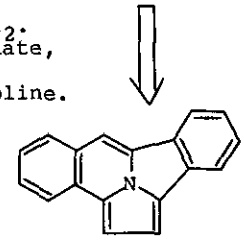
Next, we attempted the synthesis of another dibenzo-annelated [2.2.3]cyclazine, dibenzo[a,g][2.2.3]cyclazine (**48**).[55] The Wittig reaction of compounds (**54**), which is prepared by the reaction of **38** with lithium aluminium hydride followed by oxidation with chrominium oxide-pyridine complex, with diethyl (diethoxyphosphinyl)succinate gave diethyl dibenzo[a,g][2.2.3]cyclazine-4,5-dicarboxylate (**55**). Decarboxylation of 55 may give the corresponding parent dibenzo[a,g]-[2.2.3]cyclazine (**48**) (Scheme 18).



54

55
mp 123°C
Yield 3%(from 38)

i) $LiAlH_4$ in THF.
ii) Chrominium oxide-pyridine in CH_2Cl_2.
iii) Diethyl (diethoxyphosphinyl)succinate, NaH in dimethoxyethane.
iv) NaOH and then HCl, $CuCrO_4$ in quinoline.



48

Scheme 18

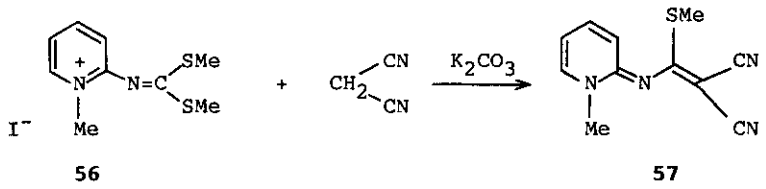
In conclusion, dibenzo-annelation in the pentacyclic compound (**47**) does not cause the expected decrease of diatropicity as evidences by the chemical shift of the peripheral protons in the ^{1}H-NMR spectrum. Although the reduction of diatropicity in the dibenzo-fused [2.2.3]cyclazine is not obvious. Compounds (**47**) and (**48**) exhibit significant 14π or 18π peripheral conjugation.

6 AZA[2.2.3]CYCLAZINES

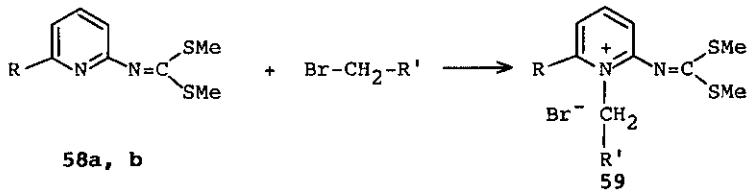
Aza[2.2.3]cyclazine is an aromatic compound involving delocalized 10π-electrons similarly to [2.2.3]cyclazines.[1-4,56] Synthesis of [2.2.3]cyclazines by the [8 + 2] cycloaddition reaction of indolizines with various acetylenic compounds is useful as a particularly convenient and general method, since it has been disclosed that DMAD reacts with indolizines in the presence of dehydrogenating reagents to give [2.2.3]cyclazine derivatives. Some aza[2.2.3]cyclazine derivatives are also prepared by the [8 + 2] cycloaddition reaction.[57-61] However, the reaction of DMAD with azaindolizines, which are not substituted on the five-membered ring, does not give the desired cyclazine derivatives. This point is a drawback of the above reaction. Therefore, in an extension of the cycloaddition reaction as shown above, we have planned the synthesis of appropriate 2-substituted imidazo[1,2-a]pyridine derivatives whose substituent may be removable after the cycloaddition reaction.

6.1 Synthesis of Imidazo[1,2-a]pyridines

It has been reported that the reaction of 1-[N,N-bis(methylthio)methyleneamino]-1-methylpyridinium iodide (**56**) with the active methylene compounds to give the displacement products (**57**) of methylthio group in good yields.[62] This method is applicable to prepare imidazo[1,2-a]pyridine derivatives by the intramolecular 1,5-dipolar cyclization of **59** with α-bromomethyl compounds. Heating a mixture of **58** and α-bromomethyl ketones and acetates at 100°C, followed by treatment of triethylamine gives the corresponding 2-methylthioimidazo[1,2-a]pyridines (**60a-g**) in good yields. This method is the most useful and convenient preparation of 5-methylimidazo[1,2-a]pyridine which is important key intermediate for the azacyclazine derivatives. Indeed, Kurata has succeeded in the synthesis of 3-azacycl[3.3.2]azin-4-one derivatives using ethyl 5-methyl-2-methylthioimidazo[1,2-a]pyridine (Scheme 19).[19,63]



56 57

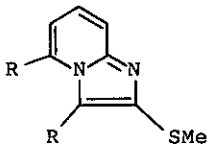


58a, b

a: R=H

b: R=Me

59



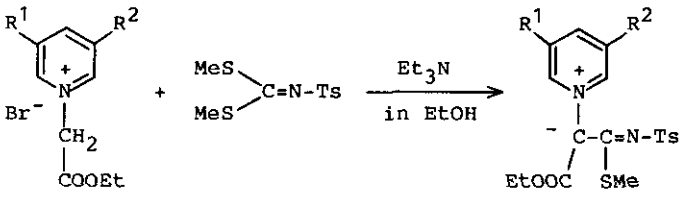
60a-g

	R	R	mp(°C)	Yield(%)
60a:	H	COOEt	139	80
b:	H	COMe	140	85
c:	H	COPh	139	75
d:	H	CH=CH-COOEt	145	75
e:	Me	COOEt	80	85
f:	Me	COPh	107	80
g:	Me	CH=CH-COOEt	141	75

Scheme 19

Next, we attempted an alternative synthesis of imidazo[1,2-a]pyridine derivatives. N-Bis(methylthio)methyleneamide derivatives.[64-81] are important and versatile reagents which have been extensively utilized in the synthesis of biological active heterocyclic compounds. Among those compounds, N-bis(methylthio)methylene-p-toluenesulfonamide (**61**)[55,64] is an extremely interesting electrophilic reagent for the introduction of not only an amino methylene group into amines and active methylene compounds but also a C=N fragment in the synthesis of heterocyclic compounds. We describe here a new synthesis of imidazo[1,2-a]pyridines by the 1,5-dipolar cyclization reaction of pyridinium N-ylides using **61**. Compound (**61**) is prepared by the condensation of p-toluenesulfonamide with carbon disulfide in dimethylsulfoxide (DMSO) in the presence of sodium hydroxide and by the successive treatment of the intermediate with dimethyl sulfate. Then

1-ethoxycarbonyl-2-methylthio-1-(1-pyridinio)-2-(N-p-toluenesulfonylimino)-ethylides (**62a-e**), key intermediates for the synthesis of imidazo[1,2-a]pyridines (**60**), are readily obtained by treatment of N-ethoxycarbonylmethylpyridinium bromides (**5a,b,f,g,l**) with **61** in boiling ethanol in the presence of triethylamine in good yields, except for the case of **62d** (Scheme 20).[82]



5a,b,f,g,l **61**

No.	R^1	R^2
5a:	H	H
b:	Me	H
f:	Me	Me
g:	Ca	H
l:	Am	H

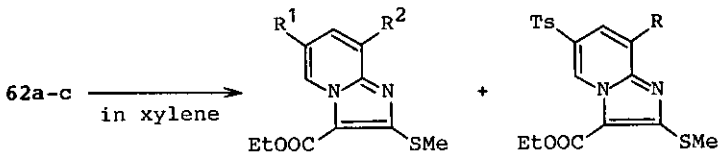
62a-e

No.	R^1	R^2	mp(°C)	Yield(%)
62a:	H	H	213	92
b:	Me	H	218	79
c:	Me	Me	192	80
d:	Ca	H	198	5
e:	Am	H	237	49

Am=Amine, Ca=Carbamoyl, Et=Ethyl, Me=Methyl,
Ts=p-Toluenesulfonyl

Scheme 20

Pyridinium N-ylides (**62a-c**) are refluxed in xylene for 30 hours to give two intramolecular cyclization products, ethyl 2-methylthioimidazo[1,2-a]pyridine-3-carboxylate (**60a, h-j**) and ethyl 2-methylthio-6-p-toluenesulfonylimidazo[1,2-a]-pyridine-3-carboxylate (**63a,b**). The formation of **60a** may be explained by the 1,5-dipolar cyclization of **62a** followed by the elimination of p-toluenesulfinic acid as illustrated in Scheme 22. It seems to be reasonable that the initially formed intermediate (**A**) by the 1,5-dipolar cyclization undergoes successively 1,5-sigmatropic shift of a hydrogen atom, then that of a tosyl group and finally the elimination of hydrogen to give **63a** (Scheme 22). However, when the reaction is carried out in DMSO instead of xylene, **60a** is obtained in 35% yield. The tosylated product **63a** is not detected in these reactions. Reaction of **62b** in DMSO gives **60h** and **60j** in 31 and 16% yields, respectively (Scheme 21).[82]
Kakehi and co-workers have reported that thermolysis of N-imidoyliminopyridinium ylides gives 1,2,4-triazolo[1,5-a]pyridines by a similar 1,5-cyclization followed by the elimination of ethyl formate as illustrated in Scheme 23.[83]



60a,h-j **63a,b**

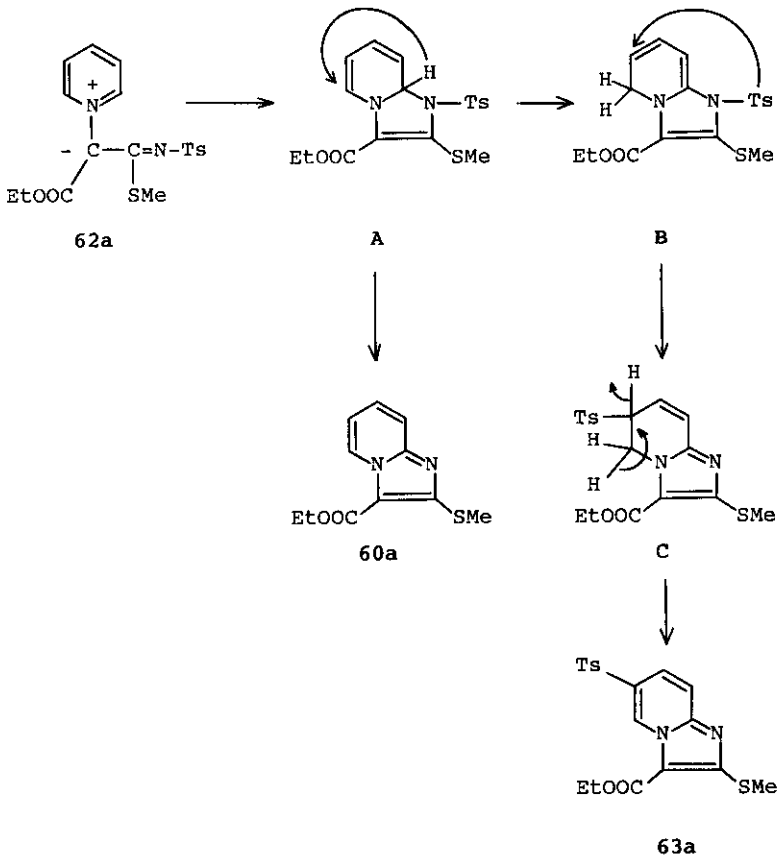
No.	R^1	R^2	mp(°C)
60a:	H	H	133
h:	H	Me	88
i:	Me	H	113
j:	Me	Me	105

NO.	R	mp(°C)
63a:	H	168
b:	Me	166

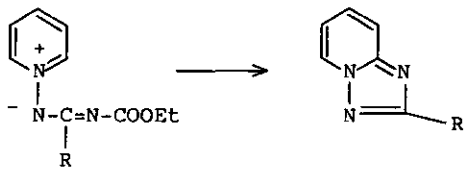
Et=ethyl, Me=methyl, Ts=p-toluenesulfonyl

Scheme 21

Reaction Mechanism



Scheme 22



Et=ethyl

Scheme 23

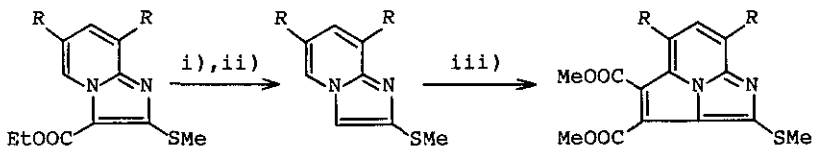
The advantage of the present method are the ready availability of starting materials and the easy preparation of polyfunctionalized imidazo[1,2-a]pyridines, although yields are not necessarily so good as compared with the Tschitschibabin type reaction. Thus, this procedure appears to have considerable promise as the preparative method of fused imidazole derivatives, and these products can be used as key intermediates for further conversion to 1-aza[2.2.3]cyclazine derivatives.

6.2 Synthesis of 1-Aza[2.2.3]cyclazines

Deesterification of **60a,j** using sodium hydroxide in methanol followed by treatment with polyphosphoric acid (PPA) gives the corresponding 2-methylthioimidazo[1,2-a]pyridine (**64a,b**) in good yields. The reaction of **64a,b** with DMAD in boiling toluene in the presence of palladium on charcoal gives a cyclized product, dimethyl 2-methylthio-1-aza[2.2.3]cyclazine-3,4-dicarboxylate (**65a,b**), in 36 and 40% yields, respectively. Hydrolysis of **65a,b** using sodium hydroxide in methanol followed by acidification with 10% hydrogen chloride gives the corresponding diacid. Decarboxylation of the diacid is conducted by copper chromate in boiling diphenyl ether (ca. 200°C) to afford 2-methylthio-1-aza[2.2.3]-cyclazine (**66a,b**) in 42 and 44% yields, respectively. The desulfurization of **66a,b** with Raney-nickel in ethanol solution occurs smoothly to give a desired parent 1-aza[2.2.3]cyclazine (**67a,b**) in 34 and 85% yields, respectively (Scheme 24).[84]

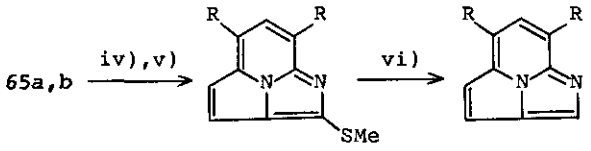
6.3 Synthesis of 5-Aza[2.2.3]cyclazines

5-Aza[2.2.3]cyclazine derivatives are also first prepared by the [8 + 2] cycloaddition reaction of 7-methyl-2-phenylpyrrolo[1,2-c]pyrimidine (7-methyl-2-



60a,j **64a,b** **65a,b**

No.	R	No.	R	mp(°C)	Yield(%)	No.	R	mp(°C)	Yield(%)
60a:	H	64a:	H	oil	92	65a:	H	133	36
j:	Me	b:	Me	oil	91	b:	Me	147	40



66a,b **67a,b**

No.	R	mp(°C)	Yield(%)	No.	R	mp(°C)	Yield(%)
66a:	H	oil	42	67a:	H	oil	34
b:	Me	47	44	b:	Me	106	85

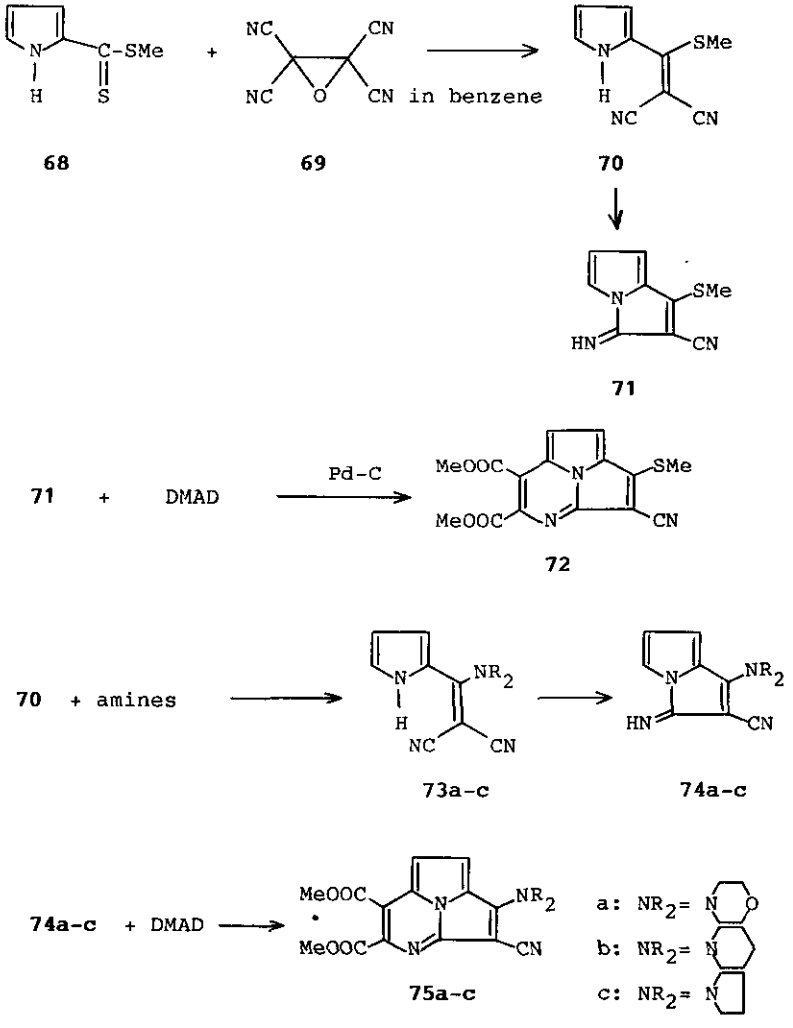
Et=ethyl, Me=methyl
i) NaOH. ii) PPA. iii) DMAD, Pd-C in toluene. iv) NaOH and then HCl. v) $CuCrO_4$ in diphenyl ether.
vi) Raney-Ni in ethanol.

Scheme 24

phenyl-5-azaindolizines) with DMAD in the presence of Pd-C. 5-Aza[2.2.3]cyclazines contain a phenyl and a methyl group in the 6- and 2-positions, respectively, have been synthesized but the parent compound is unknown.[85,86] Jessep *and Leaver have reported the interesting a unique [8 + 2] cycloaddition* reaction of 3-dimethylaminomethylene-3H-pyrrolizine bearing exo methylene group with DMAD to give dimethyl [2.2.3]cyclazine-5,6-dicarboxylate.[87] Therefore we attempted a novel synthesis of 5-aza[2.2.3]cyclazines using a new type [8 + 2] cycloaddition reaction consisting of exo imino cyclic tetraene compounds, 3-imino-3H-pyrrolizine derivatives, and DMAD. Previously, we have reported that the synthesis of polarized ethylenes having both electron-donating and electron-accepting groups on the adjacent two olefinic carbon atoms.[88] We applied this reaction to prepare 2-cyano-3-(2-pyrrolyl)-3-methylthioacrylonitrile (**70**) which is an important starting material for the synthesis of 5-aza[2.2.3]cyclazines.

Methyl pyrrolyl-2-dithiocarboxylate (**68**), readily available by the Grignard reaction of pyrrole and carbon disulfide, is allowed to react with tetracyno-

ethylene oxide (**69**) in benzene with stirring at room temperature to give the desired dicyanomethylene compound (**70**) in 88% yield. The cyclization of **70** to 2-cyano-3-imino-1-methylthio-3H-pyrrolizine (**71**) occurred smoothly by treatment with triethylamine and heating at the ca. 150°C. Cycloaddition of **71** with DMAD gives the expected 5-azacyclazine, dimethyl 4-cyano-3-methylthio-aza[2.2.3]cyclazine-5,6-dicarboxylate (**72**) in good yield. 3-Amino-5-aza[2.2.3]cyclazine derivatives (**75a-c**) are also prepared from the corresponding 1-amino-3-imino-3H-pyrrolizine derivatives (**74a-c**) and DMAD. Compounds (**74a-c**) are synthesized by the displacement of **70** with amines (morpholine, piperidine, pyrrolidine), following cyclization under heating in the presence of triethylamine. This reaction will become a useful method for the synthesis of various other aza[2.2.3]cyclazine derivatives (Scheme 25).[89]



68 **69** **70** **71** **72** **73a-c** **74a-c** **75a-c**

Scheme 25

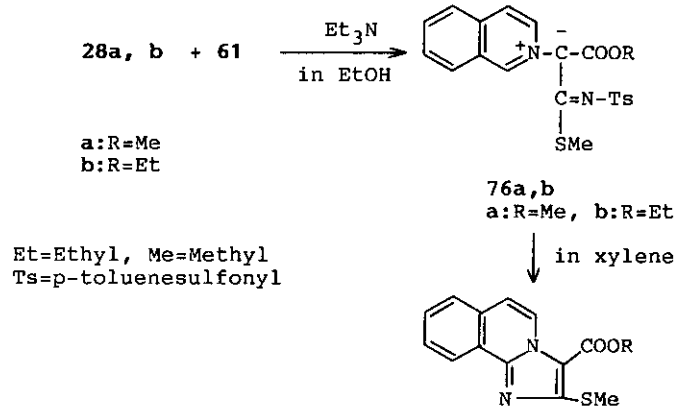
7 1-AZABENZO[h][2.2.3]CYCLAZINES

In recent years considerable efforts have been directed to elucidate the effect of benzo-fusion on annulene systems showing aromaticity.[38-44] It is of interest whether the delocalization in the cyclazine and azacyclazine is reduced by benzannelation on the macrocyclic ring or lost at all. In the previous section, we describe the synthesis of mono- and dibenzo-annelated [2.2.3]cyclazine derivatives which are very stable and typical delocalized 14π or 18π electron aromatic compounds.

7.1 Synthesis of Imidazo[2,1-a]isoquinoline

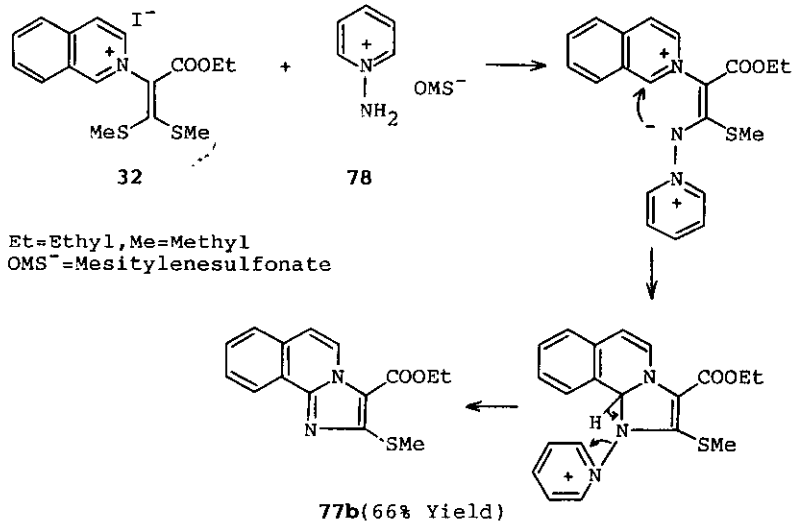
Imidazo[2,1-a]isoquinolines[90] are key intermediates for the synthesis of 1-azabenzo[h][2.2.3]cyclazines. Therefore we tried to find a new synthetic method of imidazo[2,1-a]isoquinoline, since the general and important route to these compounds has not been reported. At first, in a manner similar to the synthesis of imidazo[1,2-a]pyridine derivatives (**60a,h-j**), we attempted the reaction of isoquinolinium N-ylides with N-bis(methylthio)methylene-p-toluenesulfonamide (**61**).[63] The required isoquinolinium N-ylide (**76a**) is prepared from N-methoxycarbonylmethylisoquinolinium bromide (**28b**) and **61**, and is subjected to thermolysis in boiling xylene to give methyl 2-methylthioimidazo[2,1-a]isoquinoline-3-carboxylate (**77a**) in 69% yield. In this case, the tosylated product is not obtained. When 1-ethoxycarbonylmethylisoquinolinium (**28b**), in place of the methyl ester (**28a**), is allowed to react with **61** in boiling ethanol in the presence of triethylamine, ethyl 2-methylthioimidazo[2,1-a]isoquinoline-3-carboxylate (**77b**) is directly formed in 65% yield, without isolation of **76b** (Scheme 26).[84]

We next tried the synthesis of imidazo[2,1-a]isoquinoline (**77b**) by the reaction of isoquinolinium ketene dithioacetal (**32**) with pyridinium N-imine.[91] The reaction of (**32**) with 1-aminopyridinium methylenesulfonate (**78**) in the presence of triethylamine in ethanol gives the corresponding **77b** in 66 % yield (Scheme 27).[48]



No.	R	mp(°C)	Yield(%)
77a:	Me	120	69
b:	Et	154	65

Scheme 26

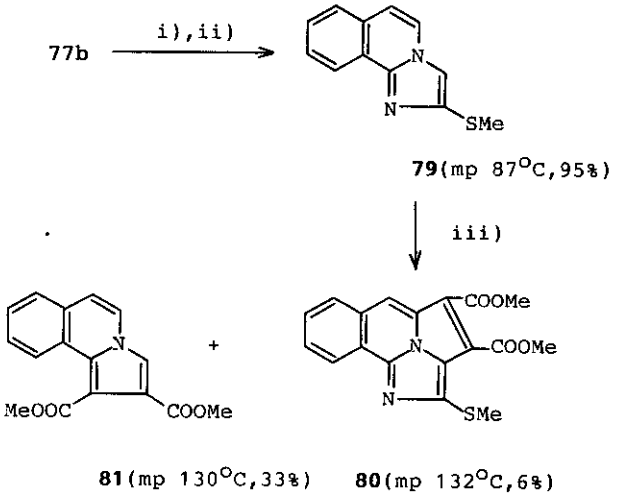


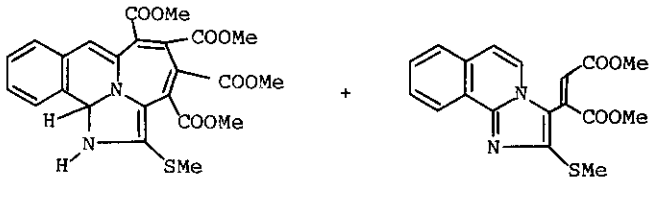
Scheme 27

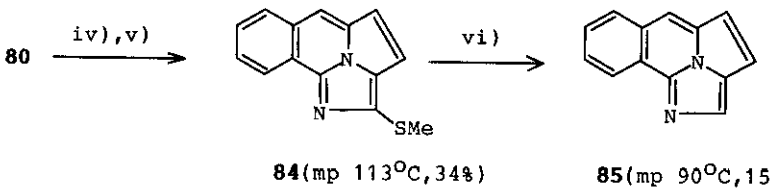
7.2 Synthesis of 1-Azabenzo[h][2.2.3]cyclazine

Hydrolysis of **77b** with sodium hydroxide in methanol to the corresponding carboxylic acid and subsequent decarboxylation of the acid by heating in poly-

phosphoric acid gives the desired compound (**79**). A solution of **79** and DMAD in toluene is refluxed for 30 hours using a 5% palladium on charcoal to give the expected dimethyl 2-methylthio-1-azabenzo[h][2.2.3]cyclazine-3,4-dicarboxylate (**80**), though in 6% yield, together with dimethyl pyrrolo[2,1-a]isoquinoline-2,3-dicarboxylate (**81**) (33%), methyl (2-methylthio)imidazo[2,1-a]isoquinolin-3-yl-α-methoxycarbonylacrylate (**82**) (4%), and tetramethyl 1,11b-methylthio-1-azabenzo-[g]cycl[4.3.2]azine-3,4,5,6-tetracarboxylate (**83**) (2%). Hydrolysis of **80** with 10% sodium hydroxide gives the corresponding diacid almost quantitatively.







Me=Methyl
i) NaOH. ii) PPA. iii) DMAD, Pd-C in toluene. iv) NaOH and then HCl. v) $CuCrO_4$ in dipheny ether. vi) Raney-Ni in EtOH.

Scheme 28

Decarboxylation of the diacid occurs smoothly on heating with copper chromate in diphenyl ether to produce 2-methylthio-1-azabenzo[h][2.2.3]cyclazine (**84**) in 34% yield. Finally, desulfurization of **84** is easily attained by a catalysis of Raney-nickel to afford the desired parent compound, 1-azabenzo[h][2.2.3]cyclazine (**85**) in 15% yield (Scheme 27).[92] Both the 1-azabenzo[h][2.2.3]cyclazines, **84** and **85**, are yellow crystals and soluble in numerous organic solvents giving pale yellow solutions. They are stable to heat, light, and acids. The aromatic proton chemical shifts (7.40-8.98 ppm) of **85** are similar to those of benzo[g]-[2.2.3]cyclazine (**26**) (7.38-8.60 ppm) and of 1-aza[2.2.3]cyclazine (**67a**) (7.46-8.58 ppm). The vicinal coupling constant between C3-H and C4-H ($J_{3,4}$=5.0 Hz) is slightly larger than the corresponding value in **67a** and benzo[g][2.2.3]cyclazine (**26**) (J=4.8 and 4.9 Hz, respectively). The methyl protons (2.93 ppm) of methylthio group of **84** are strongly deshielded relative to those (2.03-2.33 ppm) of the nonaromatic model compounds such as ketene dithioacetals. The above results apparently indicate that 1-azabenzo[h][2.2.3]cyclazine derivatives, **84** and **85**, are typical aromatic compounds.

8 CONCLUSION

It has been proved that nitro ketene dithioacetal, 1,1-bis(methylthio)-2-nitroethylene (**12**), is a very useful electrophilic reagent for the synthesis of indolizine derivatives. This access to indolizine derivatives is the most useful and convenient method for the preparation of 1,2,3-unsubstituted indolizines and benzoindolizine, pyrrolo[2,1-a]isoquinolines which are the key intermediates for the synthesis of [2.2.3]cyclazine derivatives (**24a,b, and 25a,b**). 2-Methylthioimidazo[1,2-a]pyridines are also important starting materials to obtain the 1-aza[2.2.3]cyclazine derivatives. The [8 + 2] cycloaddition reaction of the 2-methylthioimidazo[1,2-a]pyridines with DMAD has been successfully applied to the synthesis of parent 1-aza[2.2.3]cyclazine (**67a**), 5-aza[2.2.3]cyclazines (**72, 75a-c**), and 1-azabenzo[h][2.2.3]cyclazine (**85**).

The ^{1}H Nmr chemical shifts of the ring protons, and the methyl proton on the ring and the methyl proton of the methylthio group of indolizines, [2.2.3]cyclazine, monobenzo- and dibenzo[2.2.3]cyclazine, and aza[2.2.3]cyclazine derivatives, prepared in this work, are shown in Table 1. It is important to note that the ring protons of [2.2.3]cyclazines (**24a, b**) appears at lower field than the corresponding ring protons of indolizines, since the ring current increases

as is seen in polynuclear aromatic hydrocarbons (PAH). Methyl protons both of the methyl group on the cyclazine ring and the methylthio group are also shown at lower field, compared with those of the corresponding indolizine derivatives. In the case of benzo[a][2.2.3]cyclazine (**27**), the effect of benzannelation on the parent [2.2.3]cyclazine (**24**) is accompanied by the reduction in diatropicity expectedly, as evidence by the chemical shift of the ring protons in the ^{1}H nmr spectrum. However, this reduction in diatropicity is less than expectation. On the other hand, in another benzo-fused [2.2.3]cyclazine (**26**), the unexpected down field shift is observed, though very slightly. In general, it is shown that the benzannelation toward the macrocyclic compound reduces the diatropicity. Although the [2.2.3]cyclazine derivatives are little different from benzannelated annulenes prepared by McCague,[43] Mitchell,[42] Nakagawa[93] and Ojima[94] et al.. In the case of PAH, the ring protons display downfield shift with increasing numbers of aromatic rings. So [2.2.3]cyclazine (**24a**) is the intermediary aromaticity between PAH and peripheral conjugated aromatic compounds involving delocalized 10π or 14π electrons. The resulting [2.2.3]cyclazines and benzo[2.2.3]cyclazines are strongly diatropic. Further theoretical study is required before the details of these novel conjugated systems can be fully understood.

9 ACKNOWLEDGMENT

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4. W. Flitsch, "Pyrroles with Fused Six-membered Heterocyclic Rings:(i) a-Fused, in Comprehensive Heterocyclic Chemistry" Vol.4, A. R. Katritzky and

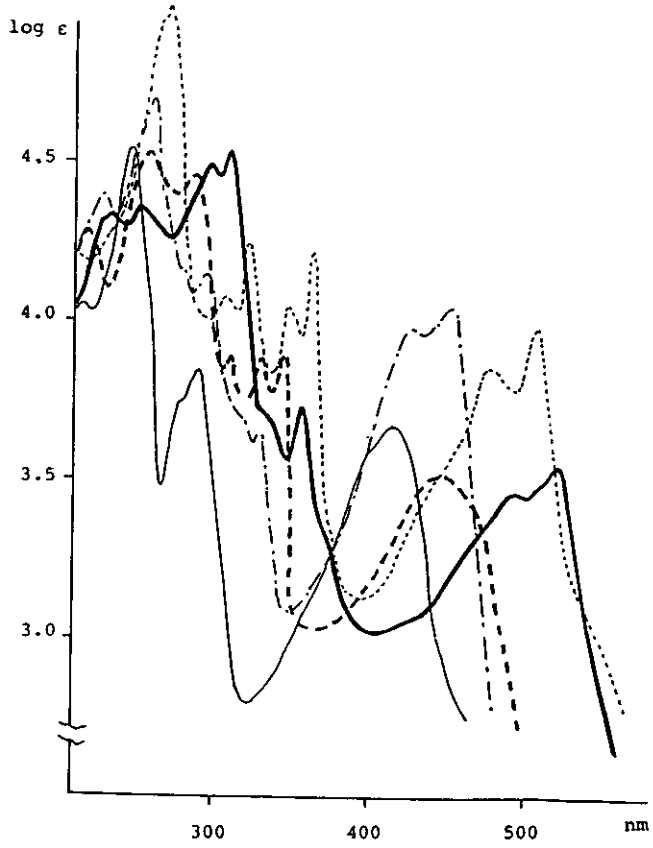
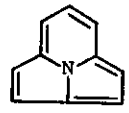
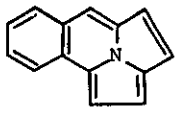


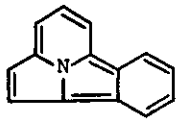
Fig. 1. UV Spectra of **24a**, **26**, **27**, **46**, and **47** in ethanol.



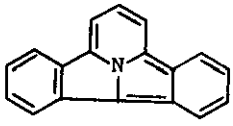
24a



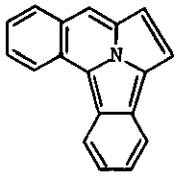
26



27

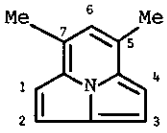


46

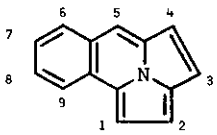


47

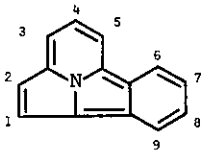
Table 1. ^{1}H- and ^{13}C-NMR spectra of [2.2.3]cyclazine derivatives (in $CDCl_3$).



24b

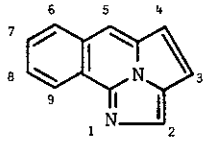


26

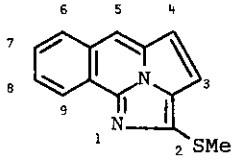


27

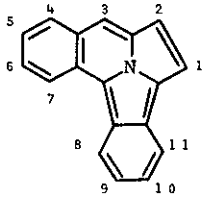
	^{1}H-NMR (400 MHz)	^{13}C-NMR	^{1}H-NMR (400 MHz)	^{13}C-NMR	^{1}H-NMR (400 MHz)	^{13}C-NMR
1	7.43(1H)	128.91(5C)	8.60(9H)	130.71(5aC)	8.43(6H)	129.90(9aC)
2	7.43(4H)	128.81(7C)	8.24(6H)	129.47(6C)	8.20(9H)	129.03(5bC)
3	7.29(6H)	127.01(4aC)	8.21(5H)	128.38(9aC)	8.09(5H)	128.44(2aC)
4	7.23(2H)	127.01(9aC)	7.74(8H)	127.19(4aC)	8.07(3H)	128.17(5aC)
5	7.23(3H)	123.66(6C)	7.73(3H)	126.67(8C)	7.66(1H)	127.89(4C)
6	2.84(5Me)	123.62(2aC)	7.63(7H)	126.02(9bC)	∫ (4H)	122.57(7C)
7	2.84(7Me)	115.09(2C)	7.62(2H)	124.70(7C)	7.71(8H)	122.44(6C)
8		115.09(3C)	7.46(1H)	123.13(9C)	7.50(7H)	122.19(9bC)
9		108.46(1C)	7.38(4H)	122.56(2aC)	7.17(2H)	119.41(8C)
10		108.46(4C)		122.32(3C)		119.25(9C)
11		17.29(5Me)		113.34(4C)		115.45(3C)
12		17.29(7Me)		111.97(2C)		112.76(1C)
13				111.41(5C)		107.96(5C)
14				105.90(1C)		105.67(2C)



85



84



47

	^{1}H-NMR (270 MHz)	^{13}C-NMR	^{1}H-NMR (270 MHz)	^{13}C-NMR	^{1}H-NMR (400 MHz)	^{13}C-NMR
1	8.98(9H)	137.31	8.89(9H)	144.29	9.06(7H)	129.85(11C)
2	8.27(2H)	132.27	8.20(6H)	137.51	8.91(8H)	129.17(3aC)
3	8.26(6H)	131.29	8.09(5H)	132.17	8.61(3H)	127.40(7aC)
4	8.21(5H)	130.84	7.79(8H)	130.18	8.37(4H)	126.84(11aC)
5	7.88(8H)	129.58	7.72(7H)	129.14	8.06(1H)	126.78(2aC)
6	7.78(7H)	128.96	7.62(3H)	127.26	7.86(6H)	126.66(6C)
7	7.68(3H)	128.05	7.29(4H)	127.00	7.72(10H)	126.04(10C)
8	7.40(4H)	127.29	2.93(SMe)	125.96	7.65(5H)	123.72(5C)
9		122.99		122.93	7.62(9H)	123.34(8C)
10		122.34		121.10	7.44(2H)	122.79(7C)
11		120.90		118.55		122.07(9C)
12		117.97		115.58		121.10(7cC)
13		113.95		110.85		120.51(7bC)
14				15.73		120.36(11bC)
15						119.64(4C)
16						118.26(1C)
17						114.09(3C)
18						107.57(2C)

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