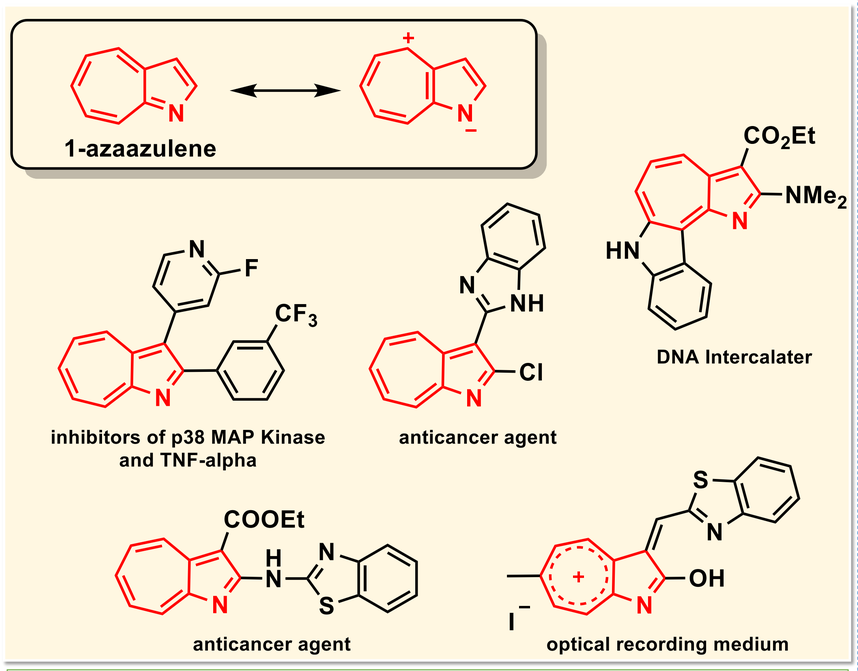
Synthesis of 1-azaazulenes from non-troponoids using the ring-opening cyclization of spirocyclopropanes with amine

Faculty of Pharmaceutical Sciences, University of Toyama

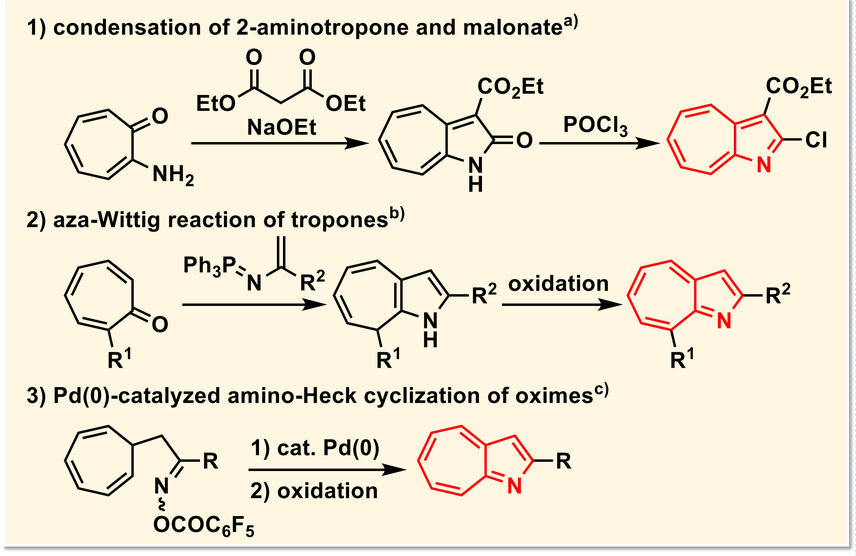
Yuta Onuki, Hisanori Nambu, Koga Yamazaki, Takayuki Yakura

Characteristics of 1-azaazulenes ①



1-Azaazulenes are nonbenzenoid aromatic compounds which have potential biological activities and attractive physical and chemical properties.

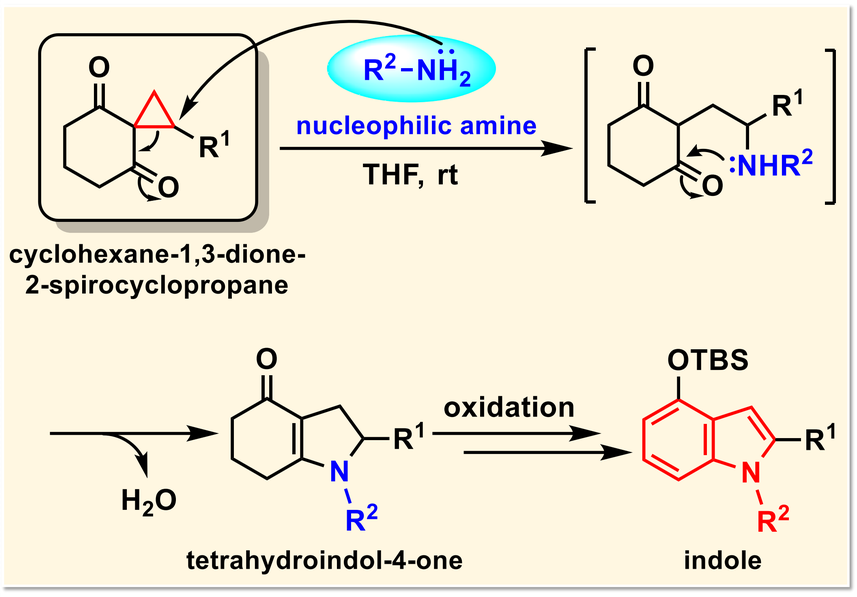
General synthetic methods of 1-azaazulenes: From troponoids that are hardly available ②



a) Nozoe T., Seto S., Matsumura S., Terasawa T., *Chem. Ind.*, 1357 (1954).
b) Nitta M. Kobayashi T., *Chem. Lett.*, **15**, 463 (1986).
c) Kitamura M., Chiba S., Saku O., Narasaka K., *Chem. Lett.*, **31**, 606 (2002).

In most cases of 1-azaazulene syntheses, troponoids were used as starting materials. These methods are efficient, but troponoids are expensive and difficult to prepare.

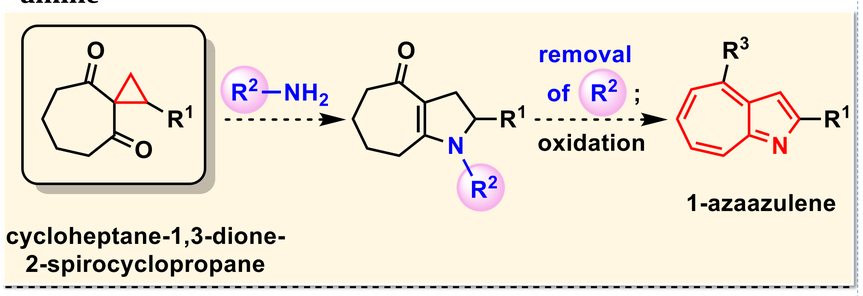
Our previous work: Ring-opening cyclization of cyclohexane-spirocyclopropanes with amines for synthesis of indoles ③

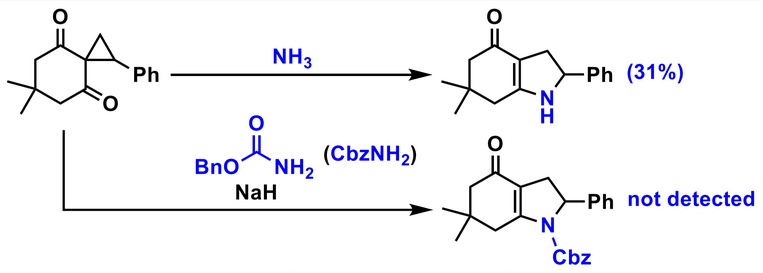


Nambu H., Fukumoto M., Hirota W., Yakura T., *Org. Lett.*, **16**, 4012 (2014).

Recently, we have developed a synthetic method of indole through the ring-opening cyclization of spirocyclopropane followed by oxidation.

This work: New synthesis of 1-azaazulenes using ring-opening cyclization of cycloheptanespirocyclopropanes with amine ④

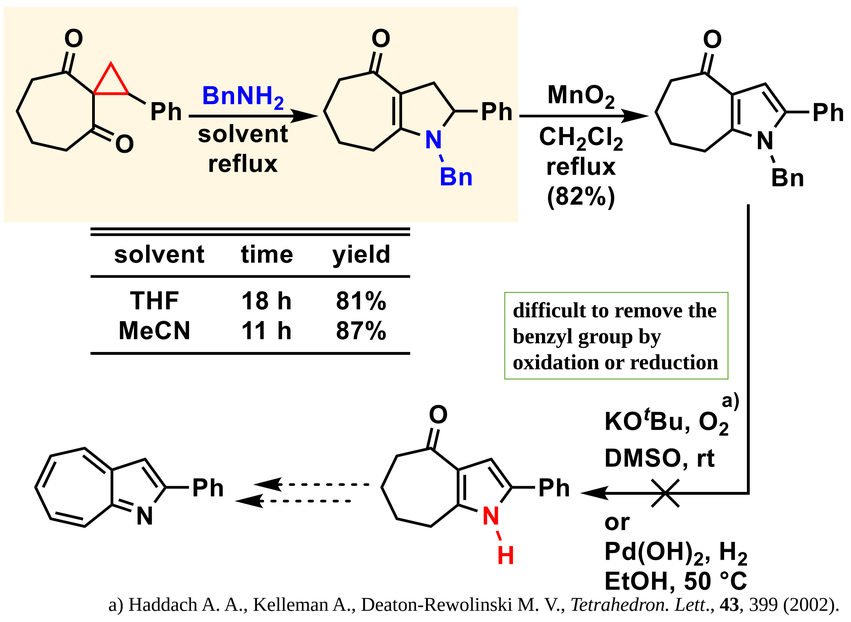




Nambu H., Fukumoto M., Hirota W., Yakura T., *Org. Lett.*, **16**, 4012 (2014).

We planed to synthesis 1-azaazulenes from spirocyclopropanes. Ammonia and $CbzNH_2$ can not react with spirocyclopropanes, so selecting the appropriate primary amine and the removal of R^2 were very important.

Unsuccessful attempt to synthesize 2-phenyl-1-azaazulene using benzylamine ⑤

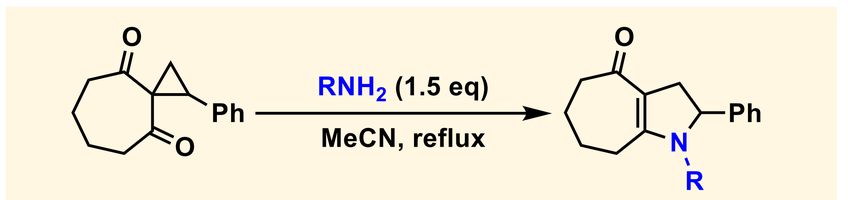


solvent	time	yield
THF	18 h	81%
MeCN	11 h	87%

a) Haddach A. A., Kelleman A., Deaton-Rewolinski M. V., *Tetrahedron. Lett.*, **43**, 399 (2002).

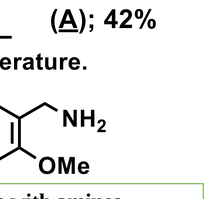
First, we attempted to synthesize 2-phenyl-1-azaazulene by using spirocyclopropane with benzylamine. However, the removal of benzyl group was unsuccessful.

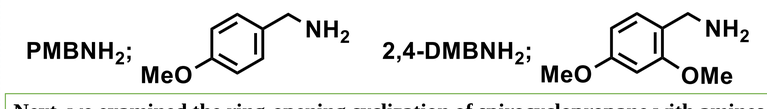
Ring-opening cyclization of spirocyclopropane with various amines to hexahydrocycloheptapyrrol-4-one ⑥



entry	RNH_2	time (h)	yield (%)
1	$PMBNH_2$	12	91
2	$2,4\text{-DMBNH}_2$	12	94
3	$PhNHNH_2$	10	(A)
4	NH_2OMe	12	not detected
5	NH_3/1,4-dioxane[a)]	48	no reaction

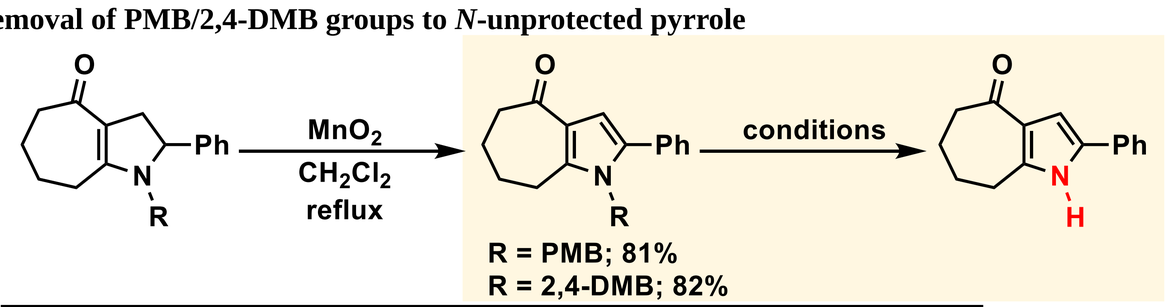
a) 10 eq of NH_3 was used in 1,4-dioxane at room temperature.





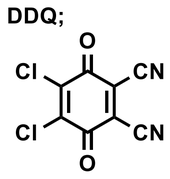
Next, we examined the ring-opening cyclization of spirocyclopropane with amines possessing an easily removable group. The reaction with $PMBNH_2$ and $2,4\text{-DMBNH}_2$ provided the corresponding product in high yields.

Removal of PMB/2,4-DMB groups to *N*-unprotected pyrrole ⑦

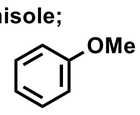


entry	R	conditions	time (h)	yield (%)
1	PMB	DDQ, CH_2Cl_2/H_2O, rt	24	not detected
2	PMB	CF_3CO_2H, reflux[a)]	24	no reaction
3	2,4-DMB	DDQ, CH_2Cl_2/H_2O, rt	24	not detected
4	2,4-DMB	CF_3CO_2H, reflux	1	<85%[1)]
5	2,4-DMB	anisole (10 eq), TFA, reflux[b)]	5	87%

DDQ;



anisole;

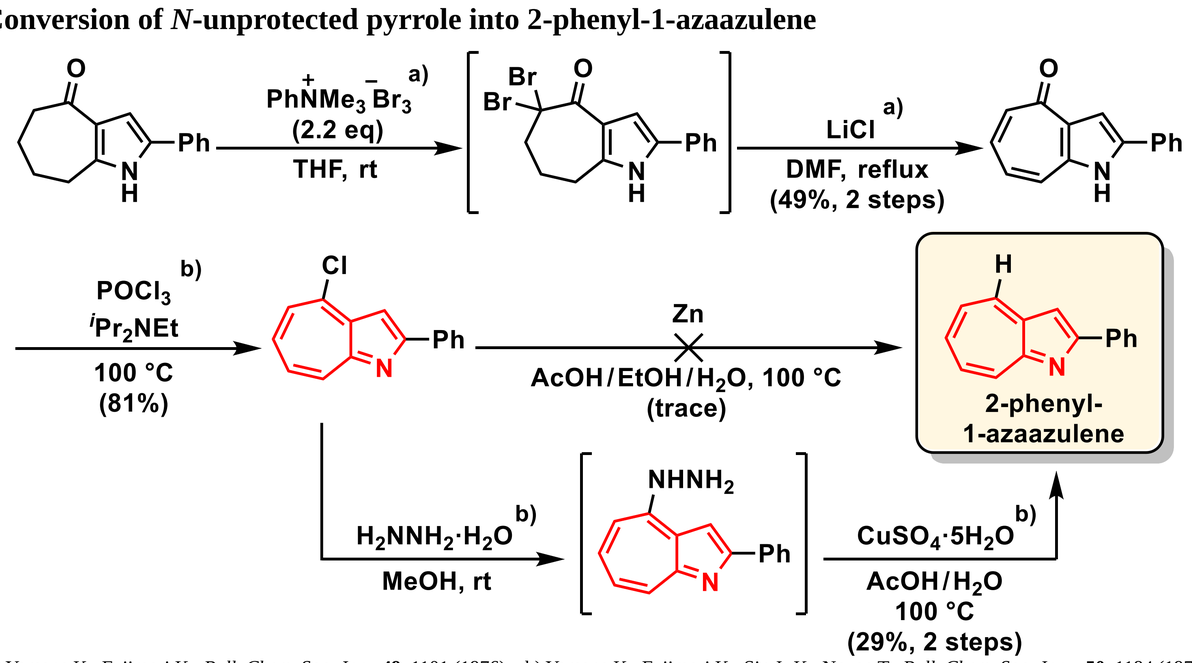


[1)] A small amount of inseparable impurity was contained in the obtained product.

a) Donohoe T. J., Johnson D. J., Mace L. H., Bamford M. J., Ichihara O., *Org. Lett.*, **7**, 435 (2005).
b) Watanabe T., Murakami Y. *et al.*, *Chem. Pharm. Bull.*, **39**, 1152 (1991).

After oxidation of PMB- and 2,4-DMB-substituted dihydropyrroles, we then investigated the removal of those groups. We found that the reaction of 2,4-DMB-substrate with anisole in refluxing TFA could provide the deprotected product in high yields.

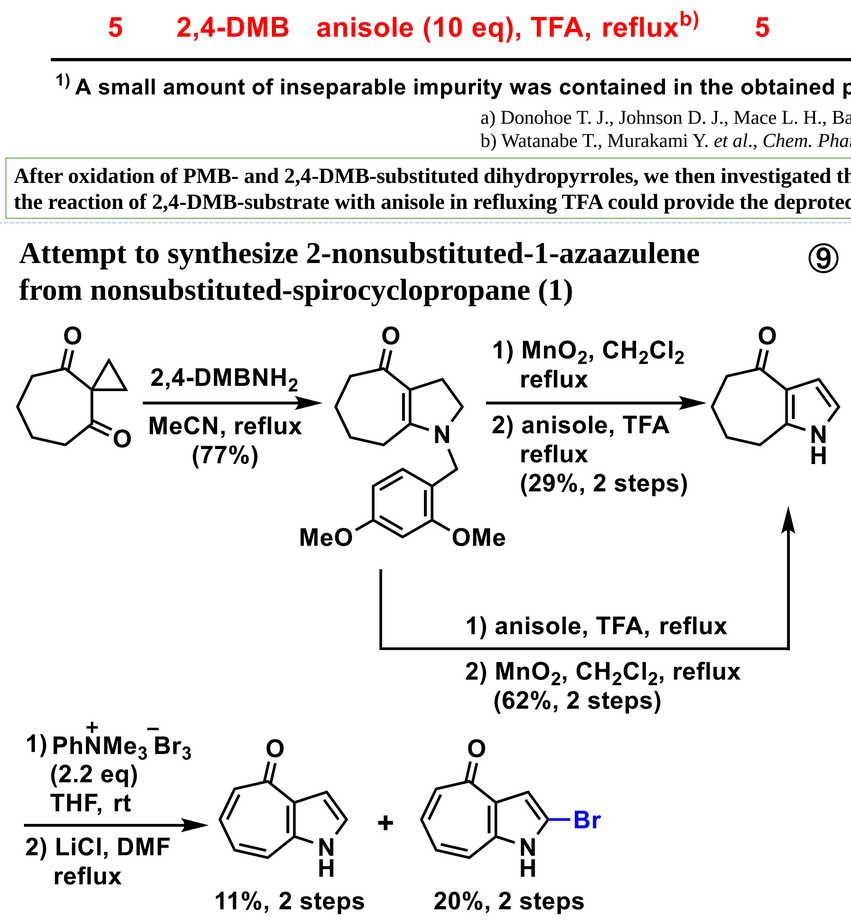
Conversion of *N*-unprotected pyrrole into 2-phenyl-1-azaazulene ⑧



a) Yamane K., Fujimori K., *Bull. Chem. Soc. Jpn.*, **49**, 1101 (1976). b) Yamane K., Fujimori K., Sin J.-K., Nozoe T., *Bull. Chem. Soc. Jpn.*, **50**, 1184 (1977).

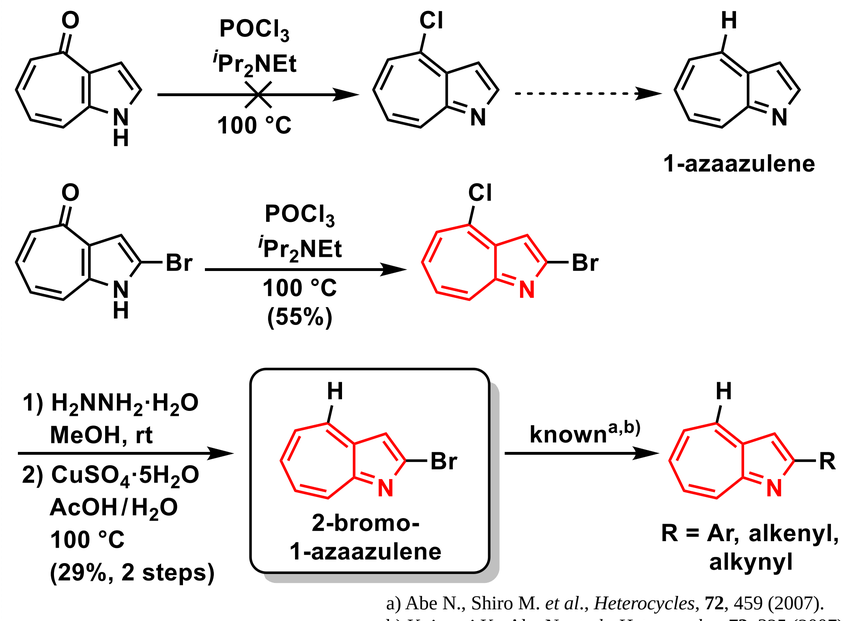
Finally, we examined the conversion of unprotected pyrrole into 1-azaazulenes. Bromination followed by elimination produced 2-phenylpyrrolotropone, which was then converted into 4-chloro-2-phenyl-1-azaazulene by using phosphoryl chloride. With the product, we also achieved the synthesis of 2-phenyl-1-azaazulene by hydrazination and then treating with copper sulfate.

Attempt to synthesize 2-nonsubstituted-1-azaazulene from nonsubstituted-spirocyclopropane (1) ⑨



Next, we examined the synthesis of nonsubstituted 1-azaazulene from nonsubstituted spirocyclopropane. Bromination of deprotected pyrrole followed by elimination provided nonsubstituted pyrrolotropone and 2-bromo-pyrrolotropone.

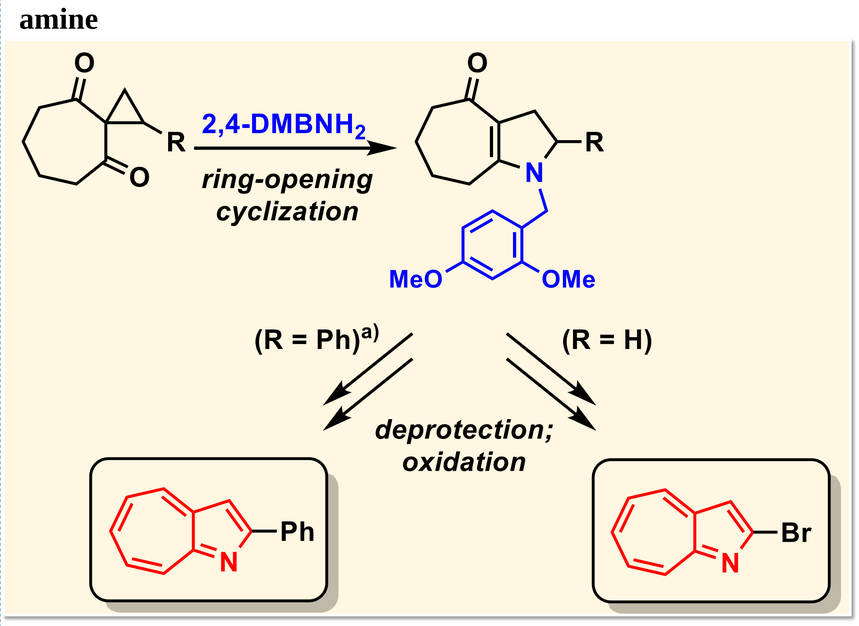
Attempt to synthesize 2-nonsubstituted-1-azaazulene from nonsubstituted-spirocyclopropane (2) ⑩



a) Abe N., Shiro M. *et al.*, *Heterocycles*, **72**, 459 (2007).
b) Koizumi K., Abe N. *et al.*, *Heterocycles*, **73**, 325 (2007).

Nonsubstituted pyrrolotropone couldn't be converted into 1-azaazulene. On the other hand, the transformation of 2-bromo-pyrrolotropone provided 2-bromo-1-azaazulene.

Summary: New synthesis of 1-azaazulenes using ring-opening cyclization of cycloheptanespirocyclopropanes with amine ⑪



a) Nambu H., Onuki Y., Yamazaki K., Yakura T., *Heterocycles*, **103**, 1099 (2021).

We have developed the synthetic method of 1-azaazulenes from a non-troponoid starting material using the ring-opening cyclization of spirocyclopropanes with 2,4-DMB-amine.