HETEROCYCLES, Vol. 82, No. 1, 2010, pp. 201 - 248. © The Japan Institute of Heterocyclic Chemistry
Received, 31st May, 2010, Accepted, 5th July, 2010, Published online, 6th July, 2010
DOI: 10.3987/REV-10-SR(E)1

THE CHEMISTRY OF AZAAZULENES †

Noritaka Abe* and Takahiro Gunji

Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan

Abstract – This review describes the synthetic methods and reactions of azaazulenes including some of their *dihydro*-, *oxo*-derivatives and *hetero-fused derivatives* published during 2000 to early in 2010. The biological and physical properties of azaazulenes are also described.

INTRODUCTION

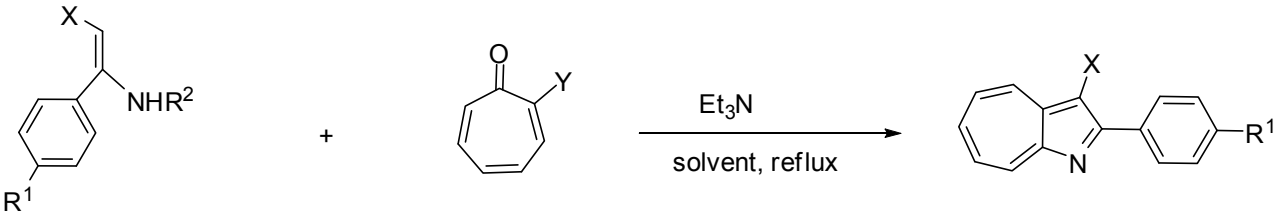
Azaazulenes are a class of the compounds that have been receiving continual interest of chemists for their relationship with the chemistry of azulenes and for remarkable characters about physical and chemical properties as well as biological activities.[1] After being previously reviewed a decade ago,[1a,b] many significant researches were developed in this field. This review covers the recent progress in the chemistry of fully-conjugated azaazulenes including some of their dihydro-, oxo-derivatives and hetero-fused derivatives published during 2000 to early in 2010.

I. SYNTHESES OF AZAAZULENES

Syntheses of 1-azazulenes from reactive troponoids were fundamental methods.[1] Recently, some novel synthetic methods of 1-azaazulenes being based on seven-menvered ring nuclei were developed. Konakahara reported the new approach to the synthesis of functionalized 1-azaazulenes by the reaction of the *N*-silylenamine or the enamine with 2-substituted tropones. (Scheme 1).[2] The reaction of *N*-silylenamine (**1a**) with 2-chlorotropone (**2a**) in the presence of KF gave 2-substituted-azaazulene (**3a)** in 24% yield. The reaction of the enamines (**1b-e**) with 2-chlorotropone or tropolone tosylate (**2b**) in the presence of Et_3N gave corresponding azaazulenes (**3b-e**) (Scheme 1). It is indicated that an aprotic polar solvent was effective for the reaction. Interestingly, the reaction of the enamines (**1c-f**) with 4-isopropyltropolone tosylate (**4**) gave 6-isopropylidene-8a-hydroxy-6,8a-dihydroazaazulene derivatives(**5c-f**), respectively (Scheme 2).

---

† Dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85th birthday.



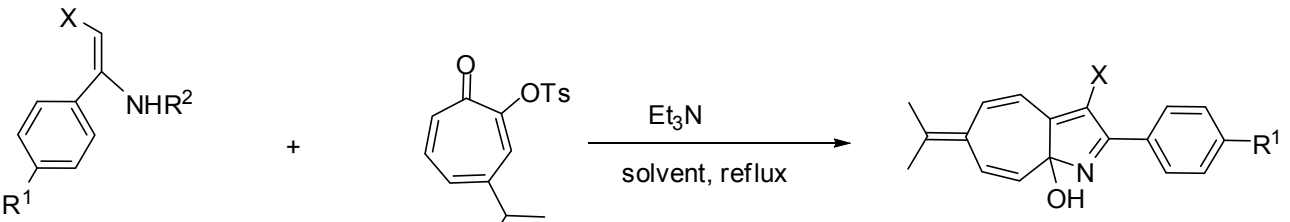
1a : X = 2-pyridyl, R^1 = H, R^2 = $SiMe_3$
1b : X = Ar, R^1 = H, R^2 = H
1c : X = Ar, R^1 = OMe, R^2 = H
1d : X = Ar, R^1 = NMe_2, R^2 = H
1e : X = 2-pyridyl, R^1 = H, R^2 = H

2a : Y = Cl
2b : Y = OTs

3a-e

Ar = 3-methyl-5-isoxazolyl

Scheme 1. Reaction of *N*-silylenamine or enamine with 2-chlorotropone or tropolone tosylate



1c : X = Ar, R^1 = OMe, R^2 = H
1d : X = Ar, R^1 = NMe_2, R^2 = H
1f : X = Ar, R^1 = Me, R^2 = H

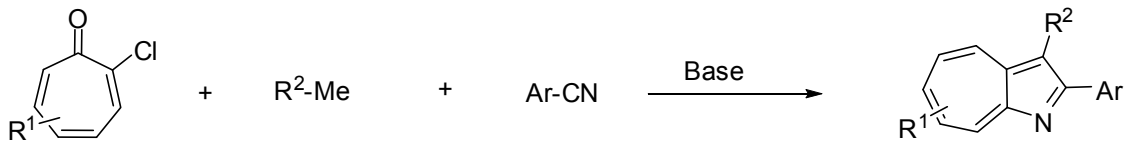
4

5c : X = Ar, R^1 = OMe
5d : X = Ar, R^1 = NMe_2
5f : X = Ar, R^1 = Me

Ar = 3-methyl-5-isoxazolyl

Scheme 2. Reaction of the enamine with 4-isopropyltropolone tosylate

As related reaction, it is reported that the reaction of chlorotropones (**2**) with the anion, prepared from active methyl compounds, with arylcarbonitriles in the presence of base gave 1-azaazulene derivatives (**5**) (Scheme 3).[3]

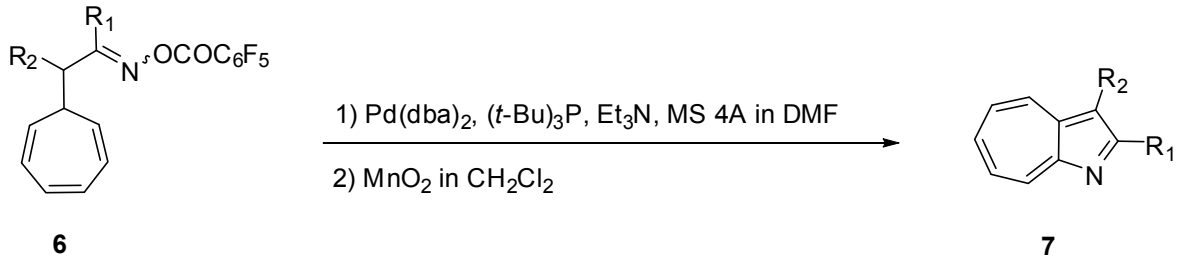


2 **5**

Scheme 3. Synthesis of 1-azaazulenes from **2** with anion derived from active methyl compounds and arylcarbonitriles in the presence of base

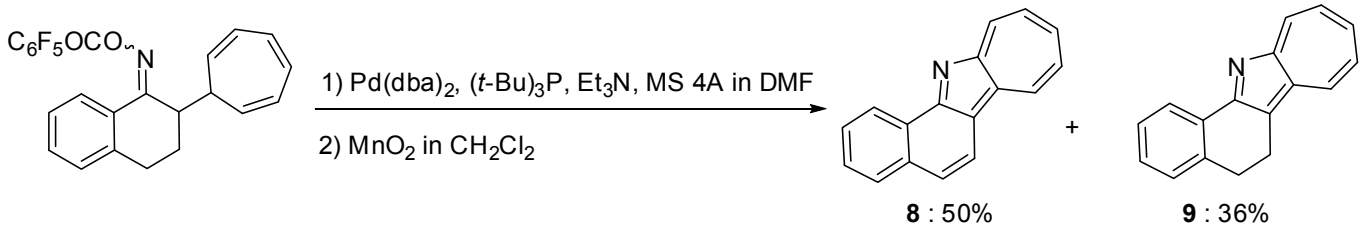
Narasaka reported elegant synthetic methods which are adopted of amino-Heck reaction to cycloheptatrienylmethyl ketone oximes.[4a-c] Thus, the treatment of cycloheptatrienylmethyl ketone *O*-

pentafluorobenzoyloximes (**6**) with a catalytic amount of $Pd(dba)_2$-*t*-Bu_3P and triethylamine in the presence of MS 4A followed by the oxidation with MnO_2 gave various 1-azaazulenes (**7**) in moderate to good yields (Scheme 4).

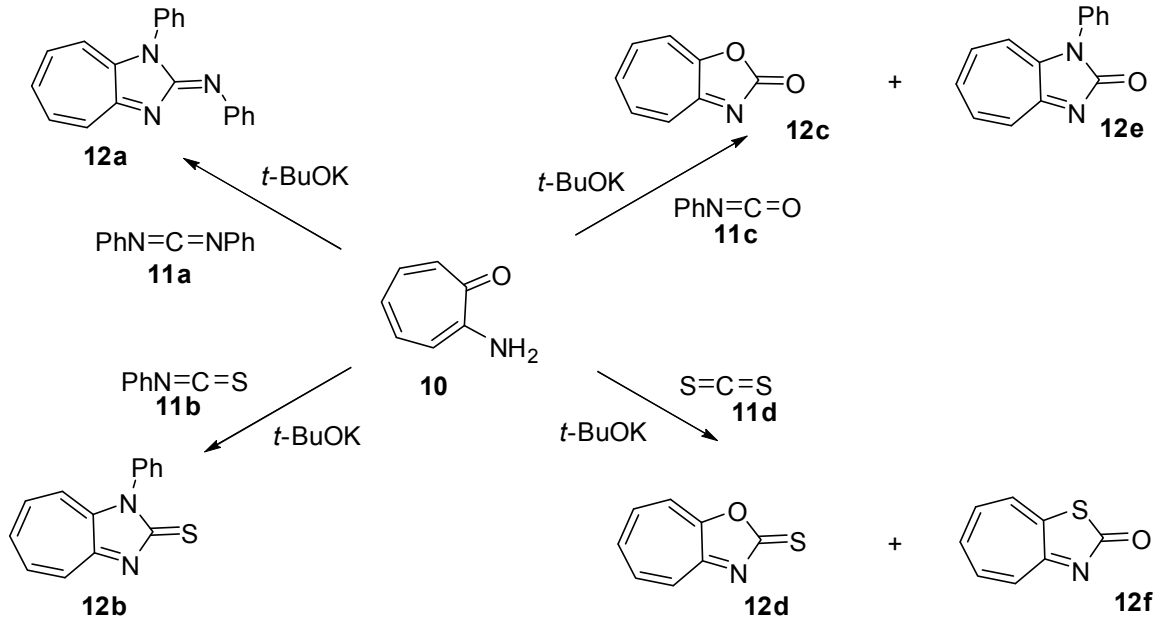


Scheme 4. Synthesis of 1-azaazulenes from the oximes by amino-Heck reaction

This method was applied to the synthesis of fused azaazulene derivatives, and 6-azanaphth[1,2-*b*]azulene (**8**) and 11,12-dihydro-6-azanaphth[1,2-*b*]azulene (**9**) were obtained (Scheme 5).



Scheme 5. Synthesis of 6-azanaphth[1,2-*b*]azulenes from the oxides by amino-Heck reaction



Scheme 6. Reaction of 2-aminotropone with heterocumulenes

Convenient preparation of heteroazulenes by the reaction of 2-aminotropone (**10**) with heterocumulenes was reported by Nitta.[5] The reaction of **10** with *N,N'*-diphenylcarbodiimide (**11a**) in the presence of *t*-BuOK gave 1,3-diazaaulene derivative (**12a**). Similarly, the reaction of **10** with heterocumulenes, such as phenyl isothiocyanate (**11b**), phenyl isocyanate (**11c**), and carbon disulfide (**11d**), in the presence of *t*-BuOK gave heteroazulenes (**12b-f**) (Scheme 6).

Nitta early reviewed the utility of (vinylimino)phosphoranes as useful building blocks for the synthesis of azaheterocycles including azaazulenes.[6] In the extension of the researches, Nitta reported the reactions of (tropon-2-ylimino)pnictoranes (**13a-d**) with heterocumulenes (**11a-d**), which are good methods for construction of azaazulene skeletons (**14a-d**) (Scheme 7).[7a-c]

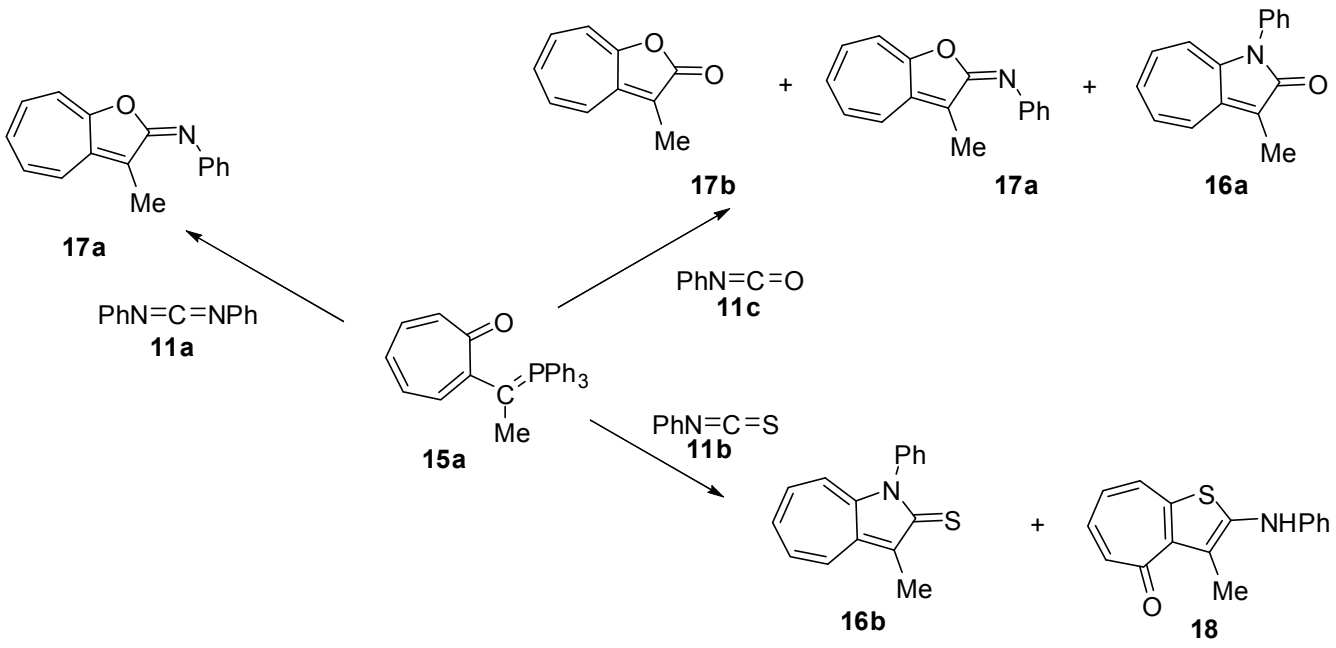
13a : M = P
13b : M = As
13c : M = Sb
13d : M = Bi

11a : X = Y = NPh
11b : X = S, Y = NPh
11c : X = O, Y = NPh
11d : X = Y = S

14a : W = Z = NPh
14b : W = O, Z = NPh
14c : W = Z = O
14d : W = O, Z = S

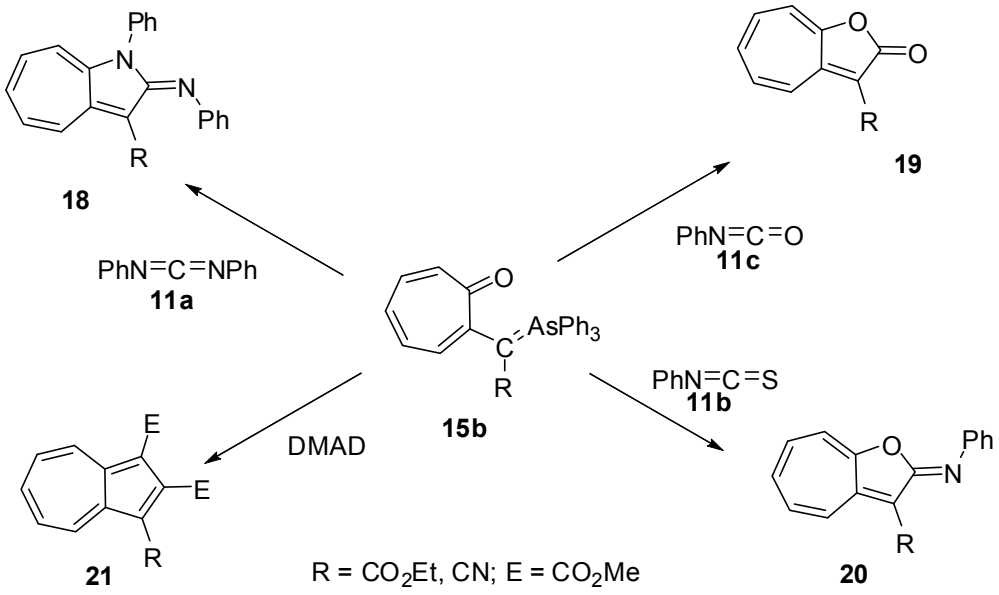
Scheme 7. Reaction of (tropon-2-ylimino)pnictoranes (**13**) with heterocumulenes

They also reported the synthesis of 2-(1-triphenylphosphoranylideneethyl)tropones (**15a**) and 2-(triphenylarsoranylideneethyl)tropones (**15b**). Reaction of **15a** with heterocumulenes (**11a-c**) gave 1-azaazulene derivatives (**16**), 1-oxaazulene derivatives (**17**), and 1-thiaazulene derivatives (**18**) (Scheme 8).[8a,b]



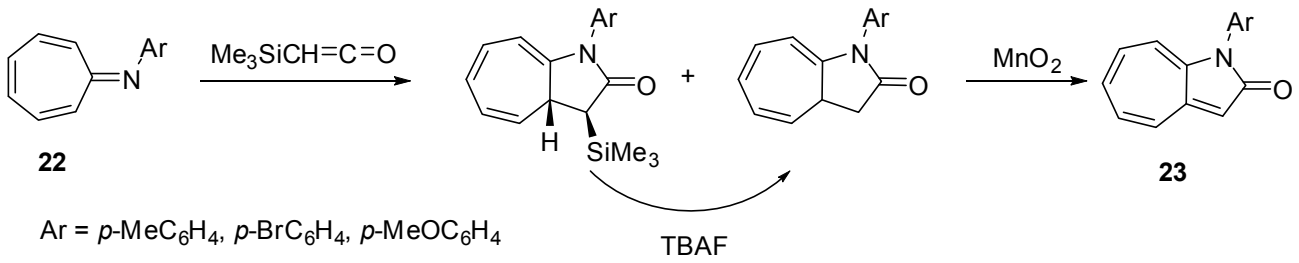
Scheme 8. Reaction of 2-(triphenylphosphoranylidenemethyl)tropones (**15a**) with heterocumulenes

The reaction of **15b** with heterocumulenes (**11a-c**) of dimethyl acetylenedicarboxylate (DMAD) resulted in the formation of heteroazulenes (**18-20**) and azulene derivatives (**21**) (Scheme 9).[8c]



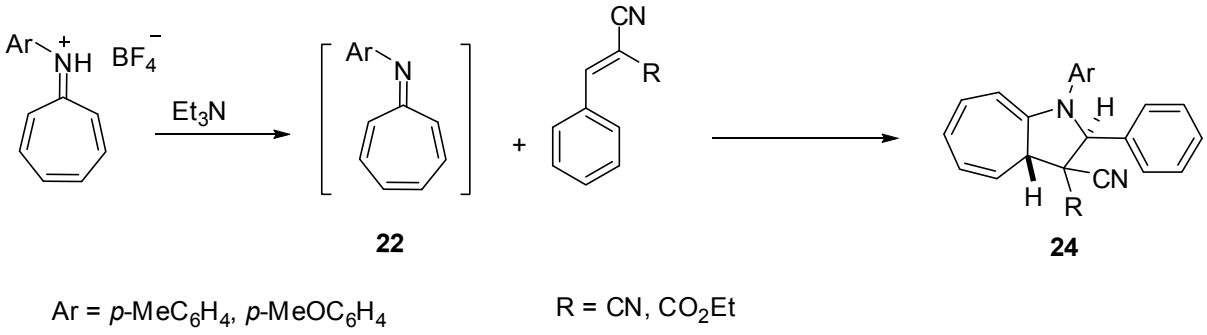
Scheme 9. Reaction of 2-(triphenylarsoranylidenemethyl)tropones (**15b**) with heterocumulenes or DMAD

The [8 + 2]-cycloaddition of 8-azaheptafulvenes (cycloheptatrienylideneamines; troponeimines) is a good method for construction of the 1-azaazulene skeleton.[9] Reaction of 8-aryl-8-azaheptafulvenes (**22**) with trimethylsilylketene followed by the desilylation with TBAF and successive oxidation with MnO_2 gave 1-aryl-1-azaazulen-2(1*H*)-ones (**23**) (Scheme10).[10]



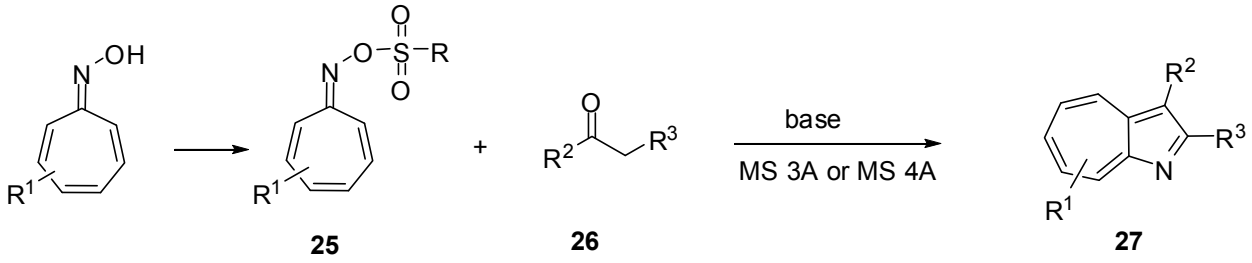
Scheme 10. Reaction of 8-aryl-8-azaheptafulvenes (**22**) with trimethylsilylketene

The reaction of 8-aryl-8-azaheptafulvenes (**22**) with activated stylenes underwent an efficient [8 + 2]-cycloaddition to give 2-aryl-1,2,3,3a-tetrahydro-1-azaazulene derivatives (**24**) (Scheme 11).[11]



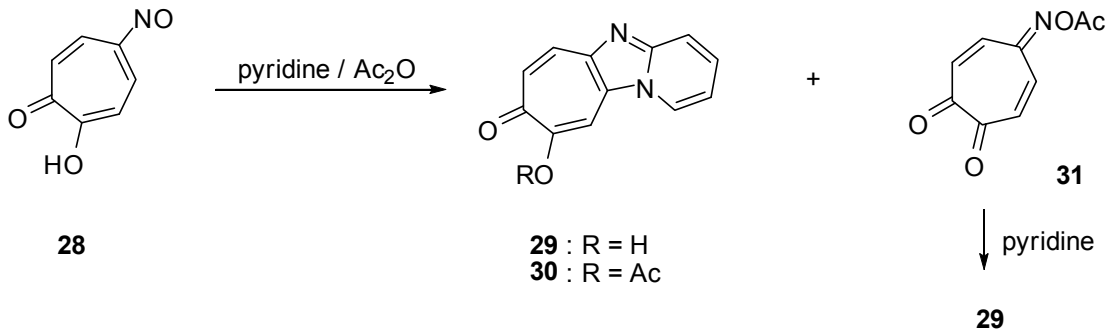
Scheme 11. Reaction of 8-aryl-8-azaheptafulvenes (**22**) with active stylenes

A facile and practical method for the synthesis of fully-conjugated substituted-1-azaazulenes from 8-azaheptafulvene *N*-sulfonates was reported. The treatment of 8-(substituted sulfonyloxy)-8-azaheptafulvenes (**25**) and the ketonic methylene compounds (**26**) with bases such as amines in the presence of MS 3A or MS 4A gave 1-azaazulene derivatives (**27**) (Scheme 12).[3]



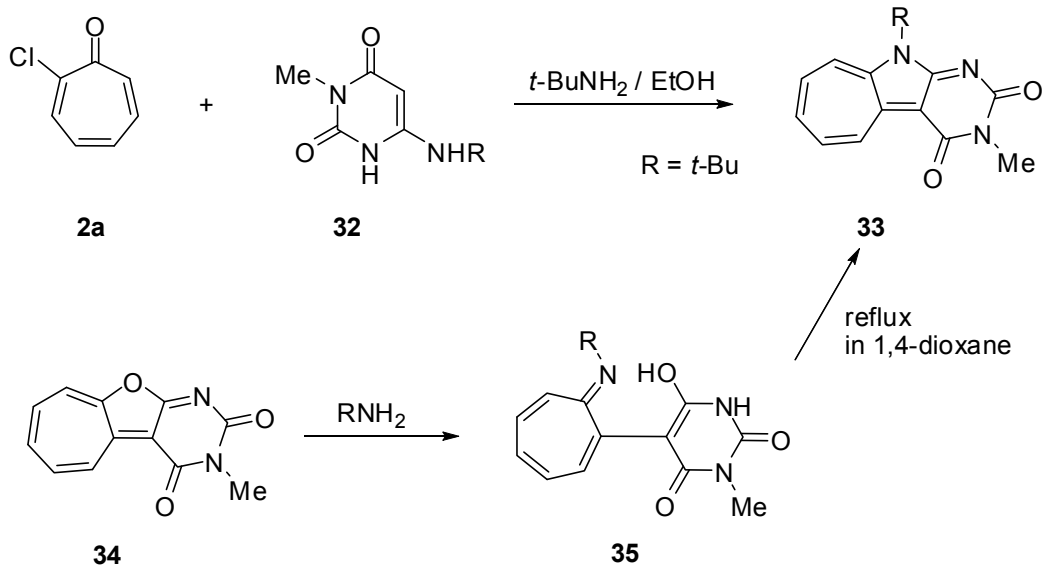
Scheme 12. Reaction of 8-(substituted sulfonyloxy)-8-azaheptafulvenes (**25**) with active methylenes

For the preparation of heteroaromatics being fused to 1,3-diazaazulene, the reaction of 5-nitrosotropolone (**28**) with pyridines was carried out, and pyrido[1',2':1,2]imidazo[4,5-*e*]tropolone (**29**) and its acetate (**30**) were obtained *via* tropoquinone derivative (**31**). (Scheme 13) [12] The treatment of **31** with pyridine afforded **29** and this result exemplified that **31** is the precursor of **29**. The reaction was applicable to azines, such as pyridazine, isoquinoline, phthalazine, or thiazole, and corresponding tricyclic heterocycles were obtained.[12]



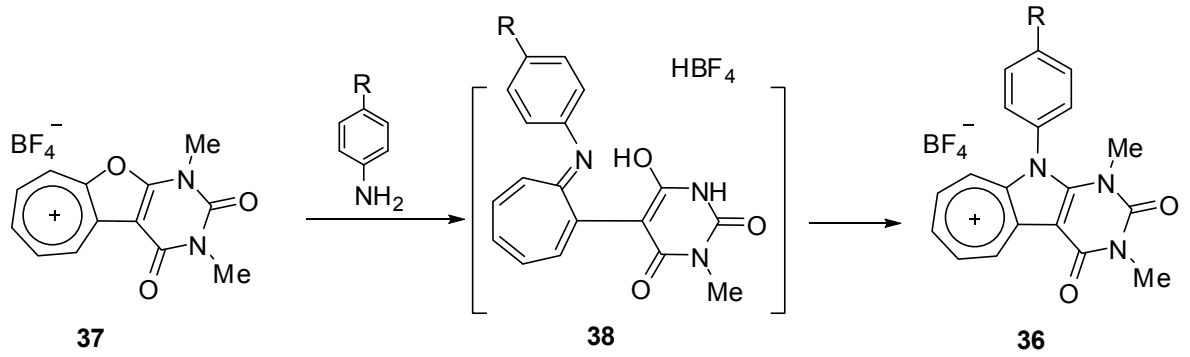
Scheme 13. Reaction of 5-nitrosotropolone (**28**) with pyridine

Nitta synthesized the uracil-annulated azaazulenes, which showed an oxidizing ability.[13a-f] The treatment of 2-chlorotropone (**2a**) with **32** in the presence of Et_3N and K_2CO_3 in refluxing 1,4-dioxane gave **33**. The reaction was improved;[13a] the treatment of **2a** with **32** in the presence of *t*-$BuNH_2$ in ethanol at rt gave **33** in good yields (Scheme 14).[13b] Compounds (**33**) were also synthesized *via* **35** by the ring transformation of **34** in good yields by the treatment with amines followed by heating at 90 ºC in 1,4-dioxane.[13b]



Scheme 14. Synthesis of 6-aminouracil-fused 1-azaazulenes

By using similar ring transformation, Nitta synthesized **36** from **37** with the amines *via* **38** (Scheme 15).[13c] The treatment of **33** with MeI followed by HBF_4 also gave 6-aminouracil fused 1-azaazulenium ions.[13d] They extended the procedure to synthesize areno-annulated 6-aminouracil-fused 1-azaazulenium ions **(39-41)**[13e] and the ions **42** and **43** (Figure 1).[13f]



Scheme 15. Synthesis of 6-aminouracil-fused 1-azaazulenium ion

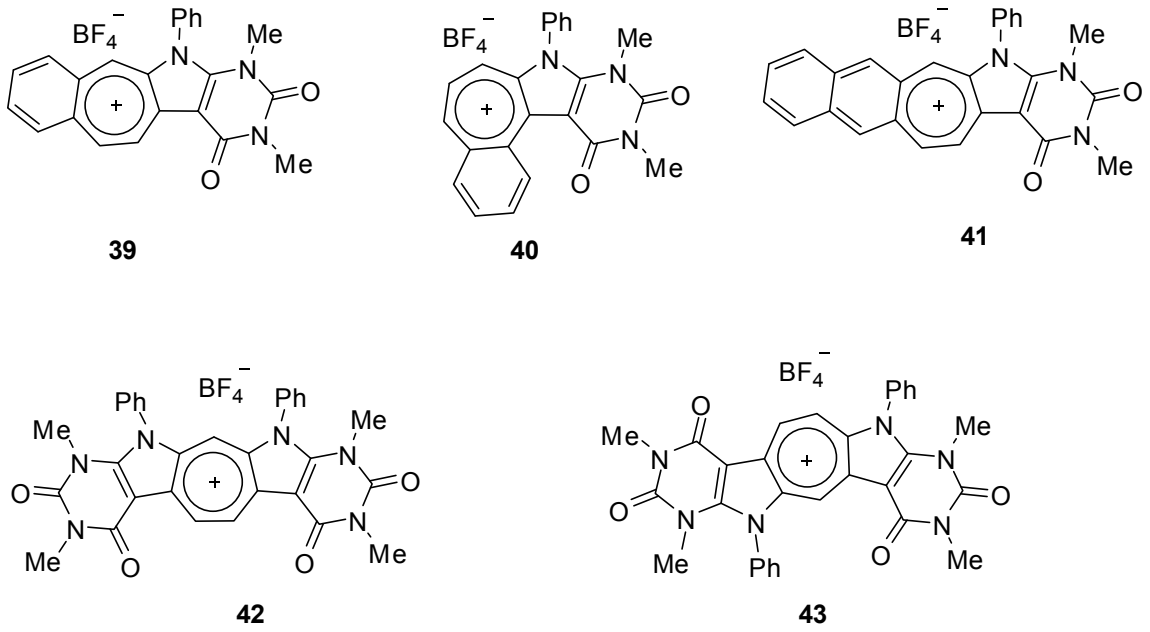
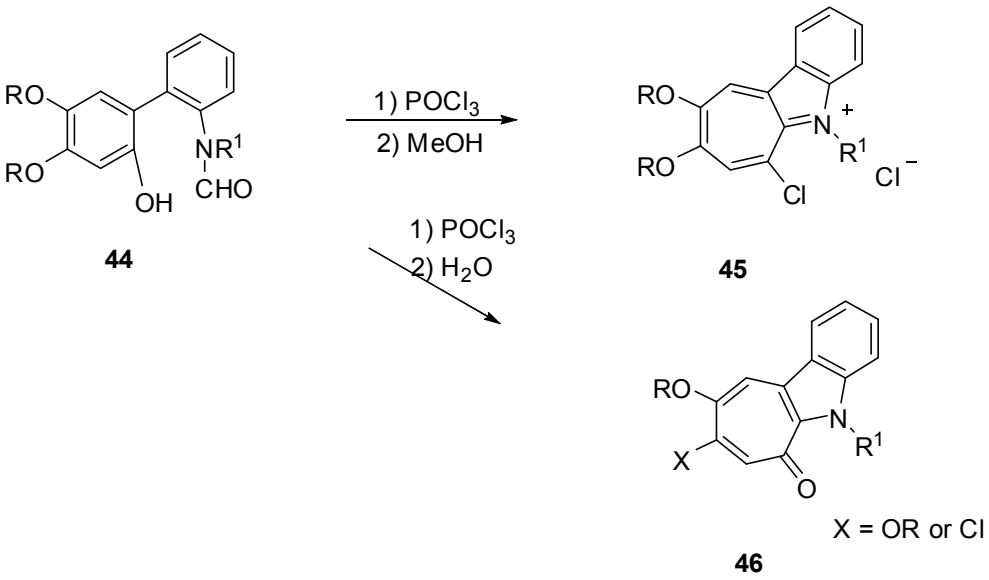


Figure 1

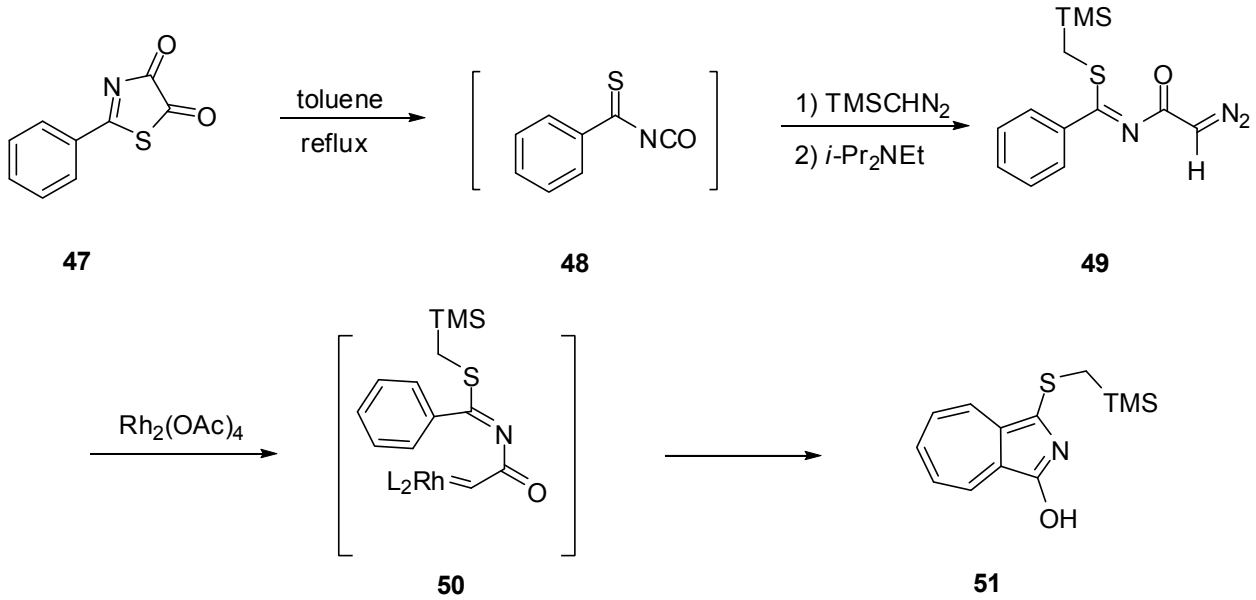
Ring expansion of benzene ring to seven-membered ring being attended with pyrrole ring formation is a fascinating synthetic method for the construction of the 7-5 ring system at a stroke.

Ishikawa reported an interesting ring expansion by abnormal Bischler-Napieralski reaction (BNR).[14a-d] The treatment of **44** with $POCl_3$ and successive evaporation and recrystallization of the product gave **45**. When the reaction product of **44** with $POCl_3$ was poured into water and successive extraction and chromatographic separation were taken, the compound (**46**) was formed. The reaction mechanism of the ring expansion on the BNR was discussed.

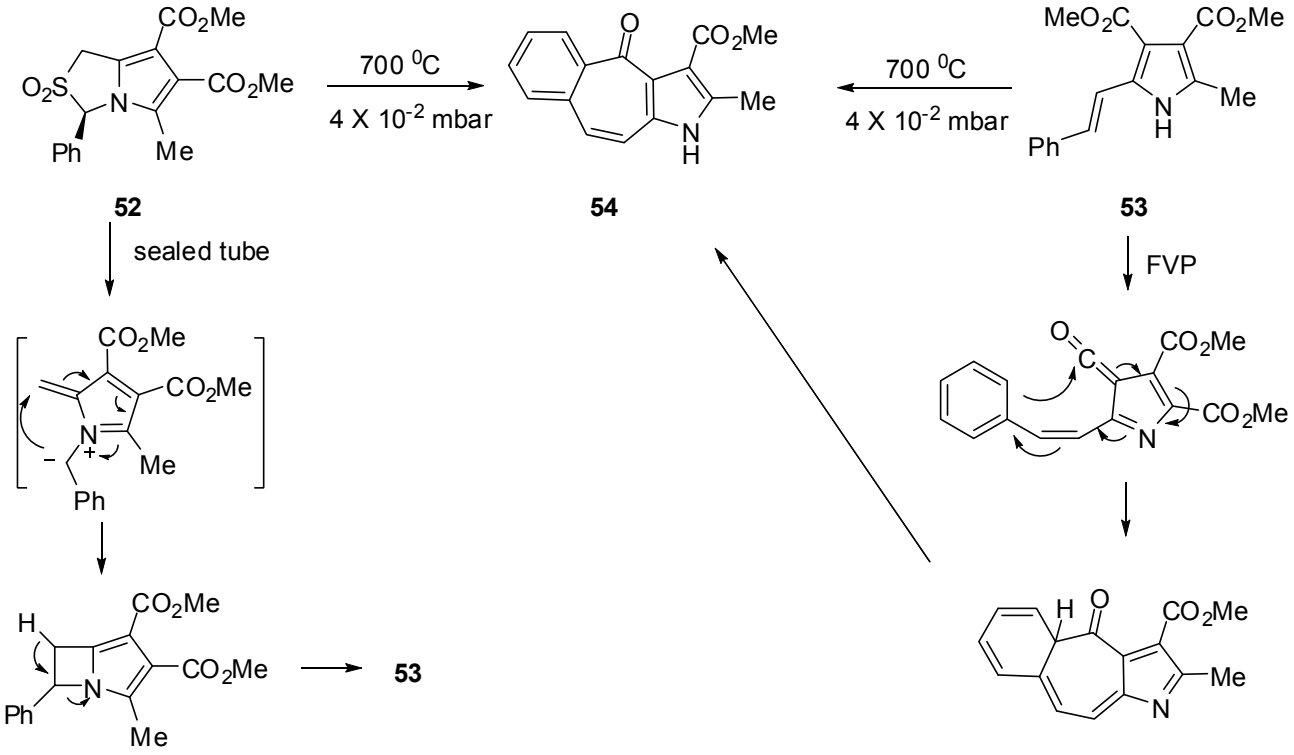


Scheme 16. Ring expansion by abnormal Bischler-Npieralski reaction

Aoyama reported a facile synthetic method of 2-azaazulenes by Buchner ring expansion reaction using trimethylsilyldiazomethane ($TMSCHN_2$) and thiobenzoyl isocyanate which was generated from 2-phenylthiazol-4,5-dione (Scheme 17).[15a,b] The intermediate **48** could be produced by the treatment of **47** in refluxing toluene for 5 min. Addition of $TMSCHN_2$ to the reaction mixture, and the successive treatment with *i*-Pr_2NH produced **49**. The treatment of **49** with $Rh_2(OAc)_4$ as catalyst gave 2-azaazulene derivative (**51**) *via* the intermediate **50**.



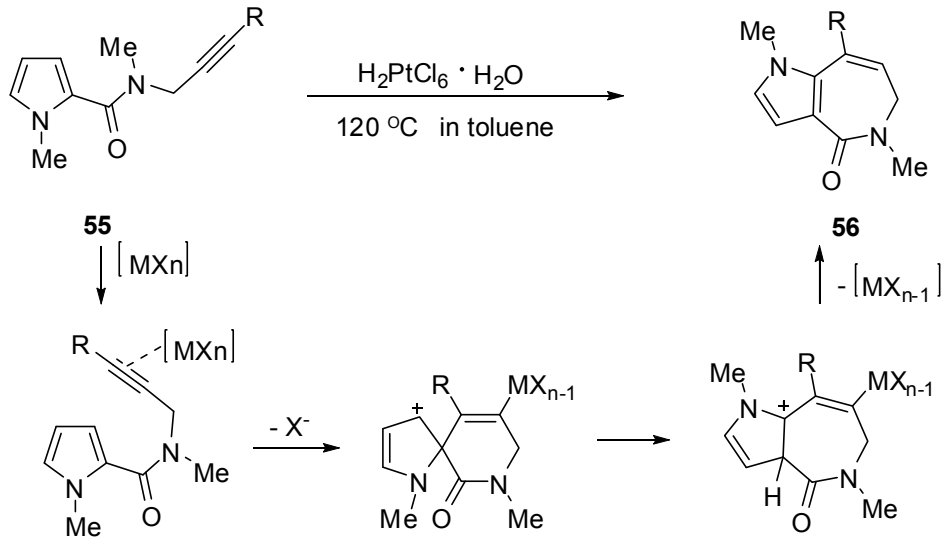
Scheme 17. Synthesis of 2-azaazulene



Scheme 18. FVP of **52** or **53**

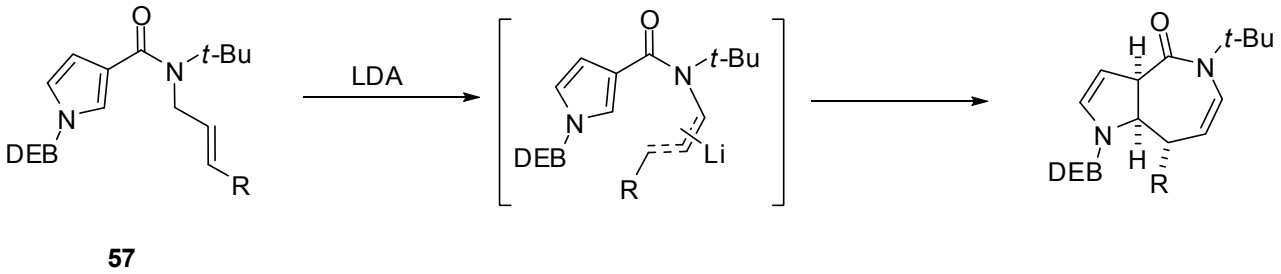
Intramolecular cyclization was often used to construct a seven-memberd ring. When the thermolysis of **52** was carried out in a sealed tube, 5-styryl-1*H*-pyrrole (**53**) was obtained and the compound **54** was not produced. The formation of **54** was achieved by flash vacuum pyrolyses (FVP) of **52** and **53** (Scheme 18).[16] The reaction mechanisms of the formation of **53** and **54** were shown in the Scheme 18.

Platinum catalyzed intramolecular cyclization of the alkynes (**55**) gave **56** as the major product (8% yield), and this method was an efficient synthetic way for 1,5-diazaazulene skeleton (Scheme 19).[17]



Scheme 19. Platinum-catalyzed intramolecular cyclization of alkynes

A pyrrole ring is susceptible to an intramolecular nucleophilic attack by organolithiums. Thus the treatment of *N*-allylpyrrolocarboxamide (**57**) with LDA yielded azaazulene derivatives (**58**) by an intramolecular cyclization (Scheme 20).[18]

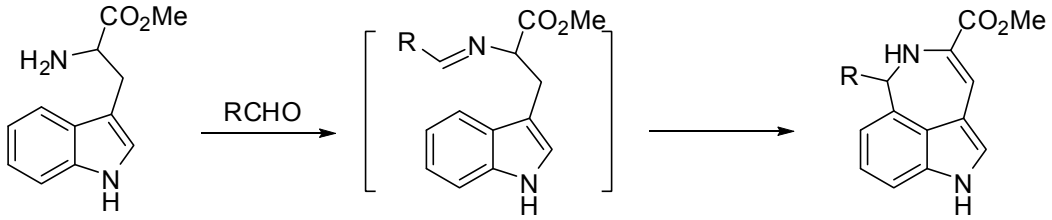


57

Scheme 20. Anionic cyclization of pyrrolcarboxamate

Synthetic routes involving Pictet-Spengler condensation or Bischler-Napieralski reaction are known as useful methods for construction of heterocyclic nuclei, and these reactions have been frequently employed for construction of azepine ring.

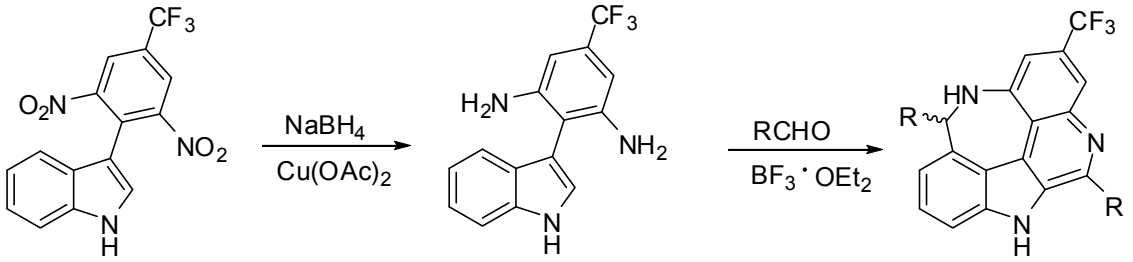
Previously, Goto reported that the acid-catalyzed condensation of dehydrotryptophan ester (**59**) with aldehydes gave respective 1,5-diazabenz[*cd*]azulene derivatives (**60**) (Scheme 21).[19]



59 **60**

Scheme 21. Acid-catalyzed condensation of dehydrotryptophan ester (**59**) with aldehydes

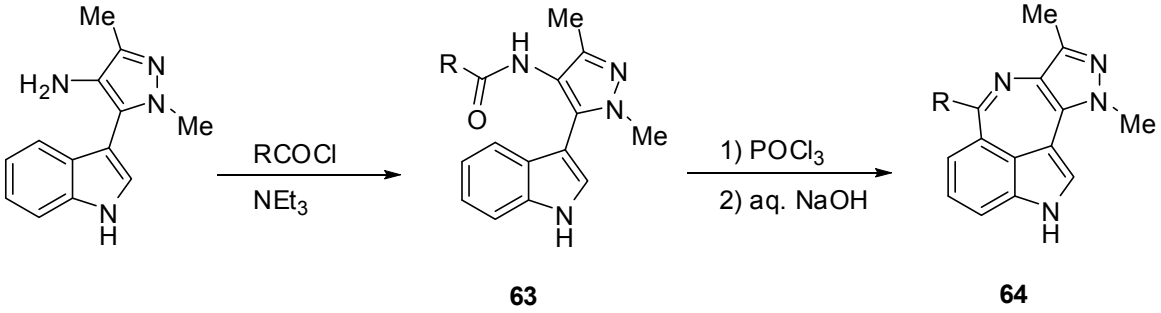
As application of the reaction, Khashashneh reported that the double Pictet-Spengler condensation of 3-(2,5-diaminophenyl)indole (**61**) with aldehydes gave **62** (Scheme 22).[20]



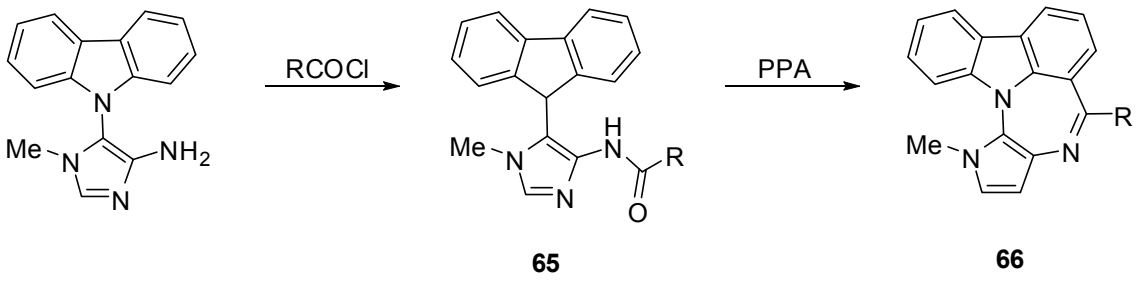
61 **62**

Scheme 22. The double Pictet-Spengler condensation of 3-(2,5-diaminophenyl)indole (**61**) with aldehydes

The Bischler-Napieralski reaction of the carboxamides (**63**) using $POCl_3$ in MeCN under reflux gave **64** (Scheme 23),[21a] and the reaction of the carboxamides (**65**) using polyphosphoric acid (PPA) at 140 ºC gave **66** (Scheme 24).[21b]



Scheme 23. Bischler-Napieralski reaction of **63**



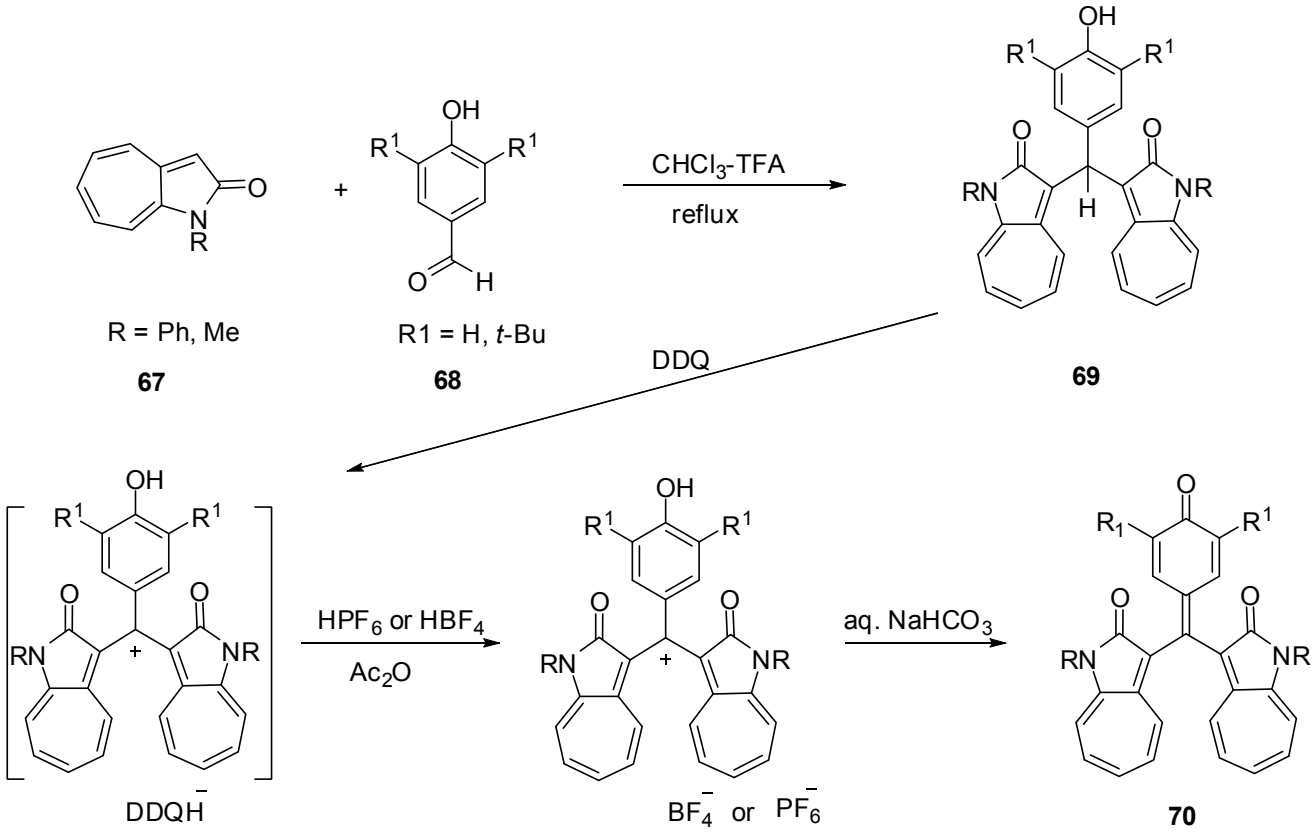
Scheme 24. Bischler-Napieralski reaction of **65**

II. REACTIONS OF AZAAZULENES

As previously reviewed,[1] 1-azaazulenes are susceptible to electrophilic attack at nitrogen and C-3 and to nucleophilic attack at C-2 and the seven-membered ring carbons (particularly at C-6 and C-8). It is also known that 1-azaazulen-2(1*H*)-one shows similar reactivity and is susceptible to an electrophilic attack at nitrogen and C-3.[1]

A. Reactions with electrophiles

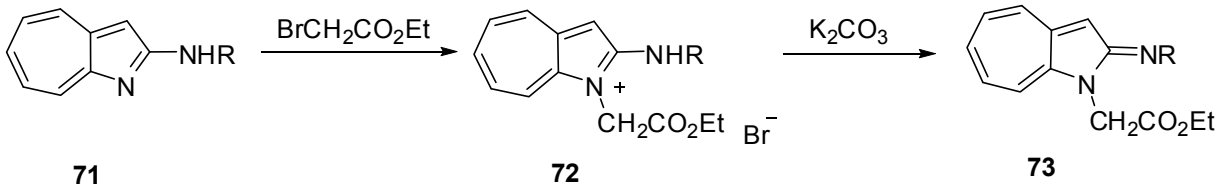
A TFA-catalyzed electrophilic aromatic substitution on the 1-azaazulen-2(1*H*)-ones (**67**) with 4-hydroxybenzaldehyde (**68**) gave the corresponding methane derivatives (**69**).[22] Oxidative hydrogen



Scheme 25

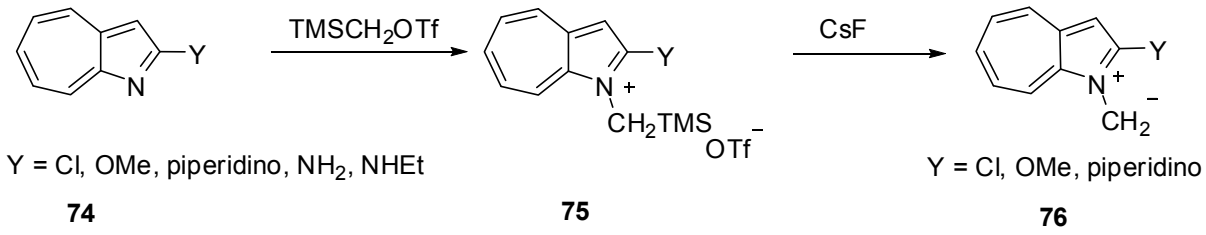
abstraction of **69** with DDQ, followed by exchange of the counter anion by using aq. HBF_4 or aq. HPF_6 and neutralization furnished to the 1,4-benzoquinonemethides (**70**) (Scheme 25).[22a] Using similar method, 7,7-bis(heteroazulen-3-yl)-8,8-dicyano-1,4-quinodimethanes were synthesized.[22b] Similar treatment of **67** with $HC(OMe)_3$ gave tris(heteroazulene)-substituted methane.[22c] The treatment of bis(1-azaazulen-3-yl)methyl cation with barbituric acid followed by oxidation with *o*-chloranil gave 5-[bis(heteroazulen-3-yl)methylidene]pirimidine-2,4,6(1*H*,3*H*,5*H*)-triones.[22d]

Quarternization products of the nitrogen in azaazulenes are important since the produced cations have interesting character,[13d,77] and some of them are potential intermediates for azaazulene *N*-ylides. 2-Alkylamino-1-azaazulenes (**71**) were alkylated at the N-1 by the treatment with ethyl bromoacetate to give **72**, and successive neutralization of **72** with K_2CO_3 gave **73** (Scheme 26).[23]



Scheme 26

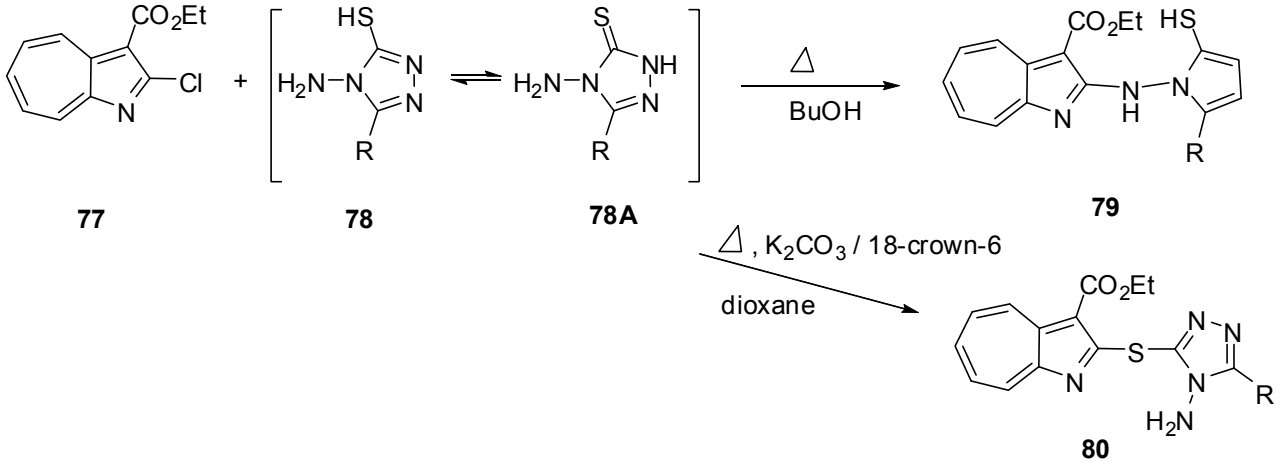
A facile *N*-trimethylsilylmethylation of 1-azaazulenes (**74**) with trimethylsilylmethyl triflate ($TMSCH_2OTf$) was presented (Scheme 27). Where the cations (**75**) were obtained in good yields, and **75** were converted to **76** using CsF.[24a,b]



Scheme 27

B. Reactions with nucleophile

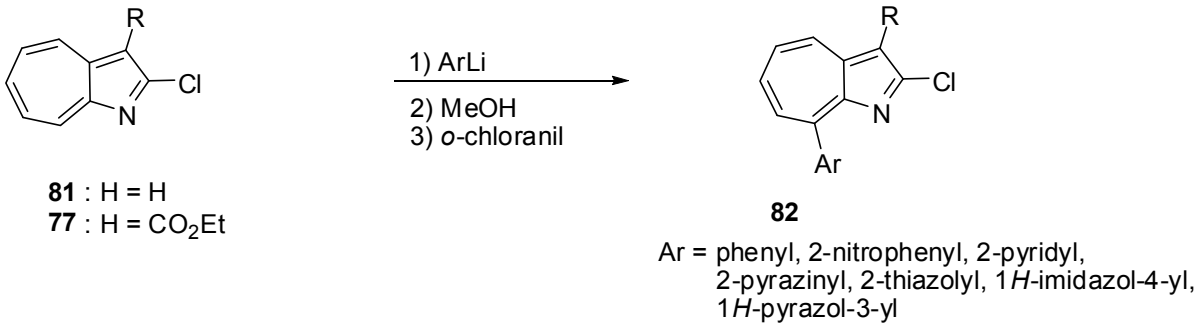
As previously reviewed, a halogen group on azaazulenes can be replaced by a nucleophile.[1] Commonly, a mercapto group is more active than an amino group on substitution reaction. Interestingly, when the reaction of 1-azaazulene (**77**) with 4-amino-3-mercapto-4*H*-1,2,4-triazoles (**78**) was undertaken in a refluxing BuOH, *N*-substitution occurred and yielded **79**. When the reaction was performed under basic conditions, *S*-substitution occurred and yielded **80** (Scheme 28).[25] These phenomena could be interpreted as follows. The compound **78** would be existed as thione form (**78A**), therefore the nucleophilicity of the *S*-atom decreases and is less reactive than amino group. In the basic conditions, the generated thiolate ion is more reactive than amino group.



Scheme 28

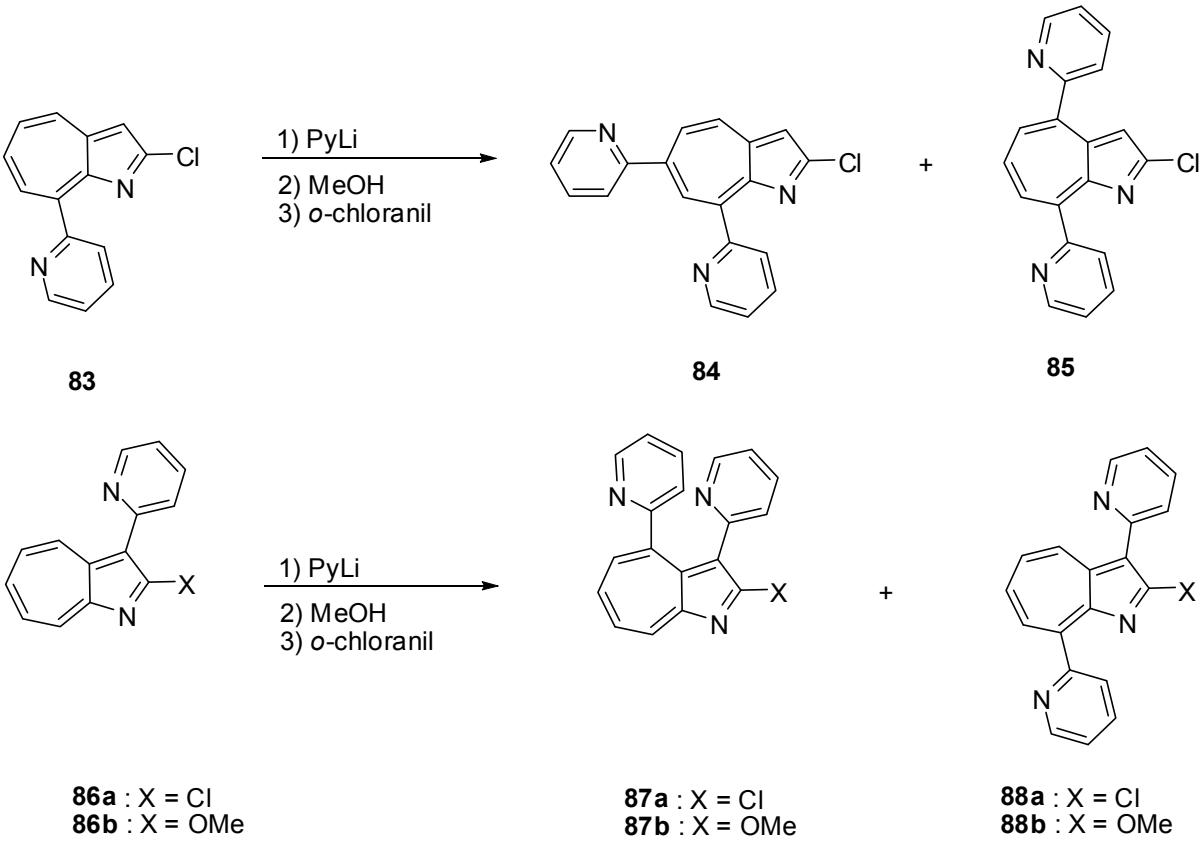
The reaction of **77** with PhMgBr followed by dehydrogenation with *o*-chloranil gave 8-, 6-, and 4-phenyl-1-azaazulenes. The addition occurred in the order of 8 > 4 > 6 in **77**.[26] The reaction of

2-chloro-1-azaazulenes (**81**) with aryllithium followed by hydrolysis and dehydrogenation with *o*-chloranil gave 8-aryl-1-azaazulenes (**82**) in good yields, regioselectively (Scheme 29).[27,28]



Scheme 29. Addition-elimination reaction of 1-azaazulenes with aryllithium

The reaction of **83** with PyLi gave **84** (58%) and **85** (4%). On the other hand, the reaction of **86a** with PyLi and subsequent quenching with MeOH followed by dehydrogenation with *o*-chloranil gave **87a** (30%), **87b** (7%), **88a** (30%), and **88b** (9%). The reaction of **86b** with PyLi gave similar result and **87b** (26%) and **88b** (30%) were obtained (Scheme 30).[29] These results show that the coordination of lithium to the ring nitrogen would be essential on regioselectivity.



Scheme 30. Reaction of 3- and 8-pyridyl-1-azaazulene with PyLi

The treatment of 8-pyridyl-1-azaazulene (**83**) with an equivalent molar of $[Cu(MeCN)_4]PF_4$ gave Cu(II)-**83** complex (**89**), and its structure was identified by X-Ray structure analysis (Figure 2).[27]

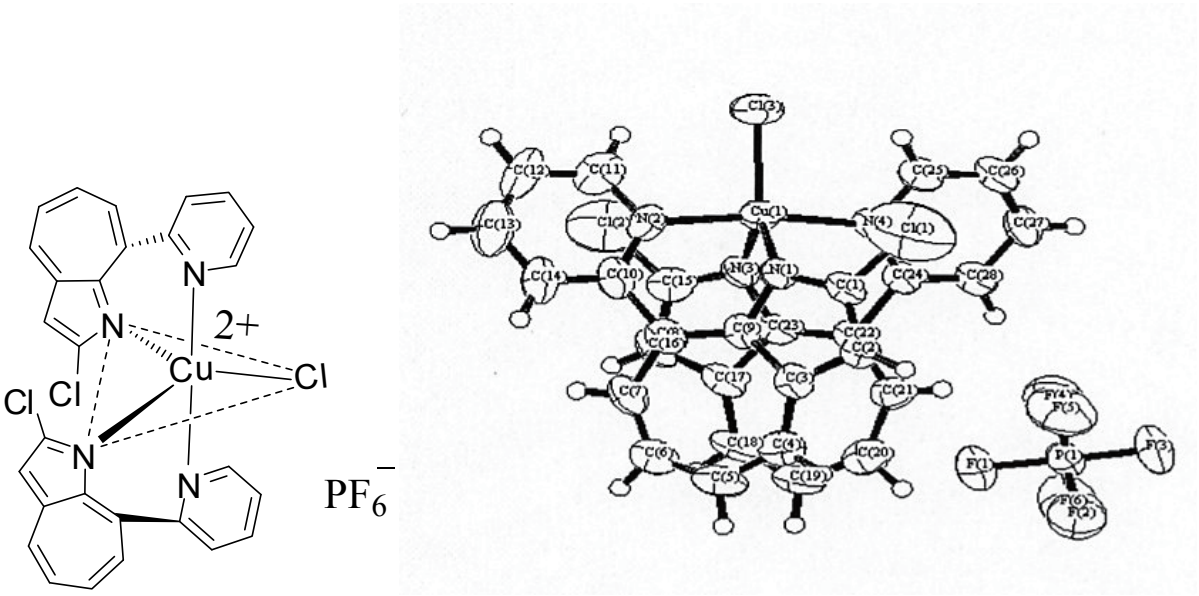
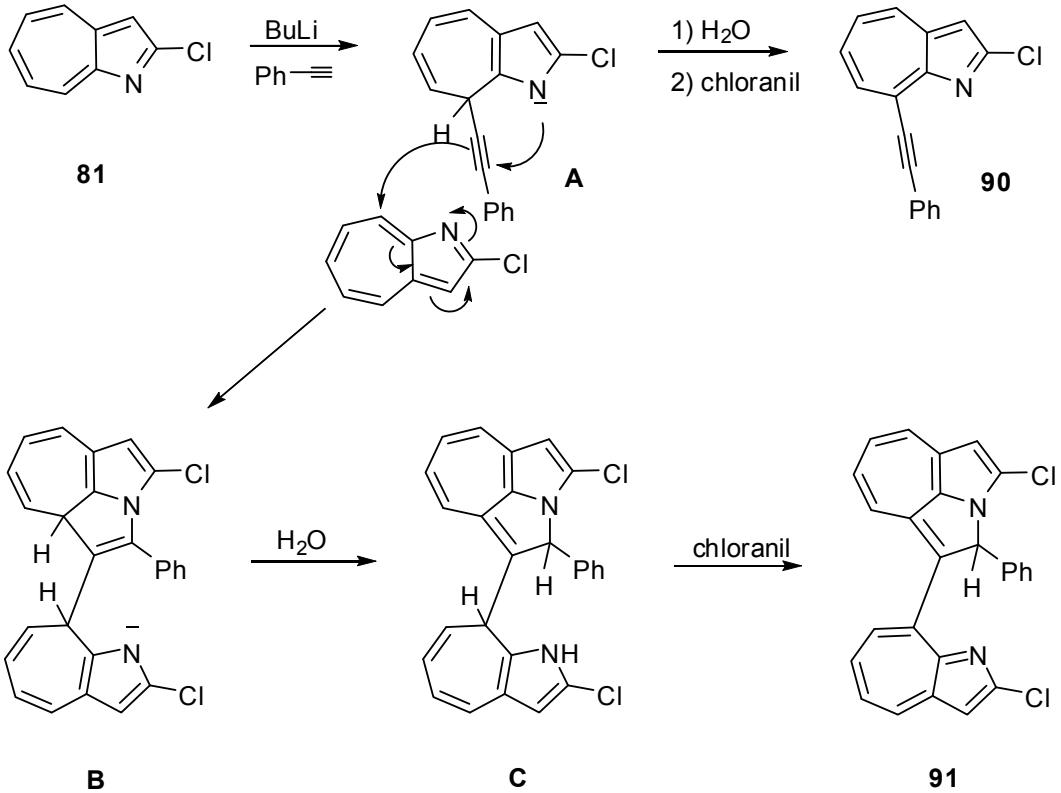


Figure 2. X-Ray structure analysis and structure of **89**

The reaction of 2-chloro-1-azaazulene with phenylethynyl lithium followed by dehydrogenation with *o*-chloranil gave 8-phenylethynyl-1-azaazulene (**90**) (13%) and **91** (86%) (Scheme 31).[30]

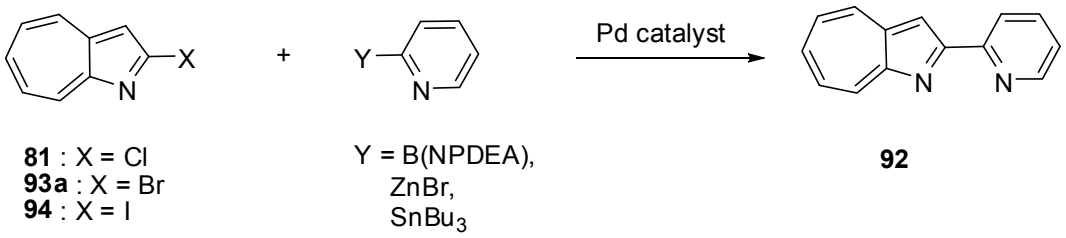


Scheme 31. Reaction of 1-azaazulene with phenylethynyllithium

C. Coupling reactions

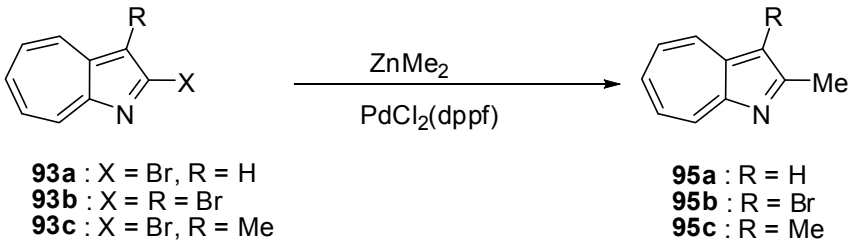
Cross-couplings of nucleophile and electrophile using transition metal catalysts are essentially important and widely applicable methods for precise syntheses.[31] In the azaazulene chemistry, the methods, such as Sonogashira-Hagihara reaction, Suzuki coupling, Negishi coupling, Hartwig-Buchwald reaction, etc., were extensively exploited recently.

For the synthesis of 2-(2-pyridyl)-1-azaazulene (**92**), which induced a specific emission (see section **IV**), Suzuki coupling, Negishi coupling, and Stille coupling of 2-halo-1-azaazulenes (**81**: X = Cl, **93a**: X = Br, **94**: X = I) were took out. Negishi coupling using 2-pyridyl bromide required a greater amount of the palladium catalyst, but when 2-iodo-1-azaazulene (**94**) was used in the reaction, the highest yield (92%) was provided (Scheme 32).[32]



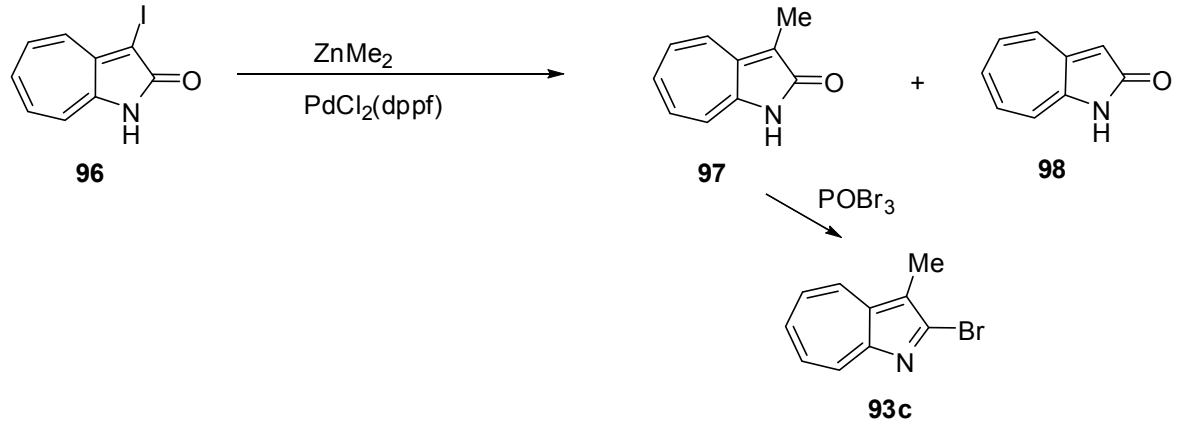
Scheme 32. Cross-coupling reaction of 2-halo-1-azaazulene

Negishi coupling of **93a-c** with $ZnMe_2$ in the presence of $PdCl_2$(dppf) gave 2-methyl-1-azaazulenes (**95a-c**) in good yields (Scheme 33).[33]



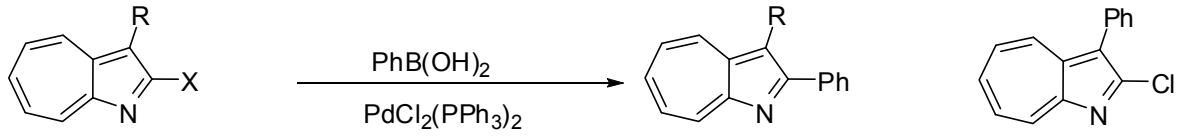
Scheme 33

The reaction of 2,3-dibromo-1-azaazulene (**95b**) occurred at only 2-position. This shows that the bromine at C-2 is more reactive than the one at C-3. Negishi coupling of 3-iodo-1-azaazulen-2(1*H*)-one (**96**) with $ZnMe_2$ gave **97** (75%) along with deiodide product (**98**: 9%) (Scheme 34). Treatment of **97** with $POBr_3$ gave **93c**.



Scheme 34

Phenylation of halo-1-azaazulenes with $PhB(OH)_2$ by Suzuki coupling proceeded well. In the reaction, it is thought that the bromine at C-2 is more reactive than the one at C-3, as in the case of Negishi coupling. Thus, the reaction of **93b** with $PhB(OH)_2$ were taken out and only **99b** was obtained in 87% yield (Scheme 35).[28]



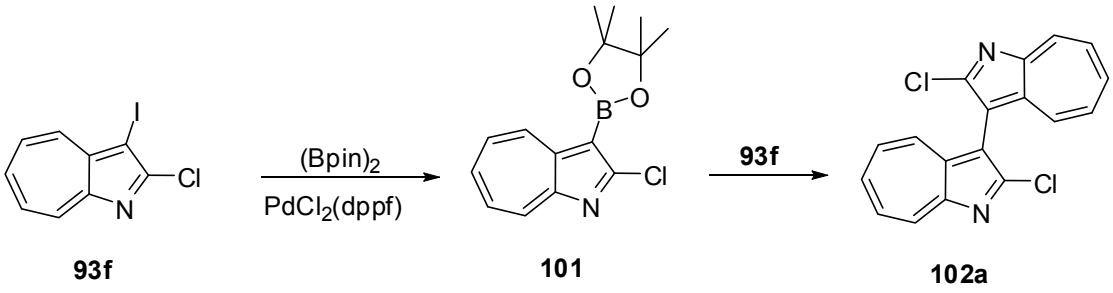
93a : X = Br, R = H
93b : X = R = Br
93d : X = Br, R = CO_2Et
93e : X = Cl, R = Br
93f : X = Cl, R = I

99a : R = H
99b : R = Br
99d : R = CO_2Et
99e : R = Ph

100

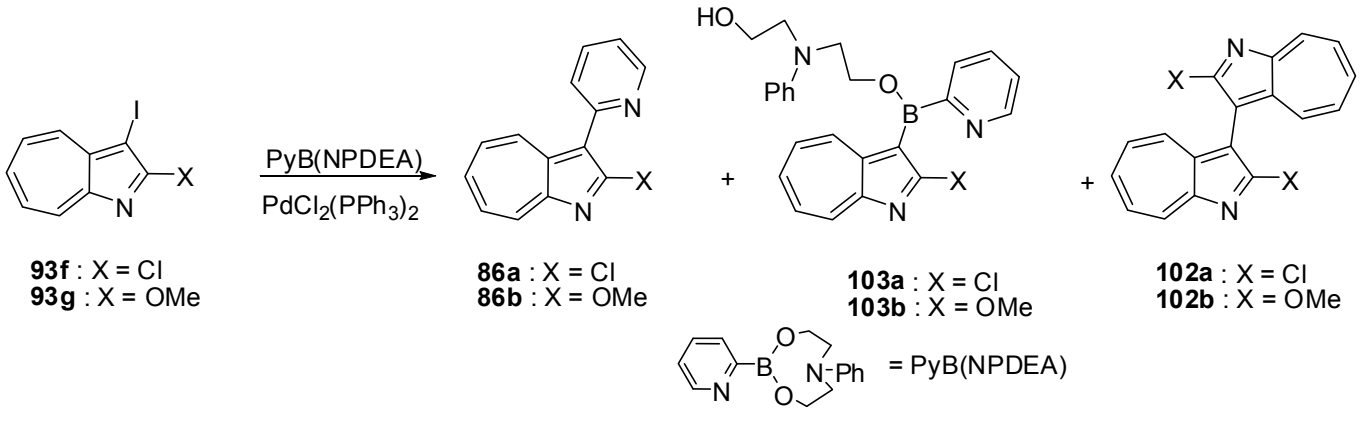
Scheme 35

Interestingly, the treatment of **93e** with $PhB(OH)_2$ gave **99e** (21%) and **100** (31%) together with a recovery of **93e** (31%). It seems that phenyl group hastened the reactivity of C-2. But the reaction of **93f** with $PhB(OH)_2$ under prolonged reaction time gave only **100** in 83% yield. The result suggests that the bromine at C-3 in **93** hasten the reactivity of C-2. For the synthesis of (1-azaazulen-3-yl)(pinacolate)boran, **93f** was treated with bis(pinacolate)diboran [$(Bpin)_2$] in the presence of $PdCl_2$(dppf), and **101** (14%) and bi(1-azaazulene) **102a** (57%) were obtained (Scheme 36).[28] Produced **101** would rapidly react with **93f** under the conditions.



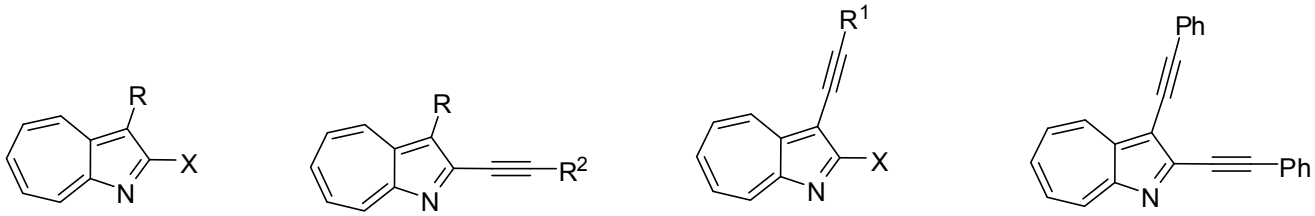
Scheme 36

On the occasion of the Suzuki coupling of **93f** with PyB(NPDEA), **103a** (3%) was isolated together with **86a** (50%), and in the reaction of **93g** with PyB(NPDEA), the dimer (**102b**) (6%) was obtained together with **86b** (84%) (Scheme 37).[29]



Scheme 37

Introduction of acetylenic moiety on the 1-azaazulene nuclei was achieved successfully by Sonogashira-Hagihara reaction. As similar as the case of Suzuki coupling, 2-bromo-1-azaazulenes and 3-iodo-azaazulenes were easily reacted with acetylenes, and gave corresponding ethynyl-1-azaazulenes (Figure 3).[30,34] The reaction of 2-chloro-1-azaazulene (**81**) with phenylacetylene in the presence of $PdCl_2(PPh_3)_2$ and CuI did not proceed, but the reaction of 2-bromo-1-azazulene (**93a**) with phenylacetylene in similar conditions gave **104a** in a good yield. The reactivities at C-2 and C-3 were similar to that on the case of Suzuki coupling. Thus the reaction of **93b** with phenylacetylene gave **104c**. The reaction of **93f** with phenylacetylene gave **105b** (76%) together with **106** (12%). The reaction of halo-1-azaazulenes with trimethylsilylacetylene afforded similar results, and **104d** and **105c** were obtained. Desilylation of **104d** and **105c** using KF gave **104e** and **105d** in good yields, respectively.[34,35]



81 : X = Cl, R = H
93a : X = Br, R = H
93b : X = R = Br
93e : X = Cl, R = Br
93f : X = Cl, R = I
93g : X = Br, R = Cl

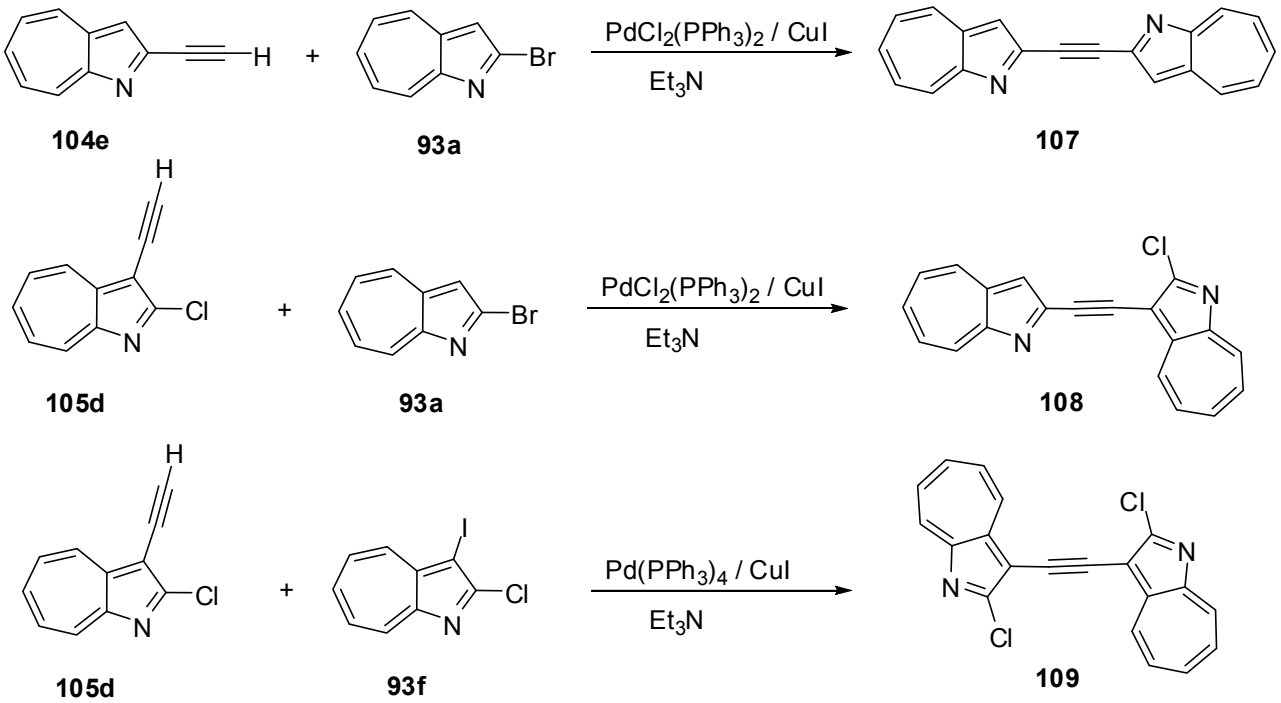
104a : R = H, R^2 = Ph
104b : R = Cl, R^2 = Ph
104c : R = Br, R^2 = Ph
104d : R = H, R^2 = TMS
104e : R = H, R^2 = H

105a : R^1 = Ph, X = Cl
105b : R^1 = Ph, X = Br
105c : R^1 = TMS, X = Cl
105d : R^1 = H, X = Cl

106

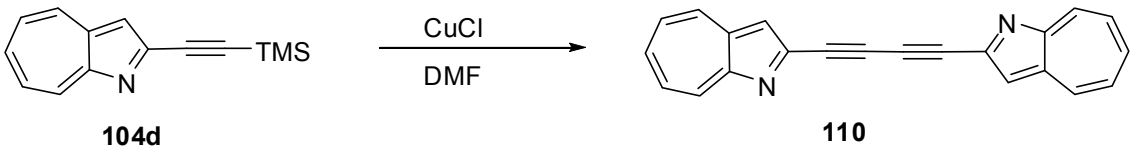
Figure 3

Suzuki coupling of **104e** with **93a**,[35] **105d** with **93a**,[35] and **105d** with **93f**[34] gave **107**, **108**, **109**, respectively (Scheme 38).



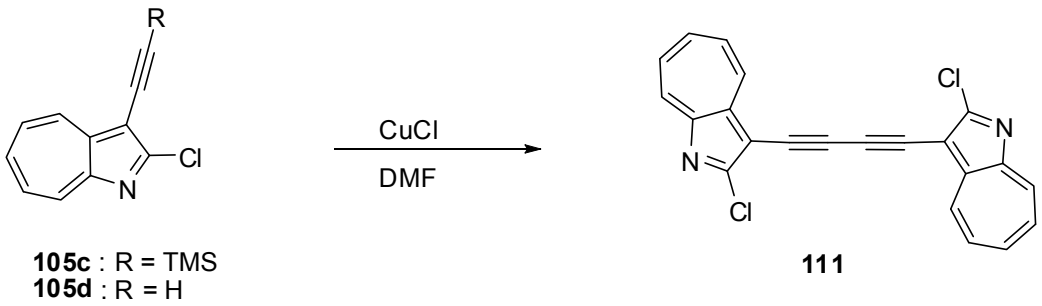
Scheme 38

Glaser coupling of **104e** was examined but the reaction did not proceed, and **110** was not obtained. But when **104d** was treated with CuCl in DMF, **110** was obtained (Scheme 39).[35]



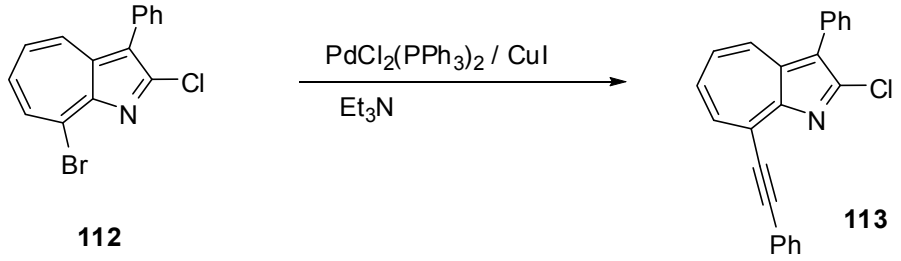
Scheme 39

On the other hand, the reaction of both **105c** and **105d** gave **111** in good yields (Scheme 40).[34]



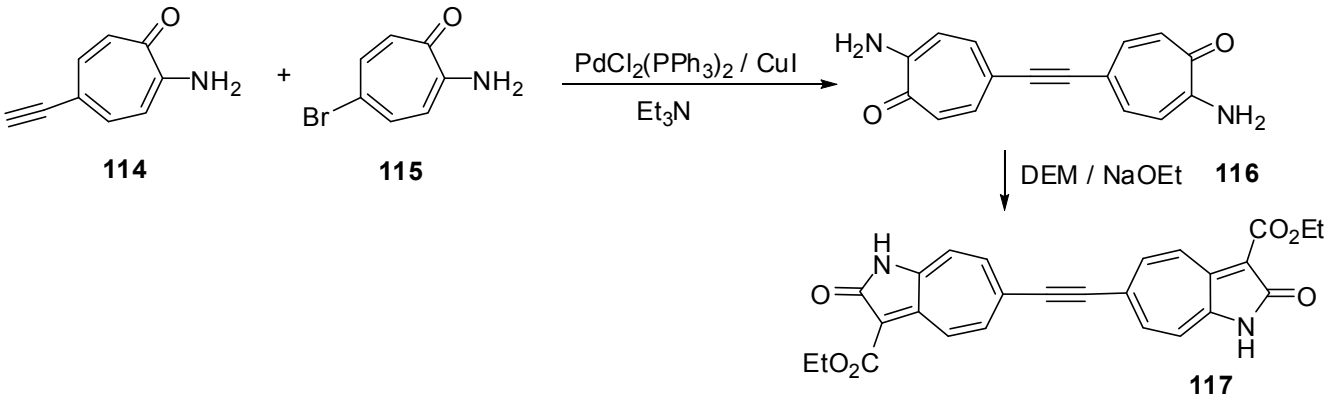
Scheme 40

Sonogashira-Hagihara reaction at seven-membered ring also proceeded. Thus the reaction of 8-bromo-1-azaazulene (**112**) with phenylacetylene in the presence of $PdCl_2(PPh_3)_2$ together with CuI gave **113** in 61% yield (Scheme 41).[34]



Scheme 41

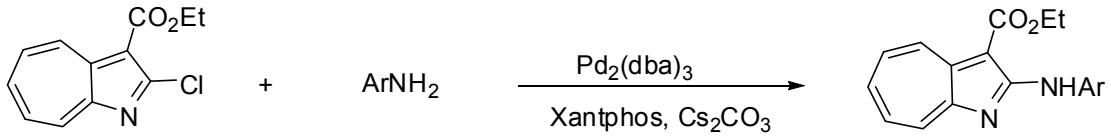
At present, 1,2-bis(1-azaazulen-6-yl)acetylene was not synthesized form the 1-azaazulene by similar methods, but it was synthesized *via* 1,2-bis(1-aminotropon-5-yl)acetylene. Sonogashira-Hagihara reaction of **114** with **115** gave **116**, and successive reaction of **116** with diethyl malonate (DEM) in the presence of NaOEt gave **117** (Scheme 42).[35]



Scheme 42

In common with other aromatics, a halogen group in the azaazulenes can be displaced by a nucleophile, and an amino group is easily introduced on the azaazulene nuclei.[1] Nevertheless, an introduction of

heteroarylamino group on the 1-azaazulene was unsuccessful.[36] Hartwig-Buchwald reaction is well known as superior method for the amination of aromatics.[37] Therefore, an application of Hartwig-Buchwald reaction was carried out to introduce heteroarylamino group on 1-azaazulene nuclei. The reaction of **77** with heteroarylamines in the presence of $Pd_2(dba)_3$, Xantphos, and $CsCO_3$ in dioxane at 120 ºC was undertaken and the corresponding 2-(heteroarylamino)-1-azaaulenes (**118**) yielded in good yields (Scheme 43).[36]

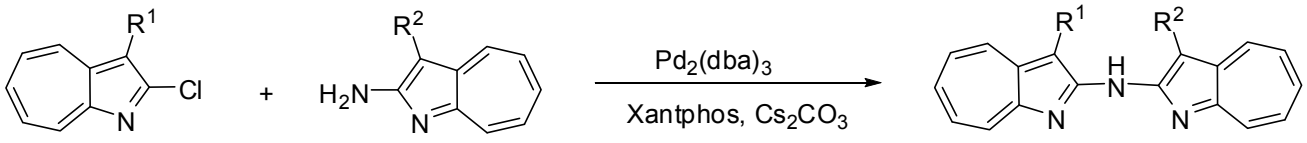


77 **118**

Ar = 2-Py, 4-Py, 2-pyrimidinyl, 2-pyrazinyl, 2-thiazolyl, 2-benzimidazolyl, 2-benzothiazolyl, 1-azaazulen-2-yl, 1-azaazulen-8-yl, 1-isoquinolinyl

Scheme 43

This method was also suited for the synthesis of bis(1-azaazulenyl)amines (Scheme 44).[38]



119 **120** **121**

R^1 = H, CO_2Et, NO_2, Ph R^2 = H, Ph

Scheme 44

D. Cycloaddition and Annulation

Cycloadditions of azaazulenes or annulations on azaazulene nuclei are extremely interest from their wide variety of reaction pattern and synthetically use for novel heterocycles.

The reaction of 2-chloro-1-azaazulene (**81**) with benzyne (**123**) in CH_2Cl_2, generated from **124** and TBAF (Kitamura's method), gave **125** and **126** in low yields together with recovered **81**. Similar treatment of **122a** gave **125** and **127a**, and the treatment of **122b** gave only **128** as distinct product. The reaction of 2-chloro-1-azaazulene (**81**) with benzyne (**123**), generated from **130** in 1,2-dichloroethane under reflux, gave **126** and **131** (Figure 4).[39] Similar reaction of **122a** gave **131** and **132**. These results suggested that the benzyne, having higher energy, can undergo Diels-Alder type reaction, but the benzyne, having lower energy, takes out Michael type addition.

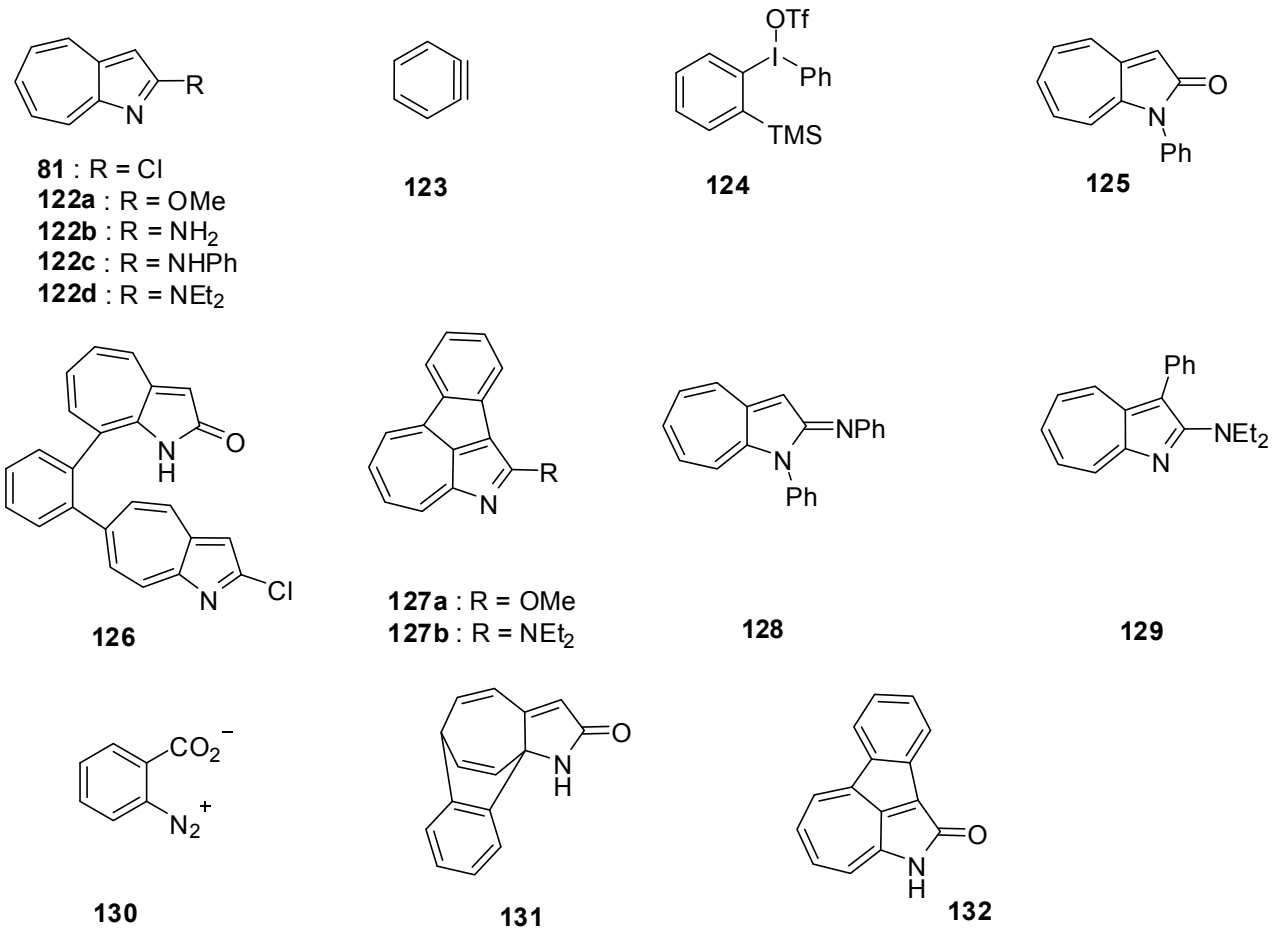
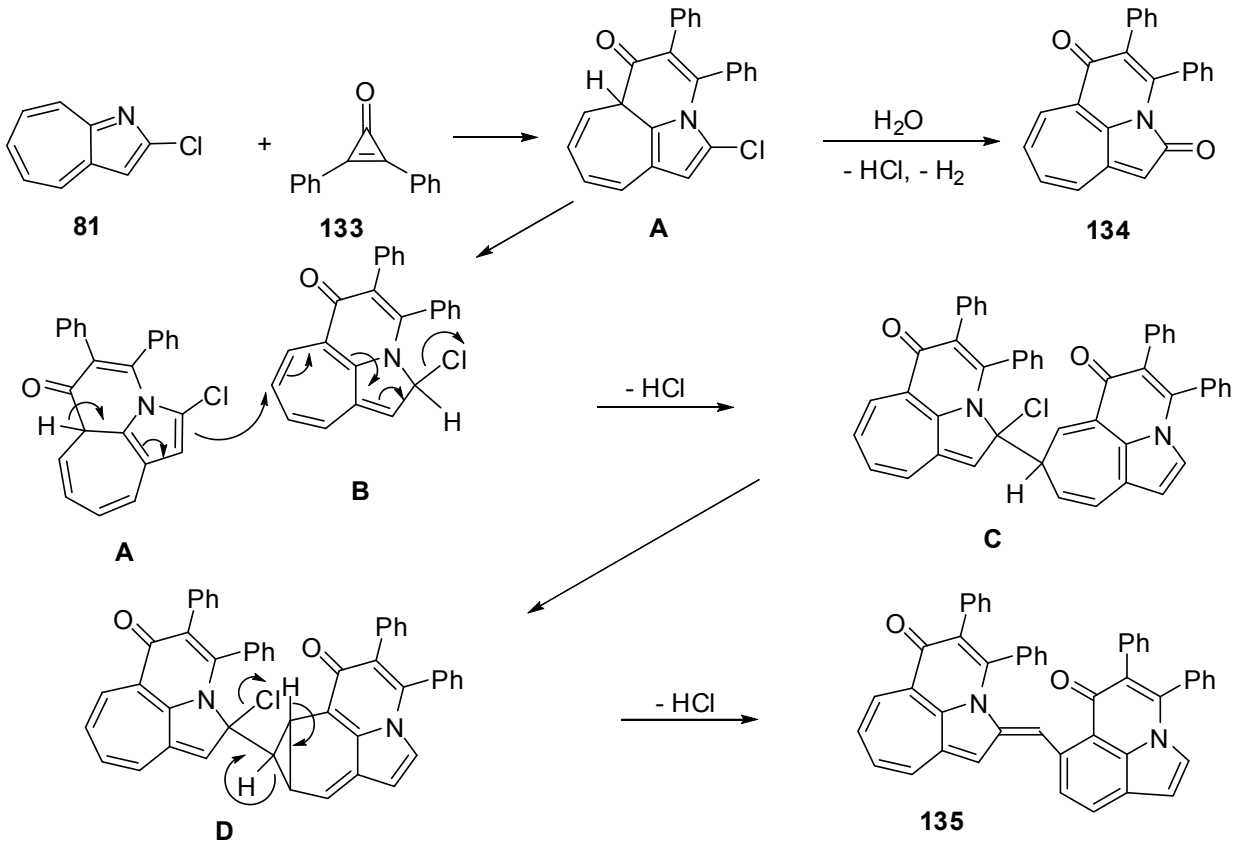


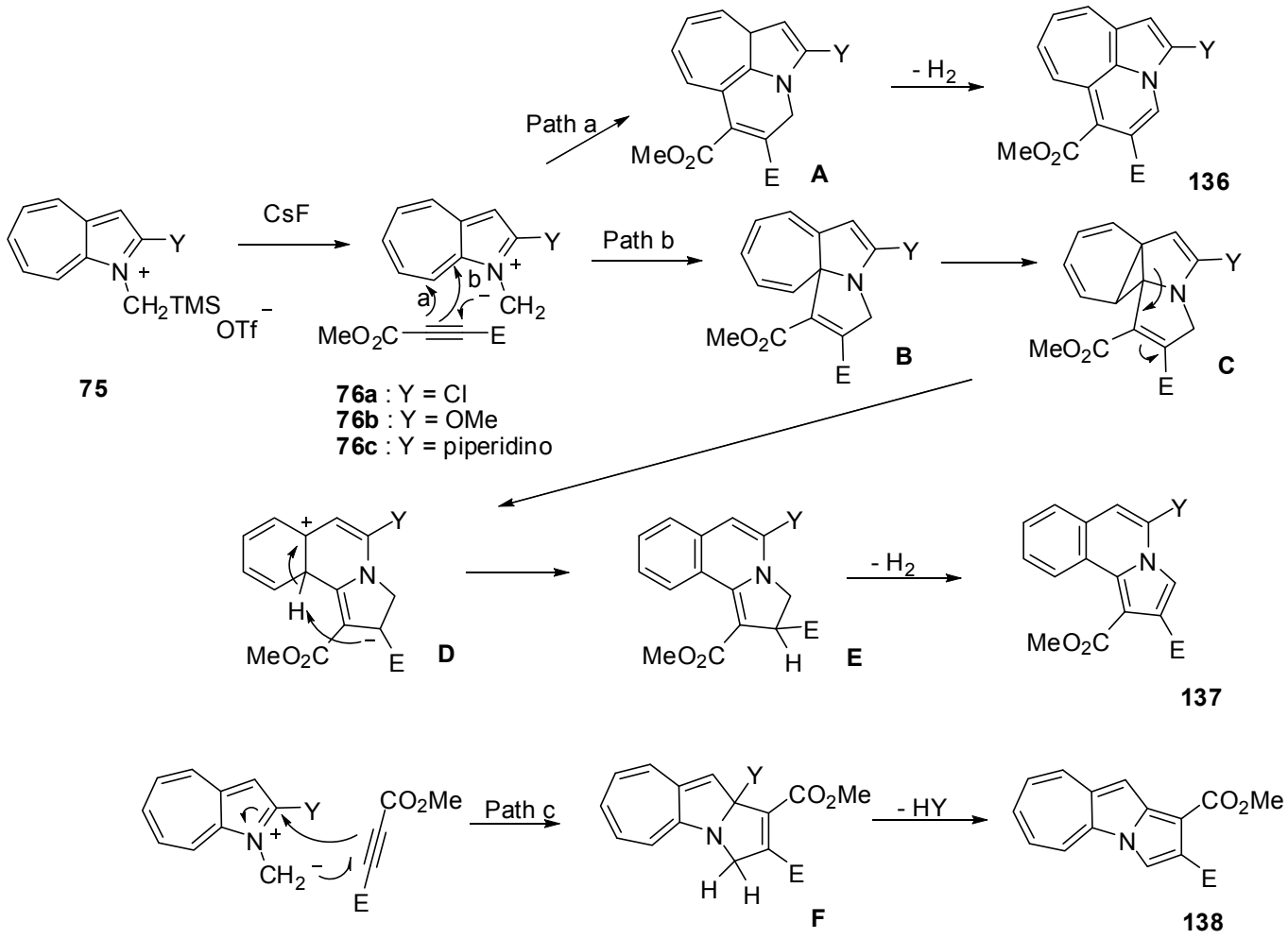
Figure 4

Cycloaddition of 2-chloro-1-azaazulene (**81**) with diphenylcyclopropenone (**133**) showed interesting feature, and gave **134** (4%) and **135** (19%) along with recovered **81** (58%) (Scheme 45).[40] The structure of **135** was confirmed by X-Ray structural analysis. At first, an extended dipolar cycloaddition of diphenylcyclopropenone occurred at N-1 and C-8 of 1-azaazulene nuclei, and an intermediate **A** would be produced. The nucleophilic attack of H_2O to **A**, accompanied with elimination of HCl and dehydrogenation, gave **134**. A hydrogen migration of **A** would give an intermediate **B**. The cine-substitution of **B** with **A** would produce an intermediate **C**. The cycloheptatriene-norcaradiene interconversion of **C** affords **D**. The ring contraction of **D** attended with elimination of HCl furnishes **135**.



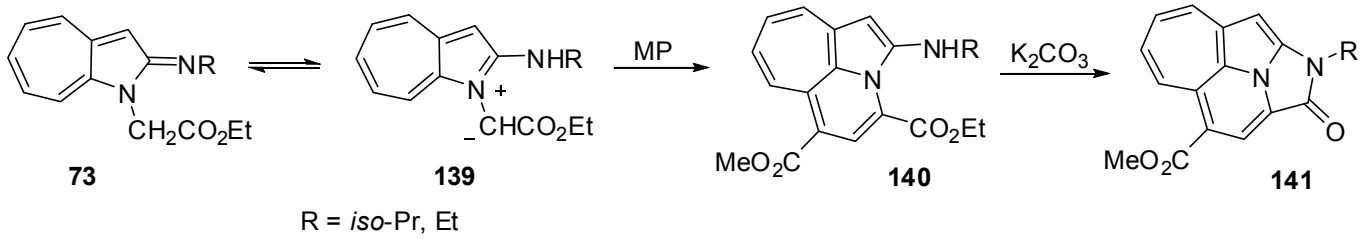
Scheme 45

Cycloadditions of 1-aza- and 1,3-diaza-azulenium 1-methylides (azaazulene *N*-ylides) with acetylenic esters were reported (Scheme 46).[24a,b] The reaction of 2-chloro-1-azaazulenium 1-methylide (**76a**) with DMAD gave **136** (23%) and **137** (32%). Reaction of 2-methoxy-1-azaazulenium methylode (**76b**) with DMAD gave **136** (7%), **137** (1%), and **138** (14%). The dipolar cyclization at the carbanion moiety (CH_2^-) and C-8 of **76** gave **136** (path a) and the dipolar cyclization at the carbanion moiety (CH_2^-) and C-8a of **76** followed by the rearrangement and hydrogen migration gave **137** (path b), respectively. The reaction of 2-(*N*-piperidino)-1-azaazulenium 1-methylide (**76c**) with DMAD gave **138** (22%) as a major product. The selectivities of the reaction site on the cycloaddition of 1-azaazulenium methylides were affected by the nature of the substituent of **76**. Although their yields were low, the regioselectivity of the reaction was established by the reaction of **76a** with methyl propiolate (MP) as shown in the Scheme 46.[24b]



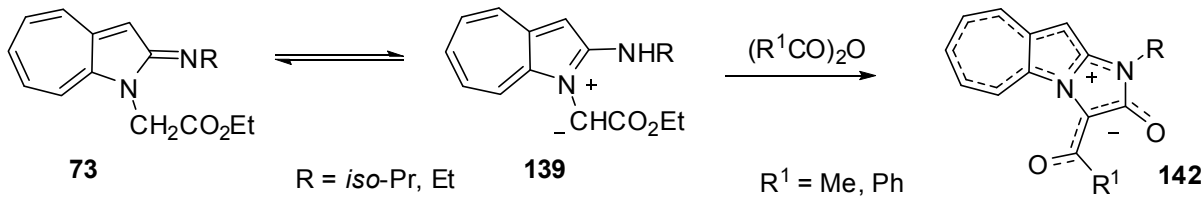
Scheme 46

Although the compound **73** exists mainly in the imino-form, a potentiality of having a tautomerism with its ylide form **139** raises some investigation. As expected, the treatment of **73** with MP in MeCN for 8 h underwent cycloaddition to give **140** (23%) (Scheme 47).[23] The treatment under prolonged reaction time or the reaction in the presence of K_2CO_3 gave **141** together with **140**. The compound **140** was quantitatively converted to **141** by the treatment of **140** with K_2CO_3 in refluxing MeCN.



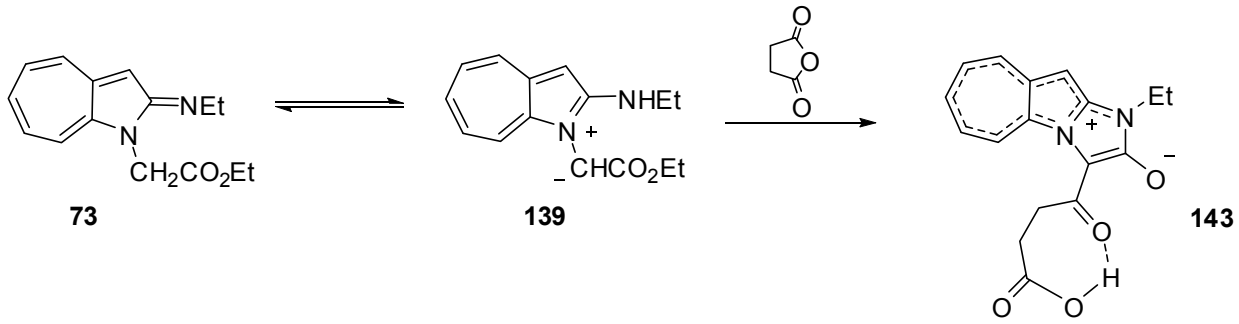
Scheme 47

The treatment of **73** with acid anhydrides such as acetic anhydride or benzoic anhydride in the presence of K_2CO_3 gave mesoionic compounds (**142**) in 90-95% yields (Scheme 48).[23]



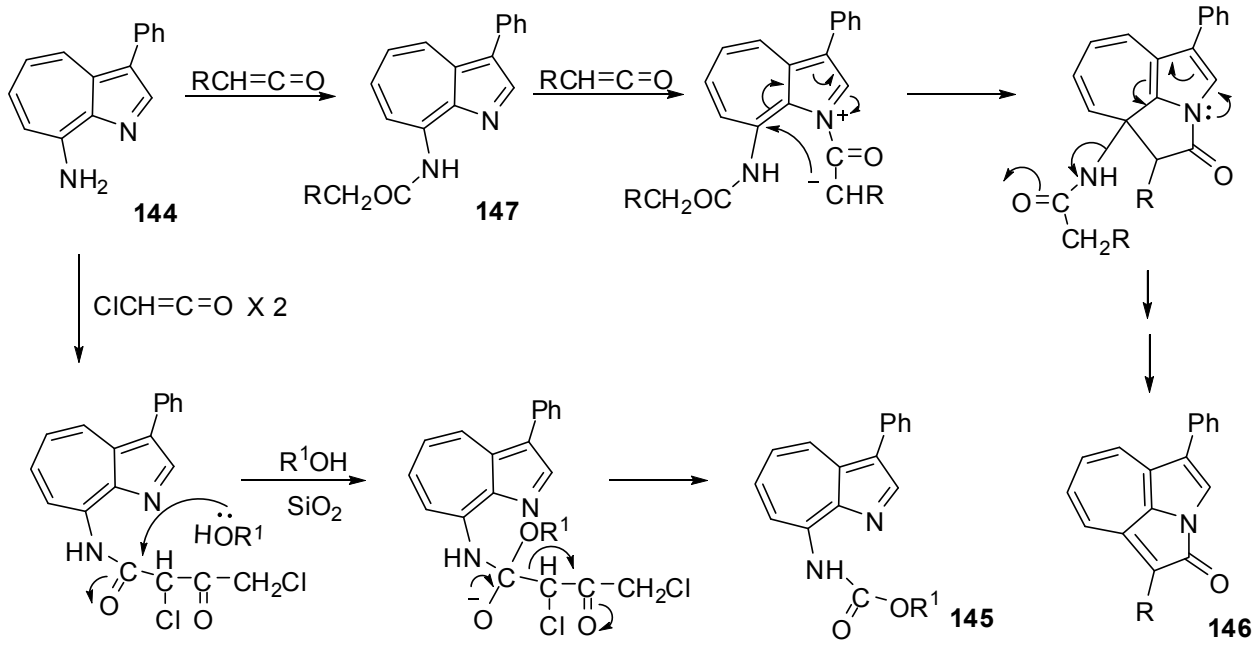
Scheme 48

The structure of **142** was confirmed by X-Ray structure analysis. Similar treatment of **73** with succinic anhydride gave **143** (Scheme 49).[23]



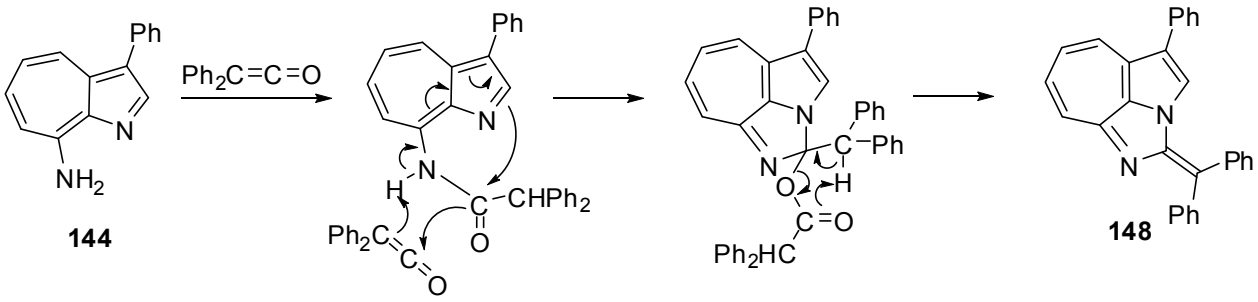
Scheme 49

It have been reported that 2-amino-1-azaazulenes reacted with halo- and phenylketenes to give various types of cycloadducts according to the nature of the substituents and the ketenes.[41] For comparison with 2-amino-1-azaazulenes, the reaction of 8-amino-1-azaazulene was performed. The treatment of 8-amino-3-phenyl-1-azaazulene (**144**) with chloroketene gave **145** and **146** in low yields together with **147** (Scheme 50).[42] Further treatment of **147** with chloroketene gave **145**. It was shown that the compound (**146**) was produced at the stage of chromatography on the silica gel in the presence of an alcohol. The reaction of **144** with phenylketene gave **145** and **147**, but the compound like **146** was not isolated (Scheme 50).



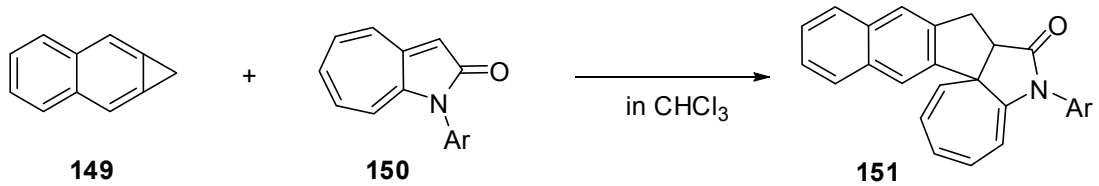
Scheme 50

The reaction of **144** with diphenylketene gave **148** (Scheme 51).[42]



Scheme 51

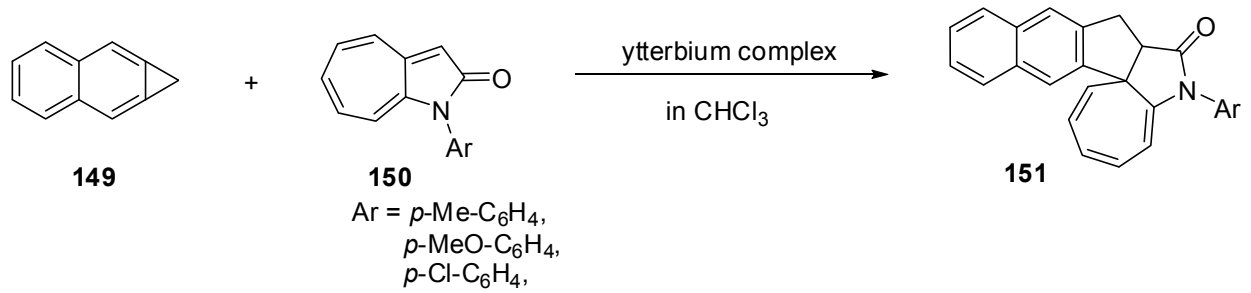
Saito reported interesting [π2 + σ2] and [π8 + σ2] type cycloaddition of 1-azaazulen-2(1*H*)-one derivatives.[43] Naphtho[*b*]cyclopropene (**149**) reacted with 1-azaazulen-2(1*H*)-ones (**150**) in the presence of ytterbium complex as catalyst in $CHCl_3$ to give [π2 + σ2] type cycloadducts (**151**) (Scheme 52).



Ar = *p*-Me-C_6H_4,
p-OMe-C_6H_4,
p-Cl-C_6H_4,

Scheme 52

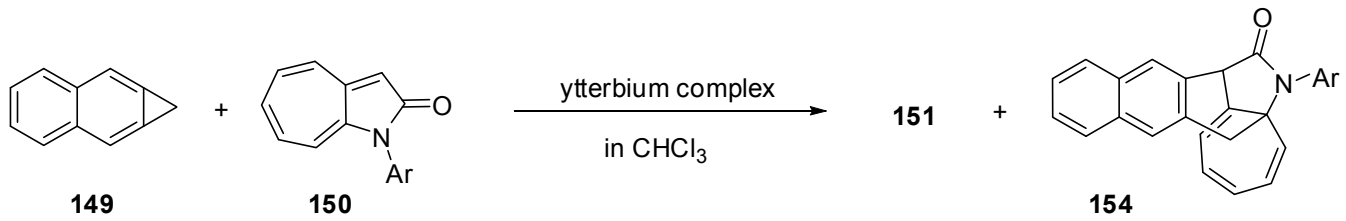
The similar reaction of **149** with 1-thia-3-azaazulen-2(1*H*)-one (**152**) gave [π8 + σ2] type cycloadduct (**153**) (Scheme 53).



149 150 151

Scheme 53

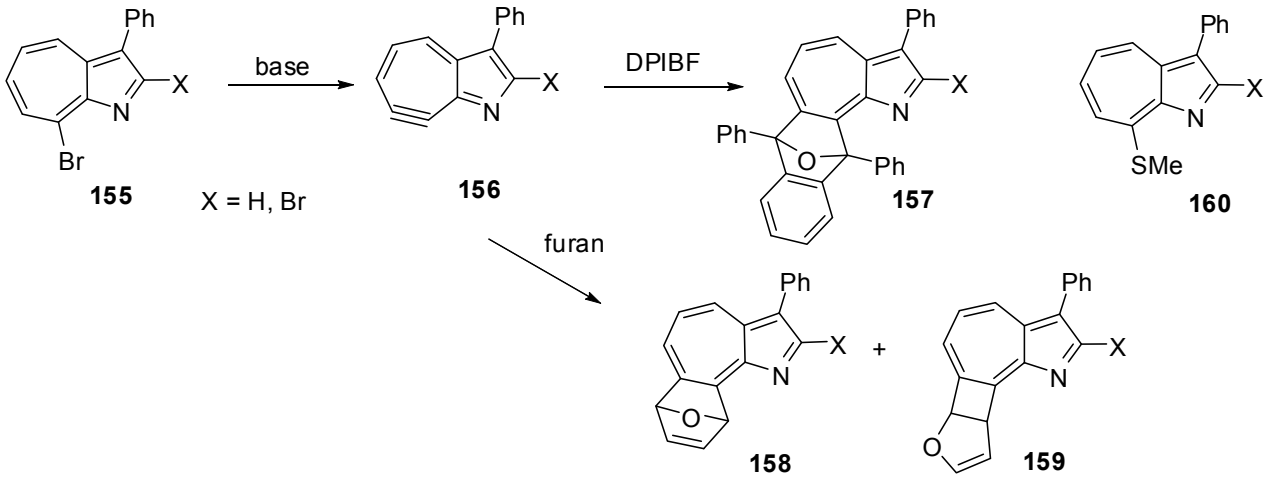
It is thought that these reactions proceeded *via* ionic processes. When the reaction **149** with **150** was performed in benzene, another type of [π8 + σ2] type cycloadducts (**154**) were obtained *via* a concerted process (Scheme 54).



149 150 151 154

Scheme 54

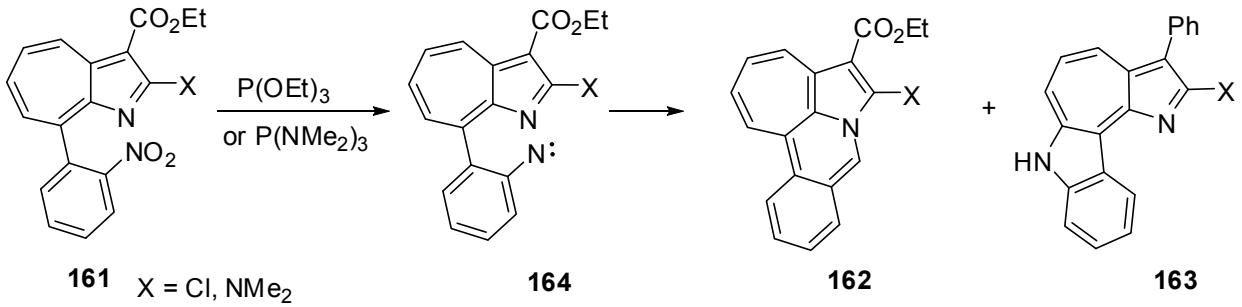
Generation and reaction of 7,8-dehydro-1-azaazulene were reported.[44] The treatment of 8-bromo-1-azaazulene (**155**) with *t*-BuOK in DMSO or in THF in the presence of 16-crown-8-ether generated 7,8-dehydro-1-azaazulene (**156**), which was trapped with diphenylisobenzofuran (DPIBF) or furan to give **157** or **158** and **159** (Scheme 55). Interestingly, when the reaction was performed in DMSO, the compound **160** was obxy-product.



155 156 157 158 159 160

Scheme 55

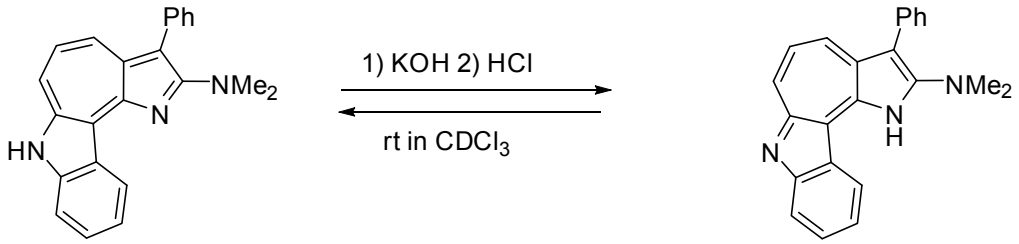
Reductive cyclization of 8-(2-nitrophenyl)-1-azaazulenes (**161**) using $P(OEt)_3$ or $P(NMe_2)_3$ produced diazanaphth[3,2,1-*cd*]azulenes (**162**) and 7*H*-1,7-diazaindeno[1,2-*e*]azulenes (**163**) *via* the nitrene (**164**) (Scheme 56).[45]



161 X = Cl, NMe_2 **164** **162** **163**

Scheme 56

Tautomerisation between **163** and **165** was investigated; **163** was converted to **165** by the treatment of aq. KOH followed by aq. HCl, and **165** was converted to **163** at rt with a half-life period of 20 d in $CDCl_3$ (Scheme 57).



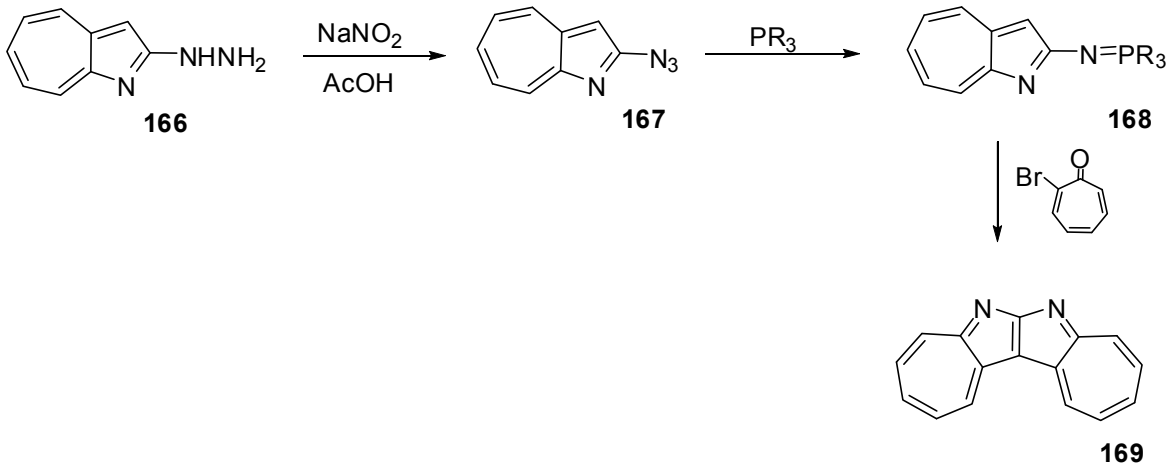
163 **165**

Scheme 57

E. Aza-Wittig reaction

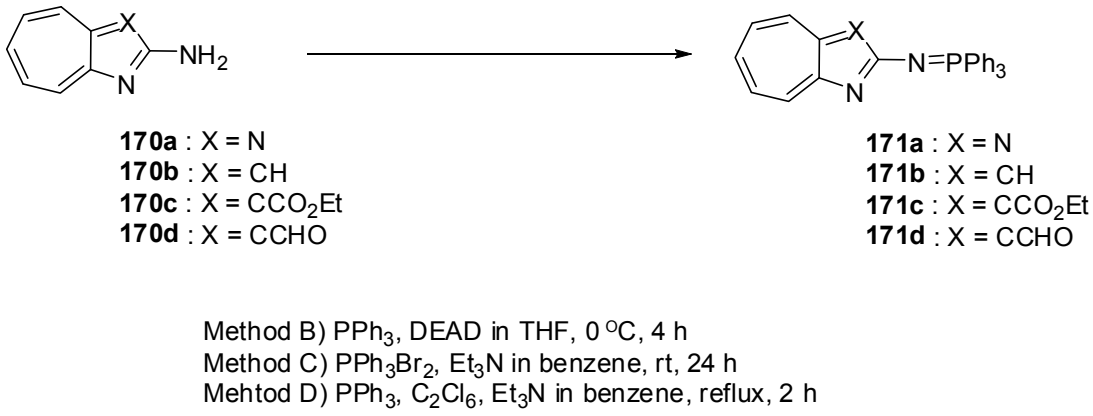
The aza-Wittig reaction of iminophosphoranes is one of the most useful methodologies for the synthesis of nitrogen-containing heterocycles.[6,46] The aza-Wittig reactions of phosphoimino-azaazulene derivatives were reported by Nitta.[47-49] and Abe,[50-54] independently. Synthesis of 2-phosphoimino-1-azaazulenes, 2-phosphoimino-1,3-diazaazulene, and 8-phosphoimino-1-azaazulene were achieved by four different methods using A) Staudinger reaction,[46,47,55] B) Mitsunobu conditions,[48,56] C) Kirsanov reaction,[50,52,57] and D) Appel reaction.[52,54,58]

At first, Nitta et al. synthesized 2-phosphoimino-1-azaazulene (**168**) from 2-azido-1-azaazulene (**167**), prepared from 2-hydrazino-1-azaazulene (**166**), by Staudinger reaction (Scheme 58). By the reaction of **168** with 2-bromotropone, they synthesized **169**.[47]



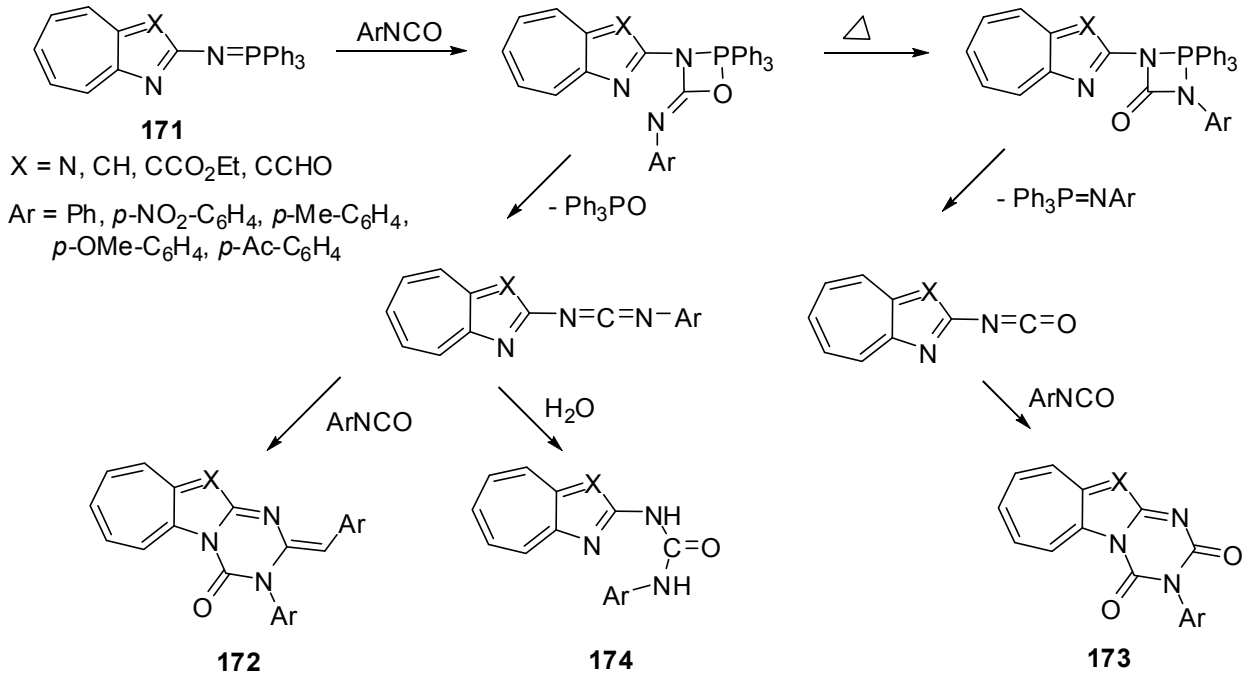
Scheme 58

2-Phosphoimino-1,3-diazaazulene (**171a**) and 2-phosphoimino-1-azaazulenes (**171b-d**) were synthesized from corresponding 2-amino-1,3-diazaazulene (**170a**) and 2-amino-1-azaazulenes (**170b-d**) by three ways (Method B,[48] Method C,[52] and Method D[52]) as shown in the Scheme 59.



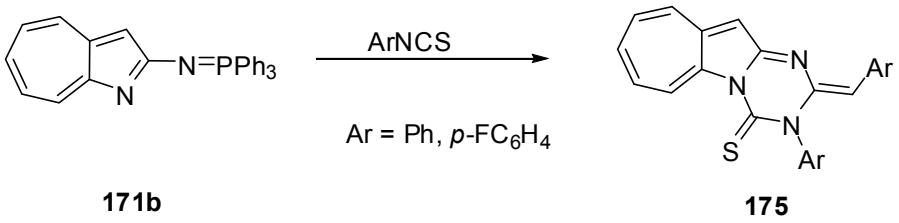
Scheme 59

The reaction of **171** with aryl isocyanates gave **172**, being produced as aza-Wittig reaction products, and **173**, being produced as abnormal aza-Wittig reaction products, along with **174**.[48,49,52] At lower temperature (rt ~ 60 ºC), **172** and **174** were obtained. Whereas the reaction was carried out at elevated temperature (benzene reflux ~ xylene reflux), **173** was obtained together with **172** and **174**. The reaction would proceed as shown in the Scheme 60.



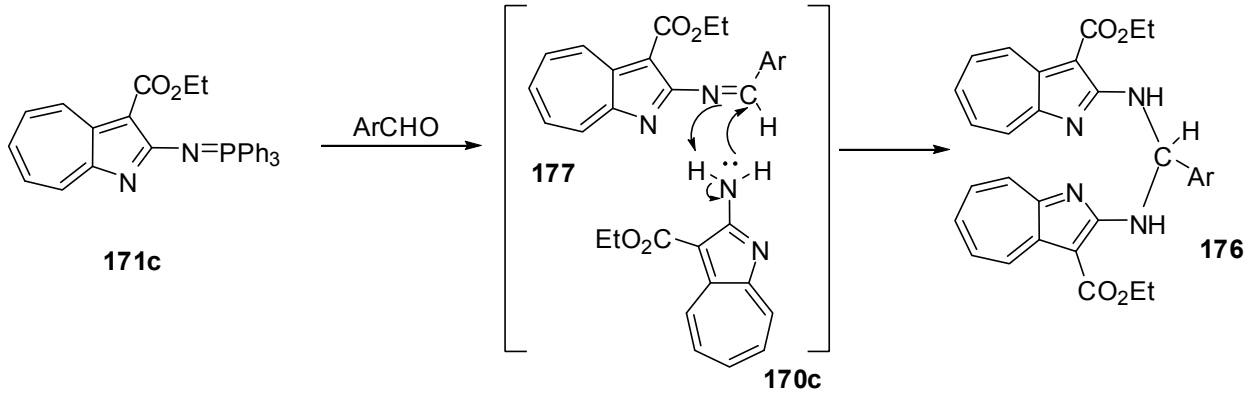
Scheme 60

Aryl isothiocyanates also reacted with **171b** and to give cycloadducts (**175**) (Scheme 61).[52,59]



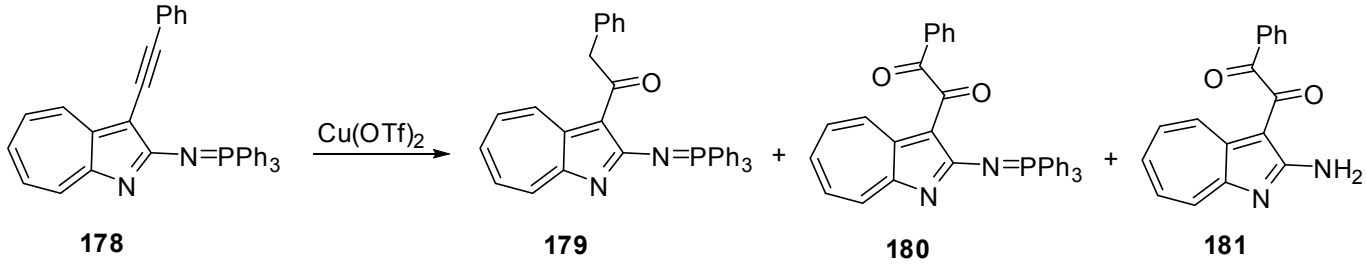
Scheme 61

2-Phosphoimino-1-azaazulene (**171c**) reacted with aryl aldehydes and to give **176** (Scheme 62).[59] In the reaction, the Schiff base (**177**) was not isolated. Addition of small amount of 2-amino-1-azaazulene (**170c**) accelerated the reaction. The results suggested that **170c**, produced by hydrolysis of **171**, easily reacted with **177**.



Scheme 62

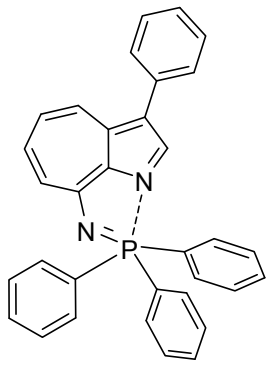
3-Ethynyl-2-phosphoimino-1-azaazulene (**178**) was synthesized from 2-amino-3-ethynyl-1-azaazulene by Appel reaction.[54] When **178** was treated with $Cu(OTf)_2$, no cyclization product was isolated; instead, compounds (**179**, **180**, and **181**) were obtained (Scheme 63).[54] The reaction of **178** with aryl isocyanate gave similar results in the case of **171** as shown in Scheme 60. The treatment of **178** with aryl isocyanate in the presence of benzoyl peroxide gave a cyclization product in low yield.[54]



178 **179** **180** **181**

Scheme 63

8-Phosphoimino-1-azaazulene (**182**) was synthesized from 8-amino-1-azaazulene (**183**) by the Kirsanov reaction (Scheme 64).[50] The structure of **182** was determined by X-Ray structure analysis (Figure 5). The bond distance between N(2) and P(1) is 2.762(6) Å, which is rather short from the value of van der Waals radii (3.4 Å). The bond distance between N(1) and P(1) is 1.597(2) Å and the bond distance between N(1) and C(1) is 1.350(2) Å; these can regard as intermediate value between single bonds and double bonds. Therefore, the existence of the resonance between the formulas **182** and **182A** can be presumed.



182

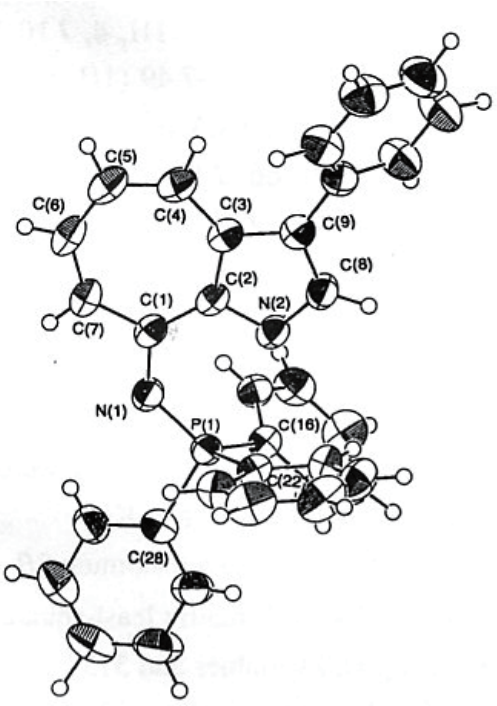
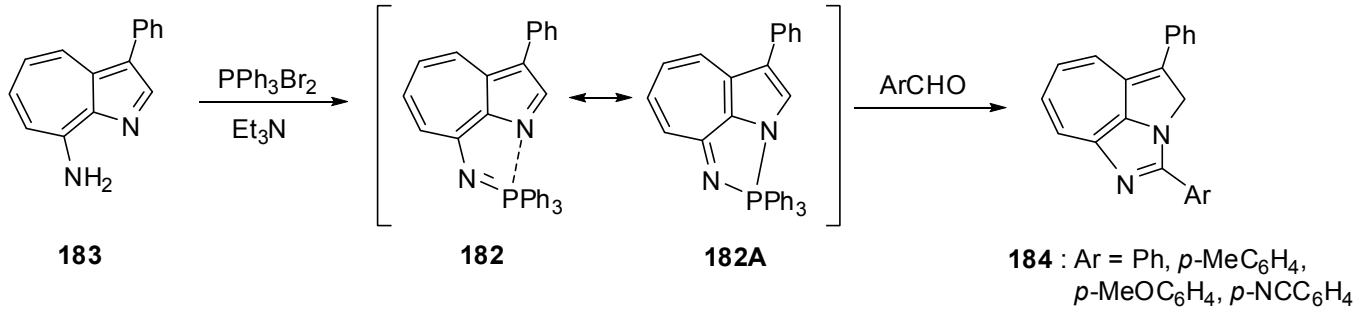


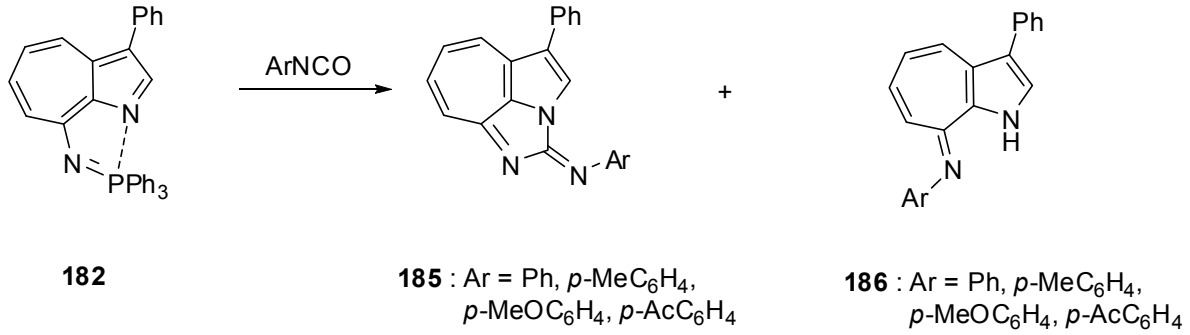
Figure 5 X-Ray structure of **182**

Some reactions of **182** were examined. The aza-Wittig reaction of **182** with aryl aldehydes proceeded, and following cyclization and hydrogen migration gave **184** (Scheme 64).[51]



Scheme 64

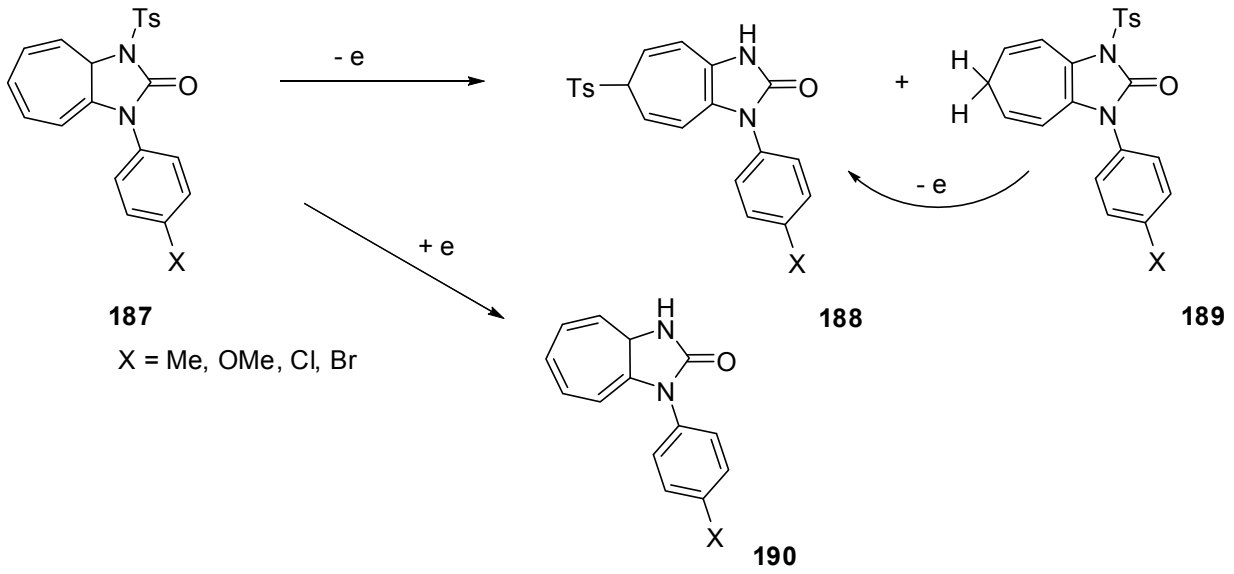
The reaction of **182** with aryl isocyanates gave the cyclization products (**185**) together with **186** (Scheme 65).[53]



Scheme 65

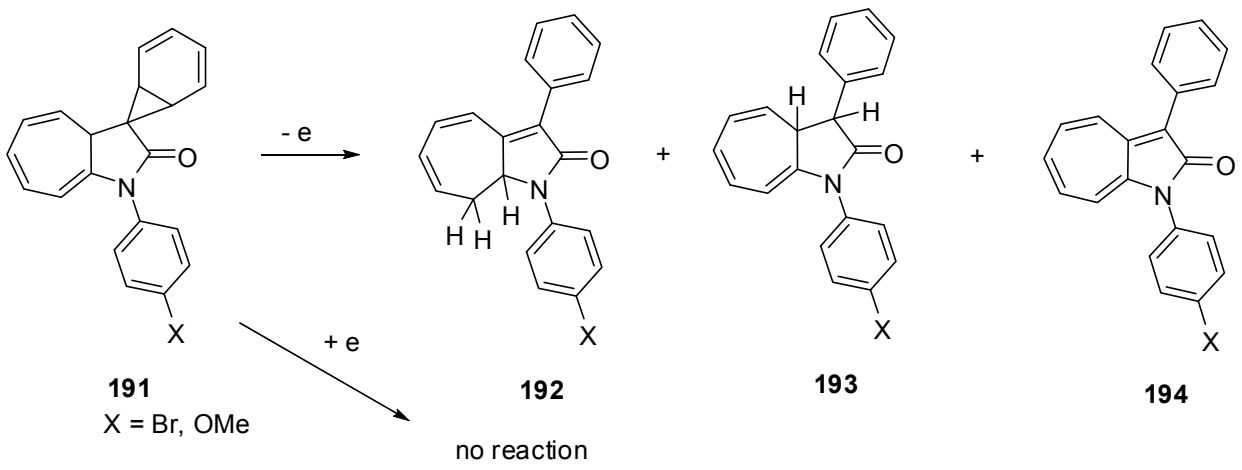
F. Electrochemical reactions and photoreactions.

Electrochemical oxidation of 1-aryl-3-tosyl-1,2,3,3a-tetrahydro-1,3-diazaazulen-2-ones (**187**) gave 6-tosyl-1-aryl-1,2,3,6-tetrahaydro-1,3-diazaazulen-2-ones (**188**) *via* migrations of the tosyl group.[60a] Circumstantial examination of the electrochemical oxidation of **187** showed that **189** was produced at first, and successive electrolysis of **189** gave **188** (Scheme 66).[60b] Electrochemical oxidation of **188** resulted in the recoveries of the starting material (**188**). On the other hand, electrochemical reductions of **187** gave 1-aryl-1,2,3,3a-tetrahydro-1,3-diazaazulen-2-ones (**190**) through eliminations of the tosyl group (Scheme 66).[60a]



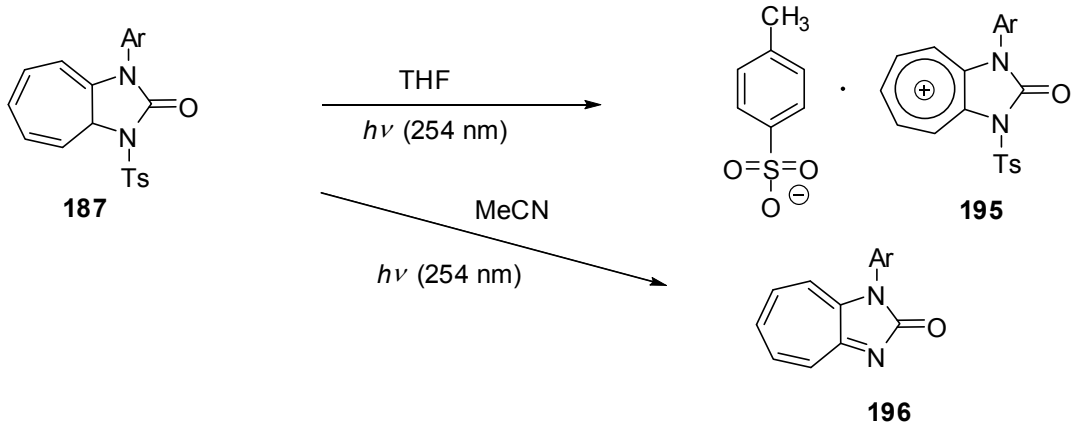
Scheme 66

Electrochemical oxidation of 1,2,3,3a-tetrahydro-1-azaazulen-2-ones (**191**), possessing a spirocyclic moiety, afforded 1,3-diaryl-1,2,8,8a-tetrahydro-1-azaazulen-2-ones (**192**) and 1,3-diaryl-1,2,3,3a-tetrahydro-1-azaazulen-2-ones (**193**) together with 1,3-diaryl-1-azaazulen-2(1*H*)-ones (**194**) (Scheme 67).[61]



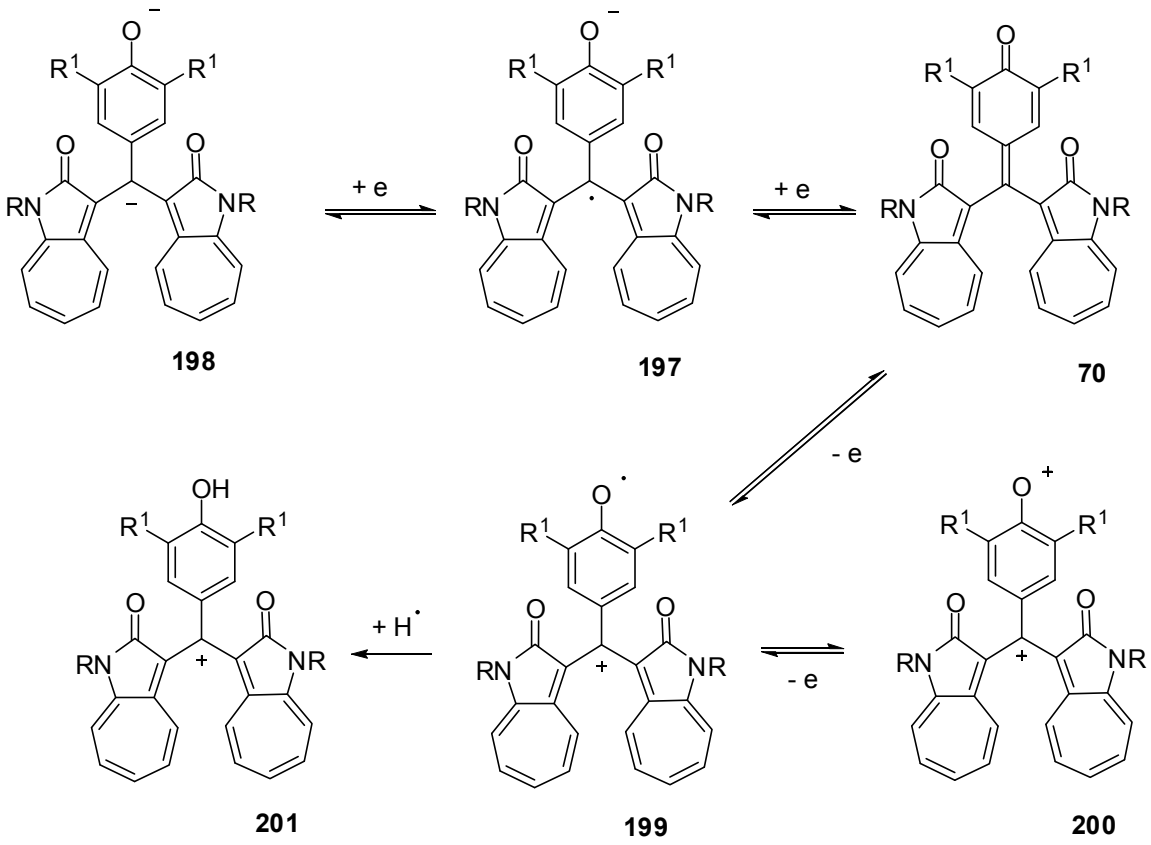
Scheme 67

The photoreaction of **187** showed a solvent effect. The reaction in THF gave ion pairs (**195**) between *p*-toluenesulfonate anion and 1-aryl-2,3-dihydro-1,3-diazaazulen-2(1*H*)-one cations. On the other hand, the reaction in polar solvent afforded **196**.[62]



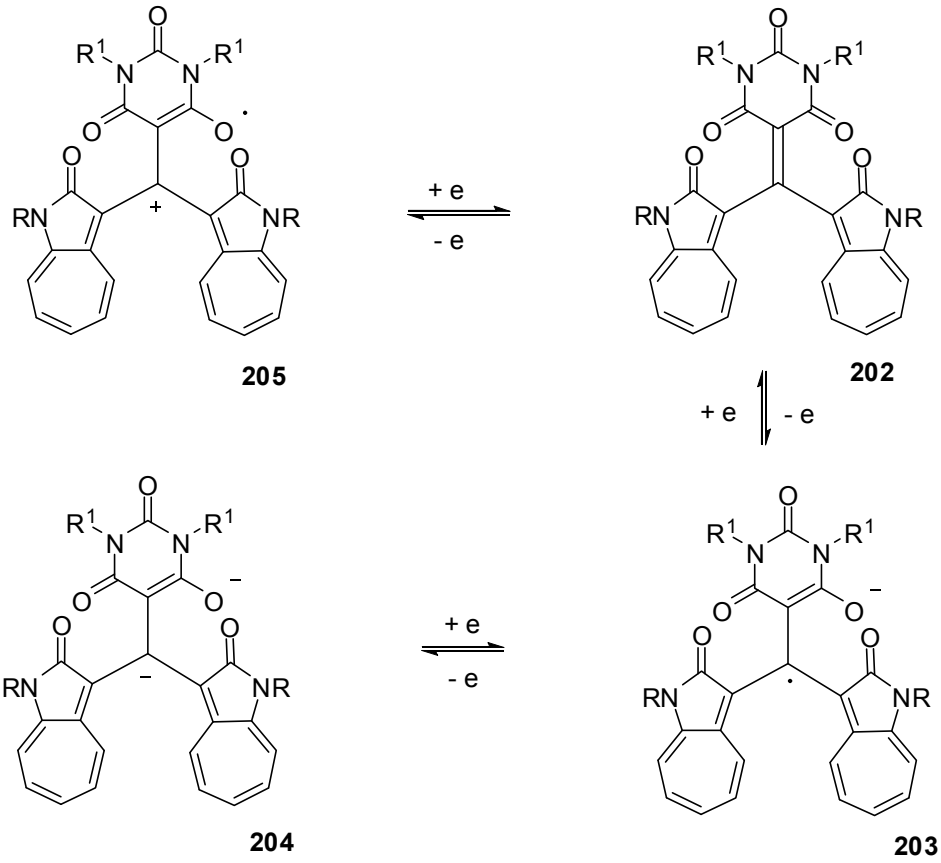
Scheme 68

In CV measurements, the reduction waves of quinonemethides (**70**) were reversible, suggesting a stabilizing effect of heteroazulenes toward the radical anions (**197**) and dianions (**198**). Quinonemethides (**70**) showed two oxidation waves owing the formation of radical cations (**199**) and dications (**200**), and the first oxidation potential of **70** (R^1 = *t*-Bu) is reversible (Scheme 69).[22a]



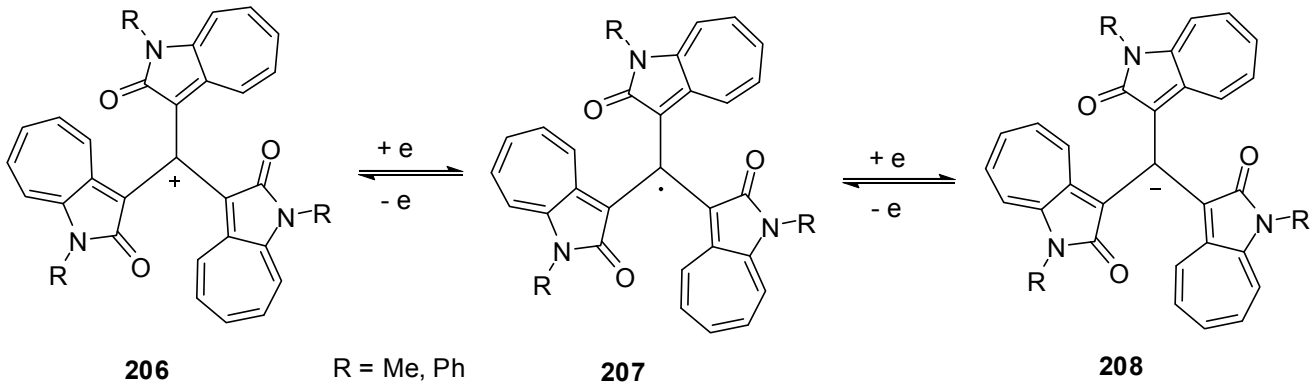
Scheme 69

In the CV of **202**, two reversible reduction waves ($E1_{red}$ -1.07 ~ -1.13 V, $E2_{red}$ -1.68 ~ -1.70 V) are observed, indicating the stabilizing ability of 1-azaazulenes toward the corresponding radical anions (**203**) and dianions (**204**), respectively (Scheme 70).[22d] Furthermore, **202** exhibits one irreversible oxidation wave ($E1_{ox}$ +0.77 ~ +0.81 V) owing to the formation of radical cations (**205**) and the corresponding reduction wave appearing in far negative region (+0.08~0.10 V), which suggested a conformational change in the radical cations during the redox process.[22d]



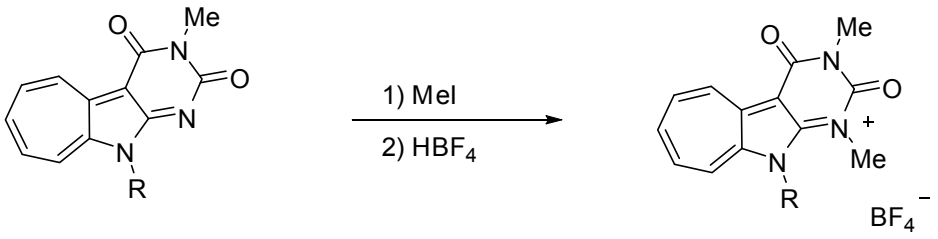
Scheme 70

The electrochemical reduction of the cations (**206**) exhibits two reversible waves and low reduction potentials at -0.58 (R = Ph) and -0.62 (R = Me) ($E1_{red}$) (V vs. Ag/Ag^{+}) owing to the formation of radicals (**207**) and -1.27 (R = Ph) and -1.33 (R = Me) ($E2_{red}$) owing to the formation of anions (**208**) upon CV, whose values are lower than that of tris(azulen-1-yl)methyl cations (Scheme 71).[22c]



Scheme 71

As mentioned as above, 6-aminouracil fused 1-azaazulenium ions (**209**) were easily synthesized form **33** (Scheme 72).[13d] The electrochemical reduction of **209** exhibited high reduction potentials at -0.84 (R = Ph) and -0.87 (R= Me) (V vs. Ag/Ag^+) upon CV. A good linear correlation between the pK_{R+} values and reduction potentials ($E1_{red}$) of **209** was obtained.[13d] The photo-induced oxidation reaction of **209** toward some alcohols under aerobic conditions afforded the corresponding carbonyl compounds in more than 100% yield, suggesting the oxidizing function of **209** toward alcohols in the autorecycling process.[13d] Similar photo-induced autorecycling oxidizing reaction of **209** prepared by methylation of **33**, **39**-**43** and related compounds toward some amines were also reported.[13c,13e,13f,48,49]



Scheme 72

III. BIOLOGICAL ACTIVITIES

In the research of biological activities, it has been reported that azaazulene derivatives have a wide variety of activities.[1a,1c] 1-Azaazulene derivatives (**5**: R^1 = H, NH_2, OH, etc.; R^2, R^3 = Ph, naphthyl, furyl, etc.) were useful for treating diseases caused by unregulated p38 mitogen-activated protein kinase (MAPK) or tumor necrosis factor-alpha (TNF-alpha) activity. E.g., the compound (**5**: R^1 = H; R^2 = 4-pyridinyl; R^3 = 4-FC_6H_4) showed IC_{50} of 1340 nM and 230 nM against p38 MAPK and TNF-alpha, respectively.[3] Detailed researches about the inhibitor activities against p38 MAPK and c-Jun *N*-terminal kinase 2-alpha

(JNK2α) of 1-azaazulenes (**5a**,**5b**) were made (Figure 6).[63] It is shown that the azaazulene class of inhibitors will be useful to decipher cellular actions of p38 MAPK (**5a**: IC_{50} = 0.6 μM, **5b**: IC_{50} = 4.7 μM) and JNK2α (**5a**: IC_{50} = 3.5 μM).

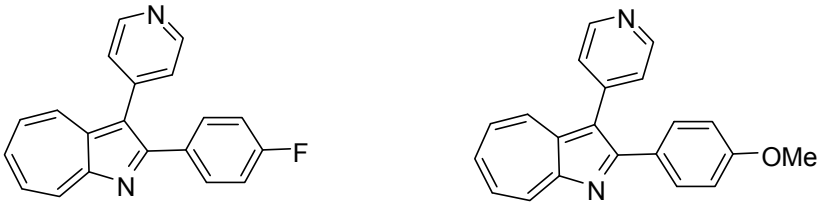
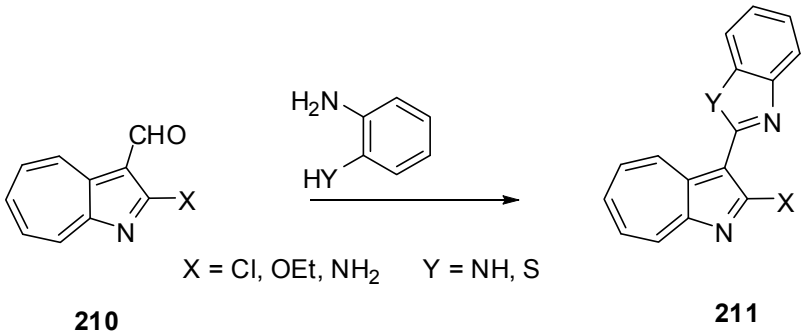


Figure 6

It is known that azaazulene derivatives showed the utility as antitumor agents.[14d] For inquiry of new antitumor agents, cytotoxic activities of 1-azaazulene derivatives against HeLa S3 cells were investigated. 3-Benzothiazolyl-1-azaazulene (**211**: X = Cl, Y = S; IC_{50} = 5.3 μM), which was obtained by the condensation of 2-chloro-3-formyl-1-azaazulene (**210**) with *o*-aminothiophenol (Scheme 73), showed strong cytotoxic activity against HeLa S3 cells.[64] Some resemble compounds (**211**) also showed cytotoxic activity against HeLa S3 cells.[64]

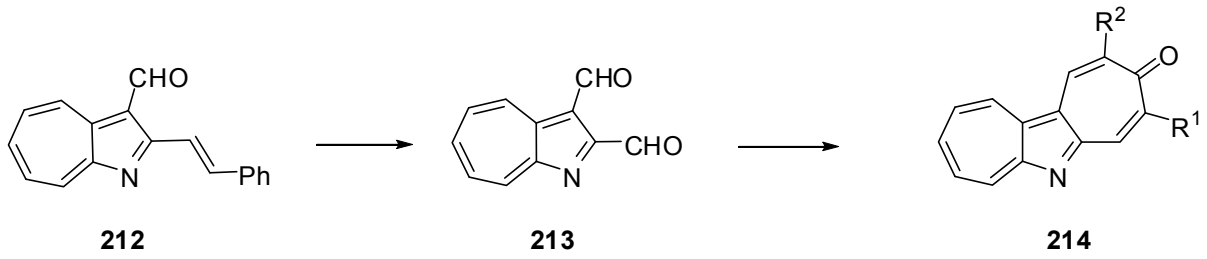
Figure 7

Some 2-(heteroarylamino)-1-azaazulenes showed cytotoxic activity against HeLa S3 cells (E.g., **118a**: IC_{50} = 6.5 μM, **118b**: IC_{50} = 23.3 μM) (Figure 7).[36]



Scheme 73

Azaazulenotropones (**214**: R^1 = H, OMe, CH_2Ph, OAc, CO_2Et, R^2 = H, CO_2Et) and azaazulenotropolone (**214**: R^1 = OH, R^2 = H) were synthesized by the condensation of 2,3-diformyl-1-azaazulene (**213**), prepared from 3-formyl-2-styryl-1-azaazulene (**212**), with acetone derivatives (Scheme 74).[65] The IC_{50} value of azaazulenotropolone (**214**: R^1 = OH, R^2 = H) against HeLa S3 cells was 19 μM.[65]



212 **213** **214**

Scheme 74

Azulene and azaazulene have characteristic photo-activity. Therefore, introduction of these molecules on bioactive compounds of known structure and function is expected to direct integrated photo-active molecules which the original biological activity is retained. Thus, analogs of peptides containing 1-azaazulene were synthesized by the replacement of tyrosine by azaazulene moiety (Figure 8). The integrated photo-active peptides and psuedopeptides could be used in a medical phototherapy.[66]

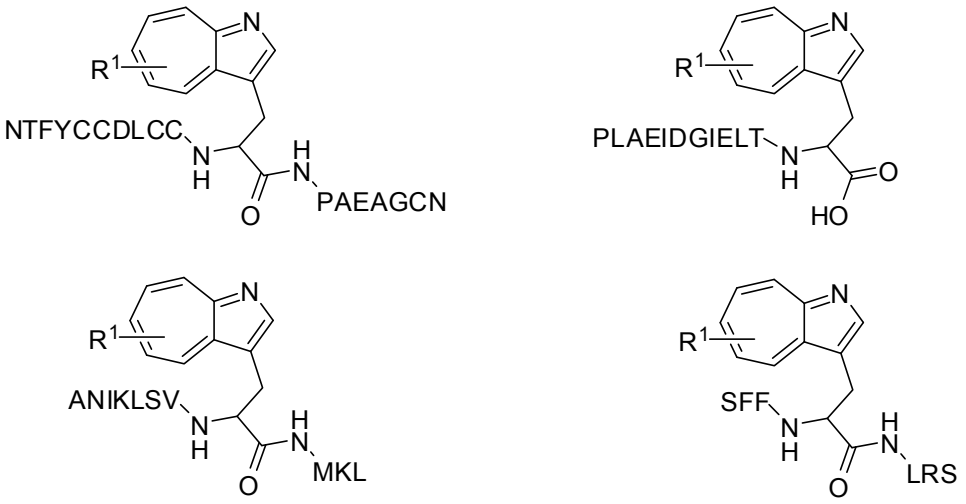
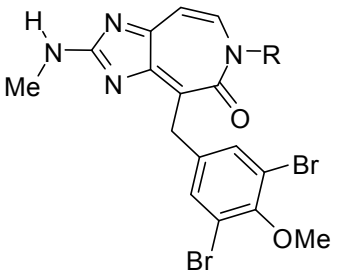


Figure 8

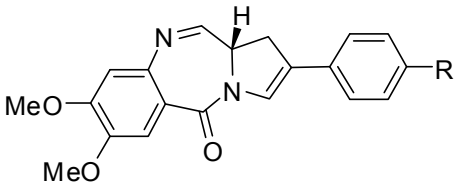
Two novel antimitotic heterocyclic alkaloids, ceratamines A (**215a**) and B (**215b**), have been isolated from the marine sponge *Pseudoceratanina* sp., collected in Papua New Guinea (Figure 9). The IC_{50} values of **215a** and **215** were 10 μM in the cell-based antimitotic assay.[67]



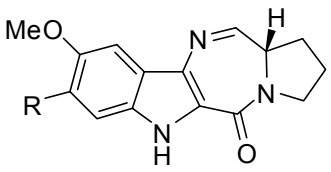
215a : R = Me,
215b : R = H

Figure 9

The 3a,10-diazabenz[*f*]azulene (pyrrolo[1,2-*c*][1,4]benzodiazepine: PBD) ring system, a group of potent naturally occurring antitumor antibiotics from *Streptomyces* species, are of considerable interest for their potentiality as antitumor agents, gene regulators, and DNA probs. Although many synthetically and pharmacological investigations related to PBD and its analogs were reported (especially, D. E. Thurston group and A. Kamal group have been investigating ardently),[68,69] only some examples, about the compounds showing bioactivity, were described here. Three novel C2-aryl substituted PBDs (**216a**,**b**,**c**) have been synthesized and evaluated in a number of cell lines revealing selective cytotoxicity at the sub-nano-molar level towards melanoma and ovarian cancer cell lines (Figure 10).[70] Cytotoxic compounds (**217**) were synthesized and evaluated in the human leukemic K_{562} cell line and were shown to have micromolar potency (Figure 10. **217a**: IC_{50} = 18 μM, **217b**: IC_{50} = 30 μM).[71]



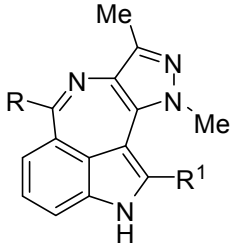
216a : R = H
216b : R = Me
216c : R = OMe



217a : R = H
217b : R = OMe

Figure 10

Compounds (Figure 11. **64a**-**e**) showed weak binding affinities to the bovine dopamine D_1 receptor and the human dopamine D_{2long}, D_{2short}, D_3 and D_4 receptor expressed by the ability to displace the corresponding radioligands only incomplete at micrometer concentration.[21a]



64a : R = Me, R^1 = H
64b : R = *p*-ClC_6H_4, R^1 = H
64c : R = 2-furyl, R^1 = H
64d : R = *p*-ClC_6H_4, R^1 = Ph
64e : R = *p*-ClC_6H_4, R^1 = Me

Figure 11

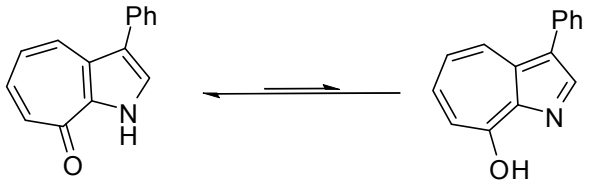
IV. THEORETICAL AND STRUCTURAL STUDIES.

AM1 calculations with complete optimization have been carried out on azulene, 1-azaazulene, and 1,3-diazaazulene.[72] The dipole moment values were estimated (1-azaazulene: 3.05 D, 1,3-diazaazulene: 4.40 D), the latter coincided with experimental data (1,3-diazaazulene: 4.39 D) by Kurita and Kubo.[73] Determination of most stable geometrical conformations and some spectroscopic values were also reported.

Electronic properties of 1,3-diazaazulenes in ground and excited states were characterized by using high level quantum chemistry methods (CASSCF/cc-pvdz).[74] The S_0-S_1 energy transition in 1,3-diazaazulene (2.77 eV) is noticeably larger than that in the parent azulene (1.97 eV). The difference in dipole moments in the ground and excited states for 1,3-diazaazulene is about twice larger than that for azulene, and presumably, its derivatives, influencing the second order non-linear optical responses of corresponding substances. The values of S_0-S_1 excitation energies of the 1,3-diazaazulene derivatives by direct calculations are in a reasonable agreement with experimental data.

2-(2-Pyridyl)-1-azaazulene (**92**) exhibits relatively strong basicity (pK_{a1} = 6.02, pK_{a2} = 2.42) and showed interesting behavior in the emission spectra. The free base (**92**) in MeCN showed an emission, assumed to be $S_2 \rightarrow S_0$ relaxation, at 434 nm upon excitation of 368 nm and no emission upon excitation of the longest wavelength maximum of 512 nm. On the other hand, the diprotonated species of **92** in 50% H_2SO_4 exhibited an emission of 484 nm upon excitation of the longest wavelength maximum of 429 nm, assumed to be $S_1 \rightarrow S_0$ relaxation. The absorption and emission spectra of **92** were also found dependent on a metal cation present in a solution. In the presence of Mg^{2+}, an emission at 543 nm from the S_1 state was observed upon excitation of 478 nm, but in the presence of Na^+, no emissions was observed from the S_1 state but an emission from the S_2 state was observed.[32]

It is decided by X-Ray crystal structure analysis that the compound (**218**) exists in the crystal in its keto form as 3-phenylcyclohepta[b]pyrrol-8(1*H*)-one (**218**) rather than in the enol form as 8-hydroxy-3-phenyl-1-azaazulene (**219**) (Scheme 75).[75]

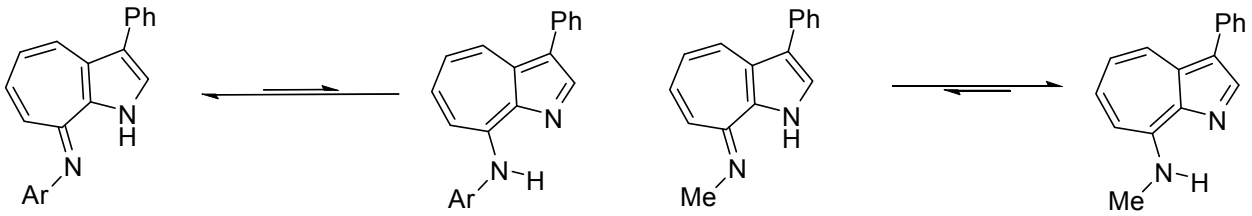


218 **219**

Scheme 75

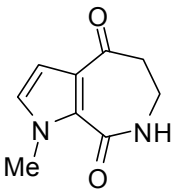
The tautomerization of 8-amino-1-azaazulenes was investigated by X-Ray crystal structure analysis and molecular orbital calculation (Gaussian 98 using RHF/6-31G*).[53,59] The results showed that 8-aryl

amino-1-azaazulene favored in imino-form (**220a**), whereas 8-methylamino-1-azaazulene favored in aminoform (**221b**). The results can be explained as follows: an aryl group causes stabilization of azaheptafulvene moiety by the conjugation with lone pair on the imino-nitrogen, while an electron-donating methyl group bring down the instability to azaheptafulvene moiety and increasing electron density of amino-nitrogen.



Scheme 76

1-Methyl-6,7-dihydropyrrolo[2,3-*c*]azepine-4,8(1*H*,5*H*)-dione (**222**) was synthesized. The X-ray crystal structure analysis of **222** showed that intermolecular N-H···O hydrogen bonds generate a one-dimensional chain (Figure 12).[76]



222

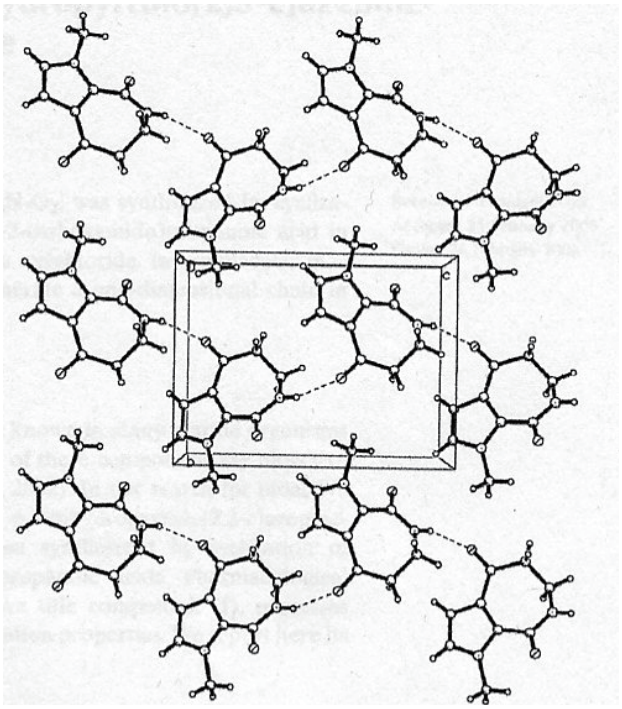
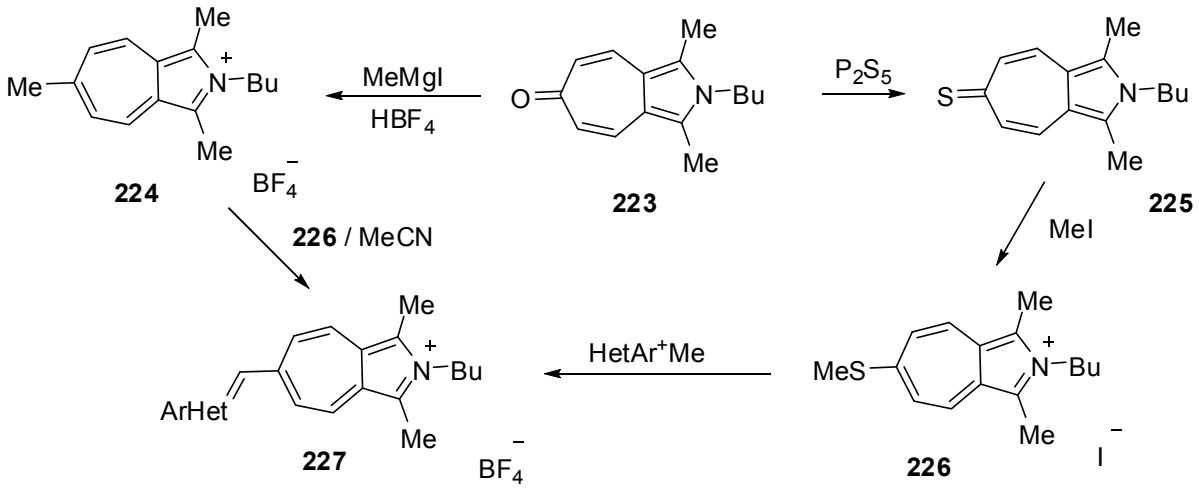


Figure 12. X-Ray crystal structure of **222**



Scheme 77

2-Azaazulenium cation and monomethine cyanine dyes bearing 2-azaazulenium moieties (**227**) were synthesized as a series of novel monomethine cyanine dyes as shown in Scheme 77.[77] The key products (**223** and **224**) were synthesized by known methods.[78] Compounds (**225** and 2**26**) were prepared also known methods.[79] The series of symmetrical and asymmetrical monomethine cyanine dyes (**227**) were synthesized by conventional cyanine chemistry synthetic approaches. Combined spectral and quantum chemical investigations of their molecular geometries and their electronic structures and the nature of their lowest electron transitions have been performed. Analysis of quantum chemical calculation and experimental spectroscopic data has shown that there is practically no difference in charge distribution over the π electron system in the ground state in **224** and in **227**. This would be attributed to the charge distribution which is not dependent on the relative location of MOs. The spectral properties, and correspondingly the nature of electron transitions in the chromophores, of compounds (**224** and **227**) are drastically different because of the different mechanisms of generation of the HOMOs.

CONCLUSION

In recent studies of azaazulene chemistry, some new synthetic methods were evolved. In addition, a variety of methodologies for functionalization of azaaulenes, such as transition metal catalyzed coupling reaction or cycloaddition and so on, were applied, and a lot of novel compounds having various patterns of the skeletons. In the azaazulene chemistry, biological and pharmaceutical pursuits are prominent. We expect the further development about azaazulene chemistry.

REFERENCES

1. For reviews see, a) N. Abe, 'Recent Research Developments in Organic and Bioorganic Chemistry',

2001, **4**, 14, Transworld Research Network; b) N. Abe, 'Trends in Heterocyclic Chemistry', 2001, **7**, 25, Research Trends; c) T. Nishiwaki and N. Abe, *Heterocycles*, 1981, **15**, 547; d) M. Kimura, *Yuki Gosei Kagaku Kyokai Shi*, 1981, **39**, 690.

2. N. Sakai, N. Hattori, N. Tomizawa, N. Abe, and T. Konakahara, *Heterocycles*, 2005, **65**, 2799.
3. R. J. Sciotti and R. Wagner, *PCT Int. Appl*., 2001, WO2001057018.
4. a) M. Kitamura, S. Chiba, O. Saku, and K. Narasaka, *Chem. Lett*., 2002, 606; b) M. Kitamura and K. Narasaka, *Chem. Rec*., 2002, **2**, 268; c) S. Chiba, M. Kitamura, O. Saku, and K. Narasaka, *Bull. Chem. Soc. Jpn*., 2004, **77**, 785.
5. Y. Matsumoto and M. Nitta, *Heterocycles*, 2001, **55**, 2131.
6. M. Nitta, *Rev. Heteroatom Chem.*, 1993, **9**, 1197.
7. a) H. Yamamoto, M. Ohnuma, and M. Nitta, *J. Chem. Res. (S)*, 1999, 173; *(M)*, 1999, 901; b) M. Nitta and Y. Mitsumoto, *Heterocycles*, 2001, **55**, 629; c) M. Nitta, Y. Mitsumoto, and H. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1901.
8. a) M. Nitta and S. Naya, J. *Chem. Res. (S)*, 1998, 522; *(M)*, 1998, 2363; b) S. Naya and M. Nitta, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1017; c) Y. Mistsumoto and M. Nitta, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2268.
9. K. Ito and K. Saito, 'Recent Research Development in Pure & Applied Chemistry', 1999, **3**, 91, Transworld Research Network.
10. K. Takaoka, T. Aoyama, and T. Shioiri, *Heterocycles*, 2001, **54**, 209.
11. V. Nair and K. G. Abhilash, *Tetrahedron Lett*., 2006, **47**, 8707.
12. O. Sato, K. Tsurumaki, S. Tamaru, and J. Tsunetsugu, *Heterocycles*, 2004, **62**, 535.
13. a) M. Nitta and Y. Tajima, *Synthesis*, 2000, 651; b) S. Naya, Y. Iida, and M. Nitta, *Tetrahedron*, 2004, **60**, 459; c) S. Naya and M. Nitta, *Tetrahedron*, 2004, **60**, 9139; d) S. Naya and M. Nitta, *Tetrahedron*, 2003, **59**, 7291; e) S. Naya, H. Ohtoshi, and M. Nitta, *J. Org. Chem*., 2006, **71**, 176; f) S. Naya, J. Nishimura, and M. Nitta, *J. Org. Chem*., 2005, **70**, 9780.
14. a) T. Ishikawa, T. Saito, S. Noguchi, H. Ishii, S. Ito, and T. Hata, *Tetrahedron Lett*., 1995, **36**, 2795; b) T. Ishikawa, K. Shimooka, T. Narioka, S. Noguchi, T. Saito, A. Ishikawa, E. Yamazaki, T. Harayama, H. Seki, and N. Yamaguchi, *J. Org. Chem*., 2000, **65**, 9143; c) T. Narioka and T. Ishikawa, *Heterocycles*, 2002, **56**, 413; d) T. Ishikawa and A. Zeimoto, *Jpn. Kokai Tokkyo Koho*, 1999, JP 11,255,746.
15. a) M. Morita, Y. Hari, T. Iguchi, and T. Aoyama, *Tetrahedron*, 2008, **64**, 1753; b) Y. Hari, T. Shioiri, and T. Aoyama, *Yuki Gosei Kagaku Kyokai Shi*, 2009, **67**, 357.
16. T. M. V. D. Pinho e Melo, M. I. L. Soares, A. M. d'A. Rocha Gonsalves, and H. McNab, *Tetrahedron Lett*., 2004, **45**, 3889.

17. M. Gruit, D. Michalik, A. Tillack, and M. Beller, *Angew. Chem. Int. Ed*., 2009, **48**, 7212.
18. J. Clayden, R. Turnbull, and I. Pinto, *Org. Lett*., 2004, **6**, 609.
19. S. Nakatsuka, H. Miyazaki, and T. Goto, *Tetrahedron Lett*., 1986, **27**, 4757.
20. A. M. Al-Khashashneh, M. M. El-Abadelah, and R. Boese, *Heterocycles*, 2003, **60**, 73.
21. a) P. Gmeiner, H. Hübner, K. A. Abu Safieh, I. I. Fasfous, M. M. El-Abadelah, S. S. Sabri, and W. Voelter, *Heterocycles*, 2003, **60**, 1339; b) K. A. Abu Safieh, F. H. Darras, M. T. Ayoub, M. M. El-Abadelah, S. S. Sabri, and W. Voelter, *Heterocycles*, 2007, **71**, 2681.
22. a) S. Naya, T. Watano, and M. Nitta, *Bull. Chem. Soc. Jpn*., 2003, **76**, 2035; b) S. Naya, K. Yoda, and M. Nitta, *Tetrahedron*, 2004, **60**, 4953; c) S. Naya and M. Nitta, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2777; d) S. Naya, K. Yoda, and M. Nitta, *Tetrahedron*, 2005, **61**, 8616.
23. N. Abe, Y. Fukumoto, H. Fujii, and A. Kakehi, *Heterocycles*, 2002, **56**, 171.
24. a) H. Fujii, K. Iwafuji, Y. Sawae, N. Abe, and A. Kakehi, *Heterocycles*, 2003, **59**, 63; b) H. Fujii, I. Kawano, K. Iwafuji, Y. Sawae, K. Nagamatsu, and N. Abe, *Heterocycles*, 2006, **70**, 207.
25. E. Yoshioka, K. Koizumi, S. Yamazaki, H. Fujii, and N. Abe, *Heterocycles*, 2009, **78**, 3065.
26. T. Morita, N. Abe, and K. Takase, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3063.
27. N. Abe, E. Hashimoto, H. Fujii, Y. Murakami, S. Tagashira, and A. Kakehi, *Heterocycles*, 2004, **63**, 2341.
28. N. Abe, M. Tanaka, T. Maeda, H. Fujii, and A. Kakehi, *Heterocycles*, 2005, **66**, 229.
29. T. Ariyoshi, T. Noda, S. Watarai, S. Tagashira, Y. Murakami, H. Fujii, and N. Abe, *Heterocycles*, 2009, **77**, 565.
30. H. Fujii, N. Abe, N. Umeda, and A. Kakehi, *Heterocycles*, 2002, **58**, 283.
31. a) 'Topics in Current Chemistry' Vol. 219, ed. by N. Miyaura, Springer, 2002; b) 'Metal-Catalyzed Cross-Coupling Reactions', ed. by F. Diederich and P. J. Stang, Willey-VCH, 1998; c) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz., and M. Lemaire, *Chem. Rev*., 2002. **102**, 1359.
32. M. Oda, K. Ogura, N. C. Thanh, S. Kishi, S. Kuroda, K. Fujimori, T. Noda, and N. Abe, *Tetrahedron Lett*., 2007, **48**, 4471.
33. K. Koizumi, C. Miyake, T. Ariyoshi, K. Umeda, N. Yamauchi, S. Tagashira, Y. Murakami, H. Fujii, and N. Abe, *Heterocycles*, 2007, **73**, 325.
34. N. Abe, Y. Harada, Y. Imachi, H. Fujii, A. Kakehi, and M. Shiro, *Heterocycles*, 2007, **72**, 459.
35. Y. Harada, H. Fujii, and N. Abe, unpublished results.
36. K. Koizumi, K. Shimabara, A. Takemoto, S. Yamazaki, N. Yamauchi, H. Fujii, M. Kurosawa, T. Konakahara, and N. Abe, *Heterocycles*, 2009, **79**, 319.
37. a) J. F. Hartwig, *Angew. Chem. Int. Ed*., 1998, **37**, 2046; b) J. P. Wolfe, S. Wagaw, J.-F. Marcoux,

and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805; c) B. H. Yan and S. L. Buchward, J. *Organomet. Chem*., 1999, **576**, 125; d) D. Prim, J.-M. Campagne, D. Joseph, and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041.

38. E. Yoshioka, K. Koizumi, S. Yamazaki, H. Fujii, and N. Abe, *Heterocycles*, 2009, **78**, 3065.
39. N. Abe, M. Mori, and H. Fujii. *J. Chem. Res. (S)*, 2002, 8; *J. Chem. Res. (M)*, 2002, 0162-0172.
40. N. Abe, H. Fujii, and A. Kakehi, *Heterocycles*, 2001, **55**, 1189.
41. N. Abe, I. Osaki, S. Kojima, H. Matsuda, Y. Sugihara, and A. Kakehi, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2351.
42. N. Abe, A. Otani, T. Nagai, and H. Fujii, *Heterocycles*, 2003, **59**, 199.
43. K. Saito, N. Ito, and S. Ando, *Heterocycles*, 2002, **56**, 59.
44. N. Abe, M. Yoshitsugu, H. Fujii, and A. Kakehi, *Heterocycles*, 2003, **61**, 237.
45. N. Abe, M. Nabeshima, H. Fujii, A. Kakehi, Y. Kageura, and T. Konakahara, *Heterocycles*, 2001, **54**, 329.
46. For reviews: a) Y. G. Gololobov and L. F. Kasukhin, *Tetrahedron*, 1992, **48**, 1353; b) S. Eguchi, Y. Maatsushita, and K. Yamashita, *Org. Prep. Proced. Int*., 1992, **24**, 209; c) P. Molina and M. J. Viapana, *Synthesis*, 1994, 1197; d) H. Wamhoff, G. Richardt, and S. Stolben, *Adv. Heterocycl. Chem*., 1995, **64**, 159.
47. M. Nitta, Y. Iino, T. Sugiyama, and A. Akaogi, *Tetrahedron Lett*., 1993, **34**, 831.
48. M. Nitta, D. Ohtsuki, Y. Mitsumoto, and S. Naya, *Tetrahedron*, 2005, **61**, 6073.
49. M. Nitta, T. Morito, Y. Mitsumoto, and S. Naya, *Heterocycles*, 2005, **65**, 1629.
50. N. Abe, H. Fujii, K. Tahara, and M. Shiro, *Heterocycles*, 2001, **55**, 1659.
51. N. Abe, K. Nagamatsu, K. Tahara, and H. Fujii, *Heterocycles*, 2004, **63**, 809.
52. K. Nagamatsu, A. Serita, J.-H. Zeng, H. Fujii, N. Abe, and A. Kakehi, *Heterocycles*, 2006, **67**, 337.
53. K. Nagamatsu, H. Fujii, N. Abe, and A. Kakehi, *Heterocycle*s, 2004, **64**, 291.
54. N. Abe, K. Nagamatsu, T. Ariyoshi, H. Fujii, Y. Murakami, S. Tagashira, and A. Kakehi, *Heterocycles*, 2007, **74**, 309.
55. Y. G. Golovov, I. N. Zhmurova, and L. F. Kasukin, *Tetrahedron*, 1981, **37**, 437.
56. C. E. Hoest, A. Nefzi, and R. A. Houghten, *Tetrahedron Lett*., 2003, 3705.
57. a) A. V. Kirsanov, I*zv. Acad. Nauk. SSSR, Otd., Kim. Nauk*, 1950, 426; b) G. I. Derkah, E. S. Gubitskaya, V. A. Shokol, and A. V. Kirsanov, *Zh. Obsh. Kim*., 1962, **32**, 1201; 1962, **32**, 1874.
58. a) R. Appel and M. Halstenberg, 'Organophosphorus Reagents in Organic Synthesis', ed. by J. I. G. Cadogan, Academic Press, London, 1979; b) T. Okawa, M. Toda, S. Eguchi, and A. Kakehi, *Synthesis*, 1998, 1467; c) T. Okawa, M. Kawase, and S. Eguchi, *Synthesis*, 1998, 1185.
59. K. Nagamatsu, Doctor Thesis, Yamaguchi University, 2007.

60. a) K. Saito, T. Ido, Y. Awada, T. Kanie, and S. Kondo, *Heterocycles*, 2000, **53**, 519; b) K. Saito, Y. Ueda, A. Kawamura, A. Kajita, H. Ishiguro, T. Ido, K. Ono, and Y. Awadu, *Heterocycles*, 2002, **58**, 63.
61. K. Saito and R. Ueno, *Heterocycles*, 2002, **57**, 219.
62. K. Saito, T. Kunisada, H. Ishiguro, M. Sato, and T. Doi, *Heterocycles*, 2001, **55**, 2315.
63. R. Somwar, S. Koterski, G. Sweeney, R. Sciotti, S. Djuric, C. Berg, J. Trevillyan, P. E. Scherer, C. M. Rondinone, and A. Klip, *J. Biol. Chem*., 2002, **277**, 50386.
64. N. Yamauchi, H. Fujii, A. Kakehi, M. Shiro, M. Kurosawa, T. Konakahara, and N. Abe, *Heterocycles*, 2008, **76**, 617.
65. T. Ariyoshi, K. Yoshinaga, K. Koizumi, H. Fujii, R. Ikeda, T. Konakahara, and N. Abe, *Heterocycles*, 2010, **80**, 427.
66. R. Rajagopalan, W. L. Neumann, and R. B. Dorshow, *PCT Int. Appl*., 2001, WO2008108941.
67. E. Manzo, R. van Soest, L. Matainaho, M. Roberge, and R. J. Andersen, *Org. Lett*., 2003, **5**, 4591.
68. a) D. E. Thurston, *Advanced in the study of Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Antitumour Antibiotics,* in 'Molecular Aspects of Anticancer Drug-DNA Interactions', ed. by S. Neidle and M. Waring, Macmillan Press Ltd., London, 1993, pp. 54-58; b) A. Kamal, M. V. Rao, N. Laxman, G. Ramesh, and G. S. K. Reddy, *Curr. Med. Chem.: Anti-Cancer Agents*, 2002, **2**, 215; c) S. J. Gregson, P. W. Howard, J. A. Hartley, N. A. Brooks, L. J. Adams, T. C. Jenkins, L. R. Kelland, and D. E. Thurston, *J. Med. Chem*., 2001, **44**. 737; d) D. E. Thurston and D. S. Bose, *Chem. Rev*., 1994, **94**, 433; e) D. E. Thurston, 'Chemistry and Pharmacology of Anticancer Drugs' CRC Press, 2006; f) A. Kamal, R. Rajender, D. R. Reddy, M. K. Reddy, G. Balalishan, T. B. Shaik, M. Chourasia, and G. N. Sastry, *Bioorg. Med. Chem*., 2009, **17**, 1557; g) A. Kamal, K. L. Reddy, G. S. K. Reddy, and B. S. N. Reddy, *Tetrahedlon Lett.*, 2004, **45**, 3499; h) M. Kotecha, J. Kluza, G. Wells, C. C. O'Hare, C. Forni, R. Mantovani, P. W. Howard, P. Mollis, D. E. Thurston, J. A. Hartley, and D. Hochhauser, *Mol. Cancer Ther*. 2008, **7**, 1319; i) P. W. Haward, Z. Chen, S. J. Gregson, L. A. Masterson, A. C. Tiberghien, N. Cooper, M. Fang, M. J. Coffils, S. Klee, J. A. Hartley, and D. E. Thurston, *Bioorg. Med. Chem. Lett*., 2009, **19**, 6463.
69. D. Antonow, M. Kaliszczak, G.-D. Kang, M. Coffils, A. C. Tiberghien, N. Cooper, T. Barata, S. Heidelberger, C. H. James, M. Zloh, T. C. Jenkins, A. P. Reszka, S. Neidle, S. M. Guichard, D. I. Jodrell, J. A. Hartley, P. W. Howard, and D. E. Thurston, *J. Med. Chem*., 2010, **53**, 2927, and references cited therein.
70. N. Cooper, D. R. Hagan, A. Tiberghien, T. Ademefun, C. S. Matthews, P. W. Howard, and D. E. Thurston, *Chem. Commun*., 2002, 1764.
71. A. Tsotinis, M. Vlachou, K. Kiakos, J. A. Hartley, and D. E. Thurston, *Chem. Lett*., 2003, **32**, 512.

72. K. Elblidi, A. Boucetta, B. Benali, A. Kadiri, C. Cazeau-Dubroca, G. Nouchi, and M. Pesquer, *Theo. Chem*., 1995, **343**, 57.
73. Y. Kurita and M. Kubo, *J. Am. Chem. Soc*., 1957, **79**, 5460.
74. K. B. Bravaya, B. L. Grigorenco, A. V. Nemukhin, Y.-J. Zhu, and J.-P. Zhang, *Theo. Chem*., 2008, **855**, 40.
75. K. Kubo, T. Tsujimoto, and A. Mori, *Acta Cryst*., 2001, **E57**, 0225.
76. X.-C. Zeng, S.-H. Xu, J. Gu, and D.-S. Deng, *Acta Cryst*., 2005, **E61**, 0795.
77. J. Bricks, A. Ryabitskii, and A. Kachkovskii, *Eur. J. Org. Chem*., 2009, 3439.
78. J. L. Bricks and N. N. Romanov, *Khim. Hetero. Soed. (Russ.)*, 1994, 193.
79. G. Seitz, R. A. Olsen, T. Kämpchen, and R. Matusch, *Chem. Ber*., 1979, **112**, 2087.

Noritaka Abe was born in Akita, Japan, in 1946. He received his B.Sc. (1969), M.Sc. (1971) degree, and Ph.D. degree from Tohoku University (Japan), completed his doctoral thesis in 1974 under the direction of Professor Kahei Takase. He was with the Yamaguchi University, research associate (1974), lecturer (1978), associate professor (1982), and Professor (1997). After retirement from Yamaguchi University in 2010, he has a position in Tokyo University of Science as Professor. He mainly worked on the research about novel aromatic chemistry and heterocyclic chemistry.

Takahiro Gunji was born in Fukushima, Japan, in 1964. He received his Ph.D. from Tokyo University of science in 1992 under the supervision of Prof. Yoshimoto Abe. He worked as a postdoctoral fellow with Prof. Robert West at University of Wisconsin in 1992-1993. He was appointed at Tokyo University of Science as a research associate in 1993 and was promoted to associate professor in 2003. The research in his group focuses on the synthetic study on the organosilicon chemistry, inorganic polymers, and organic-inorganic hybrid materials.