molecules

MDPI

Review

Indolizines and Their Hetero/Benzo Derivatives in Reactions of [8+2] Cycloaddition

Eugene V. Babaev [1,2,3,*] and Ivan A. Shadrin [1]

[1] Chemistry Department, Moscow State University, Leninskie gory, 1 str. 3, 119899 Moscow, Russia; i.shadrin666@gmail.com
[2] Higher School of Economics, National Research University, 7 Vavilova Str., 117312 Moscow, Russia
[3] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., 119991 Moscow, Russia
* Correspondence: babaev@org.chem.msu.ru; Tel.: +7-985-997-94-75

Abstract: Peculiarities of [8+2] cycloaddition of acetylenes to indolizines are reviewed. Especially mentioned are indolizines with leaving groups at positions 3 and 5. Cycloaddition to aza- and benzo derivatives are reviewed, as well as 1,10-cyclizations and processes leading to cyclazines where indolizines are intermediates. Mechanistic features (adducts and cycloadducts) and theoretical aspects (one- or two-steps mechanism) are reviewed.

Keywords: indolizine; azaindolizines; benzoindolizines; cyclazine; [8+2] cycloaddition; mechanism; 1,10-cyclizations; catalysts

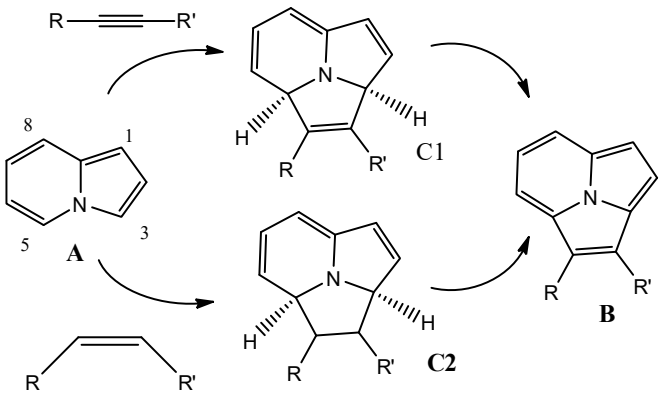
Citation: Babaev, E.V.; Shadrin, I.A. Indolizines and their Hetero/Benzo Derivatives in Reactions of [8+2] Cycloaddition. *Molecules* **2021**, *26*, 2050. https://doi.org/10.3390/molecules26072050

Academic Editor: Ionel Mangalagiu

Received: 17 March 2021
Accepted: 30 March 2021
Published: 3 April 2021

1. Introduction

Indolizine (A, Scheme 1) is the simplest heteroaromatic molecule containing both a π-excessive pyrrole and a π-deficient pyridine ring with only one bridgehead nitrogen, the whole system being isomeric with indole and possess pharmaceutical, agrochemical and fluorescent properties [1]. Although indolizine is certainly aromatic, significant alternations of the bond lengths around the ring system were detected by X-ray, NMR and UV spectroscopy and even mass spectrometry in various substituted indolizines. This prompts some tetraene-like character of the compound, in particular its ability to enter into cycloaddition reactions.

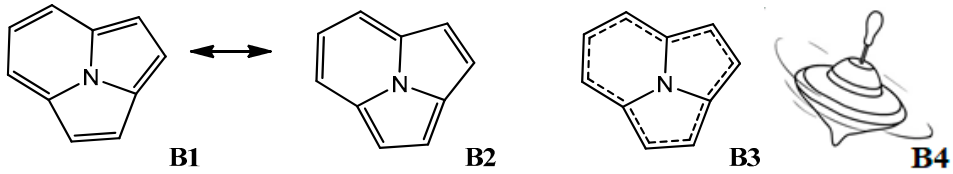


Scheme 1. Indolizines (A) in [8+2] cycloaddition reaction forming cycl[3.2.2]azines (B). The reaction may proceed with alkynes or alkenes via dihydro- (C1) or tetrahydro- (C2) cyclazines.

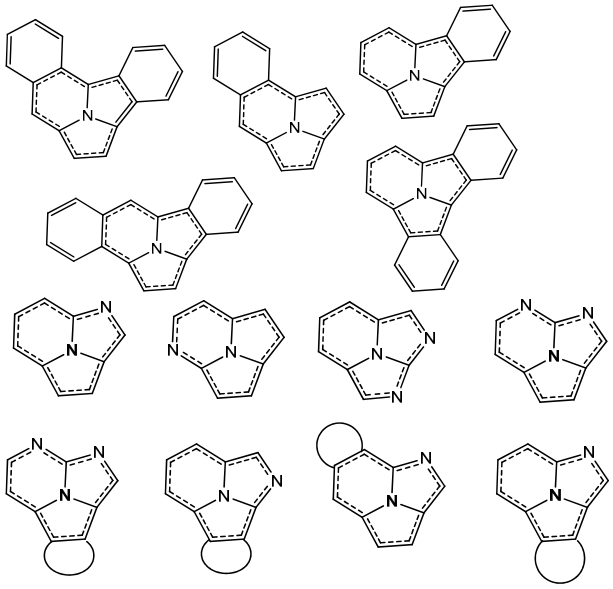
Indolizine is usually regarded as the π-excessive heterocycle with the highest electron population of the carbon atom C-3, and the major part of the chemistry of indolizines

is simple electrophilic addition and substitution at this position. Cycloaddition of various dienophiles (alkenes and acetylenes) to indolizines leading to derivatives of the cycl[3.2.2]azine (**B**, Scheme 1) is well-known. The mechanism of these reactions is frequently regarded as a rare example of [8+2] cycloaddition, where the tetraene carbon framework of the indolizine bicycle plays the role of an 8 π-electron fragment. In general, this process may be either one-step (concerted) or involve zwitterionic (and even biradical) intermediates, and there is yet no experimental evidence for the nature of the process.

Cyclazine (**B**) is an interesting 12π-electronic system that breaks the canons of aromaticity. According to X-ray data the structures **B1** and **B2** are not correct (Scheme 2), and the structure rather has a peripheral delocalization of aromatic 10 π-electron system **B3**. Therefore, cyclazine resembles the famous spinning toy **B4** where the handle (which is not rotated) corresponds to nitrogen lone pair. Hence, the structure has a symmetry plane, and this influences the number of positional isomers, say the number of aza- and benzoderivatives possible for cyclazine (Scheme 3).



Scheme 2. Different images of the structure of cyclazine.



Scheme 3. Possible benzo- aza- and benzoazacyclazines discussed in this review.

Cyclazins and their hetero/benzo derivatives are important from a practical viewpoint. They are fluorescent compounds and have excellent prospects in organic electronics [2–8]. On the other hand, biological activity was found in cyclazines, and their applications as estrogens and anti-inflammatory compounds are well known [9–11].

Cyclazine was first obtained from indolizine by Boekelheide 60 years ago. This author was the first who postulated the [8+2] mechanism. After this time the [8+2] reaction was reviewed several times. The first review by Acheson appeared in 1963 [12] and the next one by Taurins in 1977 [13]. Several reviews were written on the chemistry of cyclazines [1,14–19]. In the reviews of Nair and Abhilash [20,21] devoted to [8+2] cycloaddition reactions, only a limited number of indolizine reactions was mentioned.

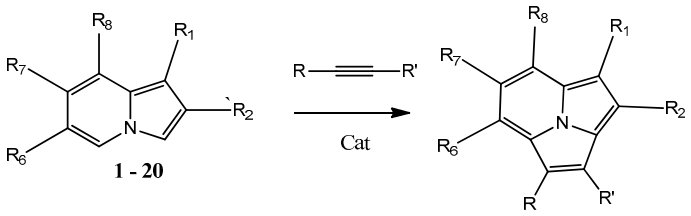
Therefore, this review may be considered as the first and comprehensive review on the [8+2] cycloaddition reactions between aza/benzo indolizines and acetylenes leading to cyclazines.

2. Cyclazines from Indolizines via [8+2] Catalytic Cycloaddition

The first cycloaddition to indolizine (entry **1** in Table 1) was observed by Boekelheide in 1959 [22] (Scheme 4) and later to **2** [23] by using DMAD and heating in toluene in presence of Pd-C. Recently reaction of **3** was reported with MnO_2 as oxidant [4]. Boekelheide was the first who made the reaction of **4** with non-symmetric alkyne [24] and performed cycloaddition with DMAD to 2-Ph-indolizine **5** [25]; this reaction was repeated recently with **8a**,**b** [26]. 2-Methylindolizine **6** was involved in the reaction with DMAD in 1965 [27], and the same reaction was done for 8-*R*-indolizines **7a–c** [28].

Indolizines **9a–c** obtained by desulfurization of 2-MeS derivatives were converted to cyclazines [29]. First indolizine **10** substituted by functional groups was involved in cyclization with DMAD in 1974 [30]. Later, this methodology was used to construct cyclophanes by applying 2-MeS-3-$CONH_2$ substituted structures **11a**,**b** [31,32]. Later 2-MeS-3-COOR derivatives were hydrolyzed and decarboxylated to **12a–c** and converted to cyclazines [29]. A similar methodology was used to construct cyclazine from 2-MeS-7-NMe_2-indolizine **13b**: desulfurization gave 7-NMe_2 derivative **13a** and the addition of DMAD gave corresponding cyclazine [2].

Fluoro-substituted indolizines are seldom [33] but 1-fluoro derivatives **14a**,**b** underwent cycloaddition in oxidative condition in presence of Cu(II) salts [34]. One more example to introduce functionality to cyclazine is catalytic cycloaddition of 6,8-diacyl indolizine **17** [35]. In our recent work, we proved that MAC could react with 2-t-Bu indolizine **18** giving cyclazine in open-air [36]. One featured reaction was cycloaddition of indolizine **19** with Mes_2B-substituted acetylene [37]. 2-Styryl indolizine reacted with DMAD and MAC without a catalyst [38]. Big series of cyclazines (though without the yields) was synthesized and described as estrogens [9,10].



Scheme 4. Symthesis of cyclazines from indolizines (Table 1).

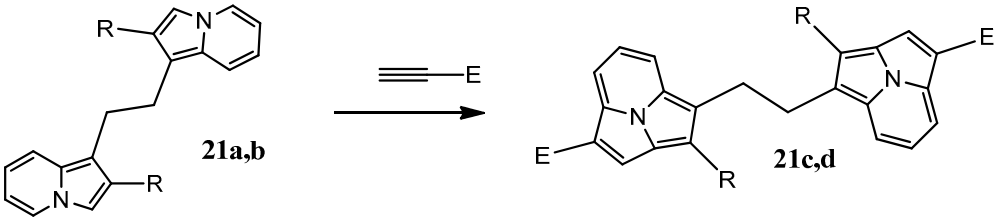
Table 1. Substituents, reaction conditions and yields of reactions of indolizines with substituted acetylenes giving cyclazines (Scheme 4).

N	R/R′	R1	R2	R6	R7	R8	Cat/Solv/T°/Time	Yield %	Ref.
1	E/E [a]	H	H	H	H	H	Pd-C/MePh/Δ	50–66	[22]
2	E/E	H	H	H	H	H	Pd-C/MePh/Δ/24 h	68	[23]
3	E/E	H	H	H	H	H	MnO_2/MePh/Δ/16 h	55	[4]
4	E/H	H	H	H	H	H	Pd-C/MePh/Δ/24 h	11	[24]
5	E/E	H	Ph	H	H	H	Pd-C/MePh/Δ/20 h	28	[25]
6	E/E	H	Me	H	H	H	Pd-C/MePh/Δ	60	[27]
7a	E/E	H	H	H	H	Me	Pd-C/MePh/Δ/1.5 h	53	[28]
7b	E/E	H	H	H	H	Pr	Pd-C/MePh/Δ/1.5 h	53	[28]
7c	E/E	H	H	H	H	Ph	Pd-C/MePh/Δ/1.5 h	53	[28]
8a	E/E	H	Ph	H	H	H	Pd-C/MePh/Δ	39	[26]
8b	E/E	H	p-tBuPh	H	H	H	Pd-C/MePh/Δ	75	[26]
9a	E/E	H	H	H	H	H	Pd-C/MePh/Δ/100 h	33	[29]

9b	E/E	H	H	H	H	Me	Pd-C/MePh/D/100 h	34	[29]
9c	E/E	H	H	Me	H	Me	Pd-C/MePh/Δ/100 h	25	[29]
10	E/E	$CONH_2$	MeS	H	H	H	Pd-C/MePh/Δ/24 h	70	[30]
11a	E/H	$CONH_2$	MeS	H	H	H	Pd-C/MePh/Δ/100 h	45	[31]
11b	E/H	$CONH_2$	MeS	H	Me	H	Pd-C/MePh/Δ/100 h	48	[31]
12a	E/E	H	MeS	H	H	H	Pd-C/MePh/Δ/100 h	38	[29]
12b	E/E	H	MeS	H	H	Me	Pd-C/MePh/Δ/100 h	40	[29]
12c	E/E	H	MeS	Me	H	Me	Pd-C/MePh/Δ/100 h	49	[29]
13a	E/E	H	H	H	NMe_2	H	Pd-C/MePh/Δ	32	[2]
13b	E/E	H	MeS	H	NMe_2	H	Pd-C/MePh/Δ	17	[2]
14a	E′/E′ [b]	F	p-Brh	H	H	H	$Cu(OAc)_2$/PhMe/Δ/5 h	63	[34]
14b	E′/E′	F	p-MeOPh	H	H	H	$Cu(OAc)_2$/PhMe/Δ/8 h	70	[34]
15	E/H	E	Me	H	H	H	Pd-C/PhH/Δ/24 h	NG [c]	[39]
16a	E/H	2-Py	Me	H	H	H	No/NO_2Ph/Δ/20 h	43	[40]
16b	E/E	2-Py	Me	H	H	H	No/NO_2Ph/Δ/20 h	47	[40]
17	E/E	H	Me	o-OHPhCO	H	COMe	Pd-C/MePh/Δ/16 h	54	[35]
18	E/H	H	t-Bu	H	H	H	O_2/MePh/Δ/4 h	79	[36]
19	Me_2B/H	H	H	H	H	H	(1) MePh/Δ/3 d (2) DDQ	55	[37]
20a	E/E	H	Styryl	H	H	H	No/PhMe/50°/31 h	44	[38]
20b	E/H	H	Styryl	H	H	H	No/PhMe/20°/120 h	64	[38]

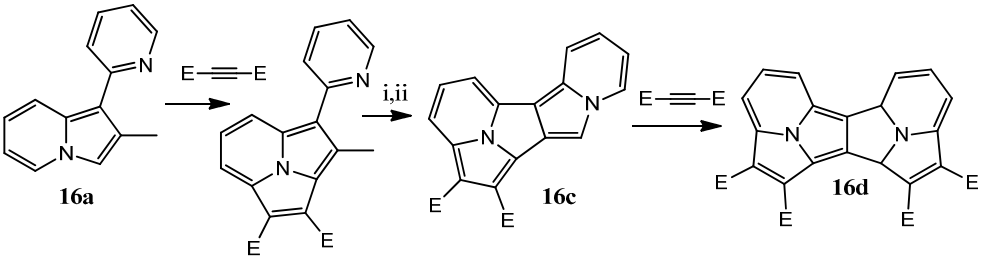
[a]: E—CO_2Me, [b]: E′ = CO_2Et, [c]: NG—not given.

1-Methoxycarbonyl indolizine **15** (Table 1) was converted to cyclazine in order to make cyclophane [39], but this methodology failed. Finally, cyclazines **21c**,**d** were obtained from bis-indolizinylethanes **21a**,**b** (R = Me, t-Bu) and further converted to cyclophanes [39], Scheme 5.



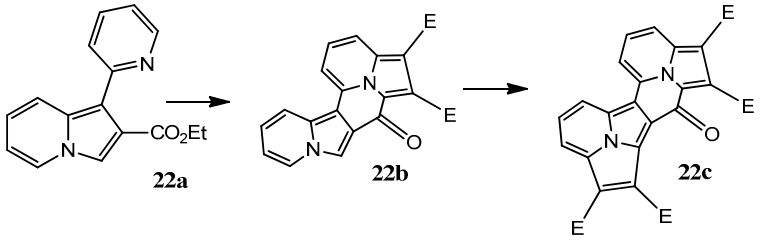
Scheme 5. Synthesis of bis-cyclazinylethanes from bis-indolizinylethanes.

1-(2-Pyridyl)indolizine in reaction with acetylenes **16a**,**b** formed cyclazine [40], Table 1. The product was converted to indolizino-cyclazine **16c**, and DMAD was added for the second time giving bi-cyclazine **16d** (20 h in boiling xylene without catalyst) with a yield of 30%, Scheme 6.



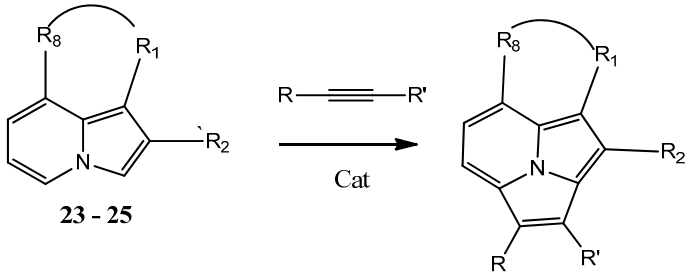
Scheme 6. i N-bromsuccinimide. 6h; ii K_2CO_3.

Analogous structure bearing 2-CO_2Et group **22a** [41] was converted to condensed indolizino-cyclazinone structure **22b**. from which cyclazino-cyclazinone **22c** was obtained with the yield 73% (Pd/C, NO_2Ph, 20 h), Scheme 7.



Scheme 7. Synthesis of cyclazino-cyclazinone.

A Japanese group made an effort to prepare cyclazines from 1,8-cycloannelated indolizines **23** [42–44] containing propylene and butylene bridges, Scheme 8, Table 2. The major finding was the use of DDQ in reaction with dibenzoyl acetylene (DBZA) under extremely mild conditions. Further studies on oxo-derivatives **24** [45] allowed to make cyclazine bearing (in 1 and 8 positions) oxo-propyl group.

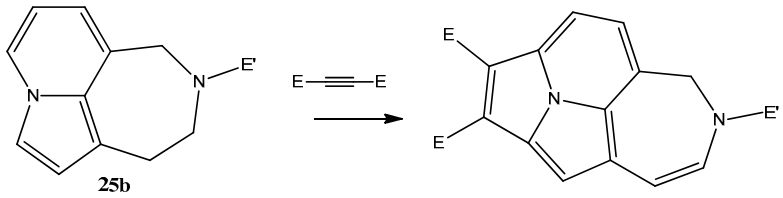


Scheme 8. Synthesis of cyclazines from 1,8-cycloannelated indolizines (see Table 2).

Table 2. Substituents and yields of cycloaddition of acetylenes to indolizines **23–25** annelated by a ring across the positions C1 and C-8 (Scheme 8).

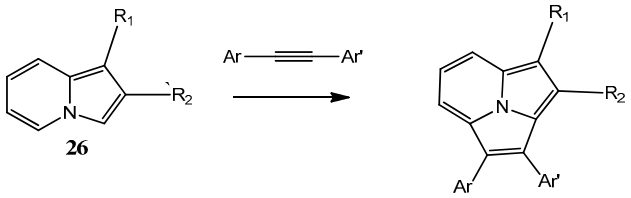
N	R/R′	R8-R1	R2	Cat/Solv/T°/Time	Yield %	Ref.
23a	E/H	$(CH_2)_4$	Me	Pd-C/PhMe/Δ/50 h	75	[42]
23b	E/H	$(CH_2)_3$	Me	Pd-C/PhMe/Δ/50 h	75	[42]
23c	E/E	$(CH_2)_4$	Me	Pd-C/PhMe/Δ/50 h	85	[42]
23d	E/E	$(CH_2)_3$	Ph	Pd-C/PhMe/Δ/50 h	58	[42]
23d	E/E	$(CH_2)_4$	Ph	Pd-C/PhMe/Δ/50 h	61	[42]
23e	E/E	$(CH_2)_3$	Me	Pd-C/PhMe/Δ/50 h	77	[42]
24f	COPh/COPh	$(CH_2)_4$	Me	DDQ/THF/0°/1 h	86	[42]
23g	COPh/COPh	$(CH_2)_4$	Ph	DDQ/THF/0°/1 h	92	[42]
23h	COPh/COPh	$(CH_2)_3$	Me	DDQ/THF/0°/1 h	68	[42]
23i	COPh/COPh	$(CH_2)_3$	Ph	DDQ/THF/0°/1 h	52	[42]
24a	E/E	$O=C(CH_2)_2$	Ph	DDQ/MePh/Δ/2 h	92	[45]
24b	E/E	$O=C(CH_2)_2$	E′	DDQ/MePh/Δ/2 h	98	[45]
25a	COPh/COPh	CH_2-NE′-CH_2	H	DDQ/THF/0°/10 m	66	[46]
25b	COPh/COPh	CH_2-NE′-$(CH_2)_2$	H	DDQ/THF/0°/10 m	84	[46]

Finally, fused indolizines **25** with saturated piperidyl or hexamethyleneimine bridges across 1,8-positions were [46] prepared and involved in cycloaddition with DBZA giving expected cyclazines, Scheme 9. Table 2. However, an attempt to perform similar reaction with DMAD caused cyclazine formation with unsaturated azepine ring.



Scheme 9. Abnormal cycloaddition to 1,8-cycloannelated indolizine combined with dehydrogenation.

Novel reaction conditions were found for cycloaddition reaction, so that the role of oxidant was played by O_2 in presence of $Pd(OAc)_2$ [47], Scheme 10. Many 1-alkoxycarbonyl derivatives (**26a–l**) were involved in the reaction with acetylenes of the type ArC≡CAr, Table 3.

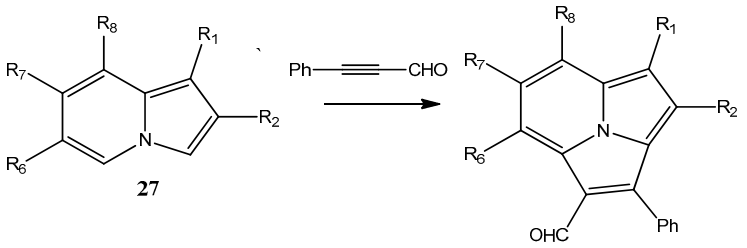


Scheme 10. 10 mol % $Pd(OAc)_2$, DMSO, O_2 (1 atm), no base.

Table 3. Substituents and yields of cycloaddition of diarylalkynes to indolizines (Scheme 10).

N	R	R′	R1	R2	Yield %	Ref.
26a	Ph	Ph	E′	E′	92	[47]
26b	4-MePh	4-MePh	E	H	88	[47]
26c	Ph	Ph	E	E	98	[47]
26d	4-FPh	4-FPh	E	E	85	[47]
26e	3-BrPh	3-BrPh	E	E	56	[47]
26f	4-NO_2Ph	4-MeOPh	E	E	80 (6:1)	[47]
26g	4-NO_2Ph	Ph	E	E	68 (20:1)	[47]
26h	4-FPh	4-MeOPh	E	E	91 (2:1)	[47]
26i	C≡CPh	Ph	E	E	41;39	[47]
26j	Ph	Ph	CO_2nBu	CO_2nBu	79	[47]
26k	Ph	Ph	E	Ph	20 *	[47]
26l	Ph	Ph	CO_2tBu	H	55	[47]
26l	Ph	Ph	H	E	70	[47]
26m	Ph	Ph	$CONMe_2$	H	76	[47]
26n	Ph	Ph	E′	H	87	[47]
26o	Ph	Ph	E	H	90	[47]
26p	Ph	Ph	CN	H	59	[47]

A range of indolizine **27** smoothly underwent visible-light-induced intermolecular cyclization with internal alkynes with acceptor group to afford cyclazines in good to excellent yields with high regioselectivity [48], Scheme 11, Table 4.

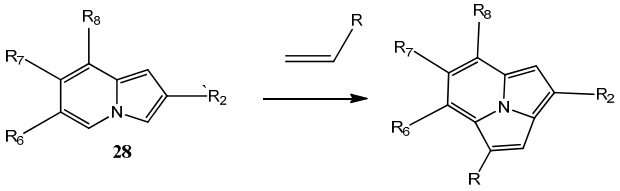


Scheme 11. Bengal rose KI, air, DMSO, 8 h, 20 W, blue LED.

Table 4. Substituents and yields of photochemical cycloaddition to indolizines (Scheme 11).

N	R′	R″	R1	R2	R6	R7	R8	Yield, %	Ref.
27a	CHO	Ph	H	Ph	H	H	H	87	[48]
27b	CHO	n-C_5H_{11}	H	Ph	H	H	H	61	[48]
27c	CHO	2-Thienyl	H	Ph	H	H	H	66	[48]
27d	CHO	3-Cl-Ph	H	Ph	H	H	H	79	[48]
27e	CHO	3-Ac-Ph	H	Ph	H	H	H	58	[48]
27f	CHO	4-Me-Ph	H	Ph	H	H	H	77	[48]
27g	CHO	3,4-Me_2Ph	H	Ph	H	H	H	57	[48]
27h	CHO	2-Naphtyl	H	Ph	H	H	H	59	[48]
27i	COPh	Ph	H	Ph	H	H	H	58	[48]
27j	Ph	Ph	H	Ph	H	H	H	0	[48]
27k	CHO	Ph	H	4-OMe-Ph	H	H	H	70	[48]
27l	CHO	Ph	H	4-F-Ph	H	H	H	81	[48]
27m	CHO	Ph	H	4-NO_2-Ph	H	H	H	58	[48]
27n	CHO	Ph	H	4-Br-Ph	H	H	H	64	[48]
27o	CHO	Ph	H	4-CF_3-Ph	H	H	H	71	[48]
27	CHO	Ph	H	2-F-Ph	H	H	H	73	[48]
27p	CHO	Ph	H	3-Me-Ph	H	H	H	63	[48]
27q	CHO	Ph	H	3,4-Cl_2-Ph	H	H	H	58	[48]
27r	CHO	Ph	H	2,4-Cl_2-Ph	H	H	H	78	[48]
27s	CHO	Ph	H	3,4-$(OMe)_2$-Ph	H	H	H	84	[48]
27t	CHO	Ph	H	1,3-Benzo-dioxolyl-5	H	H	H	67	[48]
27u	CHO	Ph	H	Furyl	H	H	H	62	[48]
27v	CHO	Ph	H	2-Naphtyl	H	H	H	60	[48]
27w	CHO	Ph	E′	H	H	H	H	59	[48]
27x	CHO	Ph	H	Ph	Et	H	H	61	[48]
27y	CHO	Ph	H	Ph	H	Me	H	73	[48]
27z	CHO	Ph	H	Ph	H	OMe	H	70	[48]
27a1	CHO	Ph	H	Ph	Me	H	Me	61	[48]
27b1	E′	H	H	Ph	H	H	H	88	[48]
27c1	E′	H	H	Ph	H	H	H	70	[48]
27d1	E′	E′	H	Ph	H	H	H	77	[48]
27e1	E′	E′	H	Ph	H	H	H	70	[48]

An efficient visible-light-induced intermolecular [8+2] alkenylation–cyclization process was developed for indolizines **28** [49], Scheme 12, Table 5. In this reaction alkene (not alkyne) formed cyclazine derivatives with oxygen as an oxidant via cascade reaction.

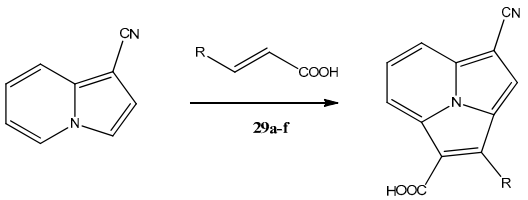


Scheme 12. Bengal Rose, TFA, CH_2Cl_2, O_2, 10 h, 20 W blue LED.

Table 5. Substituents and yields of oxidative cycloaddition of alkenes to indolizines (Scheme 12).

N	R	R2	R5	R6	R7	R8	Yield, %	Ref.
28a	E	Ph	H	H	H	H	80	[49]
28b	CO_2nBu	Ph	H	H	H	H	69	[49]
28c	CO_2CH_2CHOH	Ph	H	H	H	H	68	[49]
28d	CONHt-Bu	Ph	H	H	H	H	67	[49]
28e	2-Py	Ph	H	H	H	H	65	[49]
28f	E	Ph	Me	H	H	H	78	[49]
28g	2-Py	Ph	H	H	H	Me	69	[49]
28h	E	Ph	H	H	Me	H	77	[49]
28i	E	Ph	H	Et	H	H	70	[49]
28j	E	4-FPh	H	H	H	H	75	[49]
28k	E	4-BrPh	H	H	H	H	78	[49]
28l	E	4-MePh	H	H	H	H	74	[49]
28m	E	4-MeOPh	H	H	H	H	71	[49]
28n	E	3-FPh	H	H	H	H	75	[49]
28o	E	3-ClPh	H	H	H	H	66	[49]
28p	E	3-BrPh	H	H	H	H	70	[49]
28q	E	3-MePh	H	H	H	H	71	[49]
28r	2-Py	3-MePh	H	H	H	H	66	[49]
28s	E	3-MeOPh	H	H	H	H	68	[49]
28t	E	3-FPh	H	H	H	H	65	[49]
28u	E	$3,4\text{-}Cl_2Ph$	H	H	H	H	70	[49]
28v	E	$3,4\text{-}(MeO)_2Ph$	H	H	H	H	66	[49]
28x	E	2-Thienyl	H	H	H	H	69	[49]

Annulations of 1-cyanoIndolizine with unsaturated carboxylic acids **29a–f** was observed during the catalysis with $Pd(OAc)_2$ [50], via similar cascade reaction Scheme 13, Table 6.



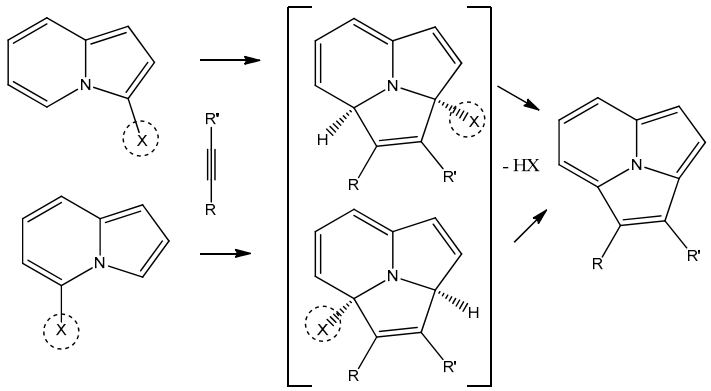
Scheme 13. 10 mol % $Pd(OAc)_2$, 1 eq benzoquinone, O_2, 2 eq KOAc, DMF. 120°, 12 h.

Table 6. Yields of catalytic cycloaddition of acrylates (Scheme 13) to 1-cyanoindolizine.

N	R	Yield, %	Ref.
29a	Me	39	[50]
29b	Ph	52	[50]
29c	4-Cl-Ph	46	[50]
29e	4-OMePh	59	[50]
29f	1-Naphtyl	45	[50]

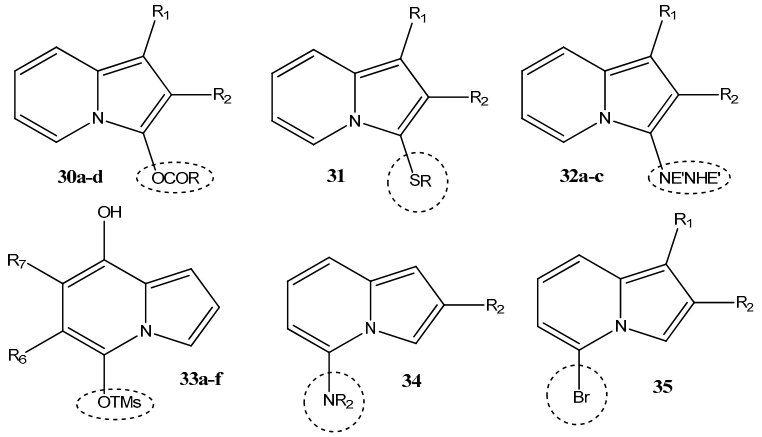
3. Non-Catalytic Cycloaddition to 3- or 5-Substituted Indolizines

If a leaving group X is located at position 3 or 5 of indolizine ring, cycloaddition reaction does not require a catalyst/oxidant for dehydrogenation, because the dihydrocyclazine intermediate can lose HX, Scheme 14.



Scheme 14. Cycloaddition of indolizines with 3(5)-leaving groups.

Such groups X can be -OR or -OCOR. -SR, -NR_2 or -NR-NR_2, halogen and some others, Scheme 15.



Scheme 15. Examples of 3(5)-substituted indolizines involved in cycloaddition (see Table 7).

Table 7. Substituents, conditions and yields in cycloaddition of acetylenes to 3(5)-substituted indolizines giving cyclazines (Scheme 15).

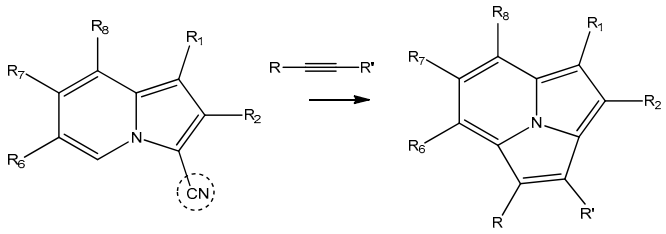
N	R/R′	R3/R5	R1	R2	R6	R7	R8	Cat/Solv/T°/Time	Yield %	Ref.
30a	E/H	OCOMe/H	H	H	H	H	H	No/Ac_2O/Δ/0.5 h	86	[51]
30b	E/H	OCOEt/H	H	H	H	H	H	No/Ac_2O/Δ/0.5 h	100	[51]
30c	E/H	OCOMe/H	Ph	H	H	H	H	No/Ac_2O/Δ/0.5 h	90	[51]
30d	E/H	OCOMe/H	CH_2E'	E′	H	H	H	No/Ac_2O/Δ/0.5 h	100	[51]
31	E/E	i-PrS/H	i-PrS	i-PrS	H	H	H	No/PhMe/Δ/40 h	96	[52]
32a	E/E	NE′NHE′/H	Ph	H	H	H	H	No/PhH/Δ/5 h	5.6	[53]
32b	E/E	NE′NHE′/H	H	H	H	H	H	No/PhH/Δ/5 h	32	[53]
32c	E/E	NE′NHE′/H	NE′NHE′	H	H	H	H	No/PhH/Δ/5 h	66	[53]
33a	E/E	H/OTms	H	H	OMe	OMe	OH	No/PhMe/Δ/23 h	56	[54]
33b	E/E	H/OTms	H	H	OMe	Ph	OH	No/PhMe/Δ/23 h	79	[54]
33c	E/E	H/OTms	H	H	OMe	n-Bu	OH	No/PhMe/Δ/23 h	52	[54]
33d	E/E	H/OTms	H	H	OMe	n-BuC≡C	OH	No/PhMe/Δ/23 h	67	[54]
33e	E/E	H/OTms	H	H	OMe	PhC≡C	OH	No/PhMe/Δ/23 h	66	[54]
33f	E/E	H/OTms	H	H	n-Bu	n-Bu	OH	No/PhMe/Δ/23 h	53	[54]
34	E/E	H/Morph	H	p-NO_2Ph	H	H	H	No/PhH/Δ/16 h	82	[55]
35	E/E	H/Br	Me	t-Bu	H	H	H	No/PhMe/80°/2 h	53	[56]

Thus, 3-acyloxy indolizines **30a–d** were converted to cyclazines with excellent yield [51]. Tris-1,2,3-(iso-propylthio)indolizine **31** also underwent such cycloaddition [52]. 3-Hydrazine-substituted derivatives **32a–c** lost the attaching group forming cyclazines [53].

Quite similarly behaved 5-substituted indolizines. After refluxing in aromatic solvents, 5-OTms indolizines **33a–f** [54], 5-morpholyl **34** [55] and 5-bromo derivatives **35** [56] smoothly formed the expected cyclazine structures in the absence of catalyst.

4. Features of Cycloaddition of 3-Cyano Indolizines and Their Benzo Derivatives

3-CN-Indolizines are the structures that looked capable to react with acetylenes without catalyst due to probable loss of HCN from intermediate. In 1980 the Matsumoto group (together with L. Paquet) reported the first reaction of 3-CN-inolizines with DMAD [57], [58]. 3-Cyanindolizine **36a** and its 6,8-dimethyl analog **36b** with DMAD in refluxing toluene gave expected cyclazines, though in presence of Pd-C (Scheme 16, Table 8). The later group of Tominaga converted 2-MeS-derivatives of 3-CN-indolizines-**37a,b** to MeS-cyclazines (again in the presence of the same catalyst) [59] (Scheme 16, Table 8).

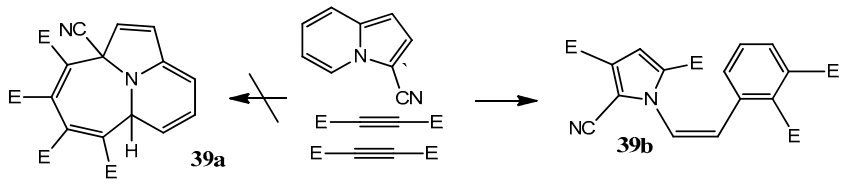


Scheme 16. Cycloaddition to 3-CN-substituted indolizines (see Table 8).

Table 8. Substituents, conditions and yields in cycloaddition of acetylene acetylenes to 3-CN-substituted indolizines giving cyclazines (Scheme 16).

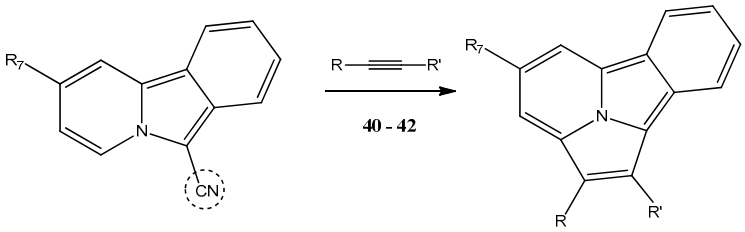
N	R/R′	R1	R2	R6	R7	R8	Cat/Solv/T°/Time	Yield %	Ref.
36a	E/E	H	H	H	H	H	Pd-C/PhH/Δ/24 h	40	[58]
36b	E/E	H	H	Me	H	Me	Pd-C/PhH/Δ/24 h	25	[58]
37a	E/E	H	MeS	H	H	H	Pd-C/PhH/Δ/30 h	22	[59]
37b	E/E	H	MeS	Me	H	Me	Pd-C/PhH/Δ/30 h	12	[59]
38a	E/E	H	H	H	H	H	Pd′C/MePh/Δ/24 h	40	[60]
38b	E/E	H	H	H	Me	H	Pd′C/MePh/Δ/25–74 h	10-7	[60]
38c	E/E	H	H	H	$PhCH_2$	H	Pd′C/MePh/Δ/30 h	5	[60]
38d	E/E	H	H	H	Ph	H	Pd′C/MePh/Δ/215 h	13	[60]
38e	E/E	H	H	Me	H	Me	Pd′C/MePh/Δ/77 h	25	[60]
38f	E/E	H	H	H	CN	H	Pd′C/MePh/Δ/260 h	7	[60]
38g	E/E	H	H	H	E	H	Pd′C/MePh/Δ/336 h	2	[60]

The most dramatic story happened to another adduct of CN-indolizines and DMAD. In 1980 the Matsumoto group found that 7-methyl- and 7-benzyl derivatives gave 1:2 adduct with proposed structure **39a** [58], Scheme 17. Later the same group tested the reaction of 3-CN indolizines **38a–g** in the presence and absence of a catalyst [60,61], Table 8. Finally, the structure of the 1:2 adduct formed without the catalyst was proved by X-ray, and it was unexpectedly styryl pyrrole **39b** [60,61], Scheme 17. Different mechanisms of benzene ring formation and E-group migration have been proposed.



Scheme 17. Structure of 1:2 adduct of 3-cyanoindolizine and DMAD.

Cyano-derivative of benzo[a]indolizine is easily available from pyridinium-dicyanmethylide and dehydrobenzene. Matsumoto first published the results of cycloaddition of dibenzoylacetylene to the structures **40a–d** (Scheme 18, Table 9) [62,63]. Again, the reaction required a catalyst. Tominaga group made this cycloaddition **41** with DMAD [64]. Finally, this reaction was tested extensively with various acetylenes **42** [65].



Scheme 18. Cycloaddition to 3-CN-substituted benzoindolizines (see Table 9).

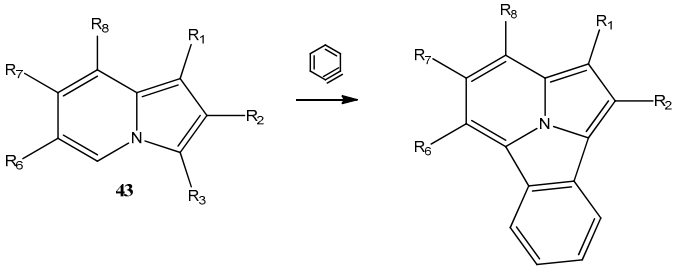
Table 9. Substituents, conditions and yields in cycloaddition of acetylene to 3-CN-substituted benzoindolizines giving benzocyclazines (Scheme 18).

N	R/R′	R7	Cat/Solv/T°/Time	Yield %	Ref.
40a	COPh/COPh	H	Pd-C/PhH/rt/46 h	82	[62,63]
40b	COPh/COPh	Me	Pd-C/PhH/rt/24 h	82	[62]
40c	COPh/COPh	Ph	Pd-C/PhH/rt/24 h	69	[62]
40d	COPh/COPh	COPh	Pd-C/PhH/Δ/5.5 h	59	[62]
41	E/E	H	Pd-C/PhMe/Δ/20 h	54	[64]
42a	E/E	H	Pd-C/PhMe/Δ/2 h	13	[65]
42b	E″/E″ [a]	H	Pd-C/PhMe/Δ/20 h	14 (R′ = H)	[65]
42c	Ac/Ac	H	Pd-C/PhMe/Δ/20 h	8	[65]
42d	E/H	H	Pd-C/PhMe/Δ/34 h	NG	[65]
42e	E/$SiMe_3$	H	Pd-C/PhMe/Δ/72 h	11:14 [b]	[65]
42f	E/Ph	H	Pd-C/PhMe/Δ/72 h	52:6 [b]	[65]
42g	Ac/Ph	H	Pd-C/PhMe/Δ/72 h	48:7 [b]	[65]

[a]: E″—CO_2tBu; [b]: regioisomers.

5. Cycloaddition to Benzoindolizines: Synthesis of Benzo Derivatives of Cyclazines

Cycloaddition of benzyne (generated differently) to indolizine **43** is the simplest route to benzo derivatives of cyclazine [3], Scheme 19, Table 10. The resulting structures are strongly fluorescent.



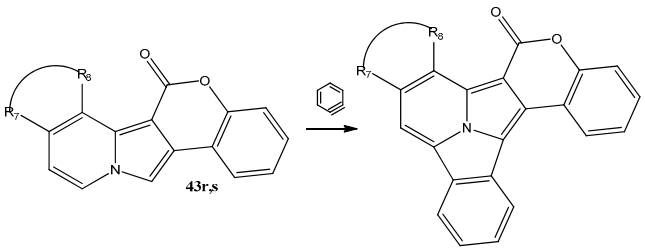
Scheme 19. CsF, MeCN, 90°. A—ortho-substituted benzene with $SiMe_3$ and OSO_2CF_3; B—1-Aminobenzotriazole/$Pb(OAc)_4$.

Table 10. Substituents and yields of cycloaddition of benzynes to indolizines (Scheme 19).

N	Benzyne	R1	R2	R3	R5	R6	R7	R8	Yield, %	Ref.
43a	A	H	Ph	H	H	H	H	H	23	[3]
43b	A	Me	Ph	H	H	H	H	H	49	[3]
43c	A	H	Ph	H	H	H	H	Me	44	[3]

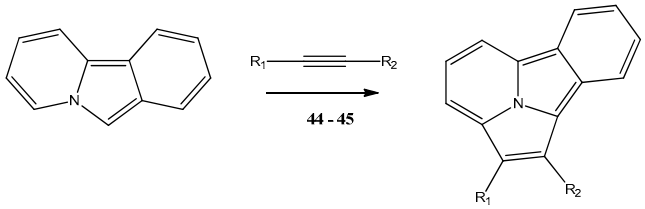
43d	A	H	Ph	H	H	H	Me	H	55	[3]
43e	A	CN	H	H	H	H	Me	H	51	[3]
43f	A	E	H	H	H	H	H	H	50	[3]
43g	A	E	E	H	H	H	H	H	50	[3]
43h	A	E′	E′	H	H	H	H	H	37	[3]
43i	A	E′	E′	H	H	H	Me	H	30	[3]
43j	A	E	E	CN	H	Me	H	H	75	[3]
43k	A	COPh	Ph	H	H	H	Me	H	51	[3]
43l	B	Me	Ph	H	H	H	H	H	40	[3]
43m	B	H	Ph	H	H	H	H	Me	18	[3]
43m	B	H	Ph	H	H	H	Me	H	42	[3]
43o	A	E	H	H	H	H	7,8-Benzo		60	[3]
43p	A	CN	H	H	H	H	7,8-Benzo		52	[3]
43q	A	E′	E′	H	H	H	7,8-Benzo		58	[3]

Condensed structures from **43r**,**s** with coumarin ring were similarly obtained, Scheme 20 [3].



Scheme 20. CsF, MeCN, 90°. **43r** (R7R8 = H, 93%), **43s** (R7,R8 = benzo, 62%), Method A.

Another route to the same benzo-skeleton is cycloaddition of alkynes to benzo[a]indolizines. This reaction was studied with acetylenes containing boron substituents, alone **44a–c** [37] or together with nitrogen-containing heterocycle on another end of acetylene **45a–e** [5], Scheme 21, Table 11. In one experiment **46** benzyne was generated from PhBr; this resulted in dibenzocyclazine was obtained with low yield [66].

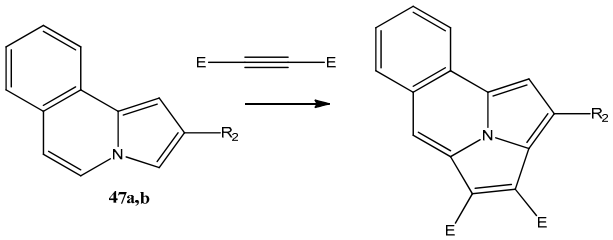


Scheme 21. Cycloaddition to benzoindolizines see Table 11).

Table 11. Substituents and yields (ratio of isomers) of cycloaddition to benzoindolizines (Scheme 21).

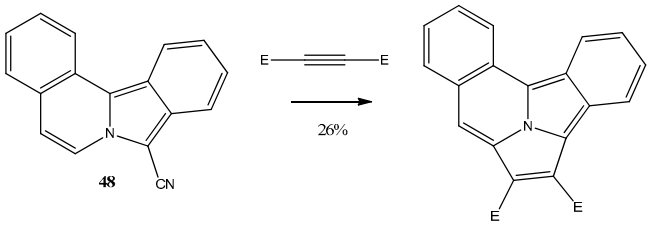
N	R1	R2	Solv/T°/Time/Oxidant	Yield, %	Ref.
44a	Mes_2B	H	PhMe/rt/30m/DDQ	89	[37]
44b	2-(Mes_2B)Ph	H	PhMe/Δ/3d/DDQ	75	[37]
44c	4-(Mes_2B)Ph	H	PhMe/Δ/3d/DDQ	83	[37]
45a	4-(Mes_2B)Ph	2-Py	(1) PhMe/120 °C/5–6d; (2) DDQ/rt/0.5 h	79:2	[5]
45b	2-(Mes_2B)Ph	2-Py	(1) PhMe/120 °C/5–6d; (2) DDQ/rt/0.5 h	82:4	[5]
45c	2-(Mes_2B)Ph	2-Isoquinolyl	(1) PhMe/120 °C/5–6d; (2) DDQ/rt/0.5 h	72:18	[5]
45d	2-(Mes_2B)Ph	2-Benzotiazolyl	(1) PhMe/120 °C/5–6d; (2) DDQ/rt/0.5 h	62:19	[5]
45e	2-(Mes_2B)Ph	2-Tiazolyl	(1) PhMe/120 °C/5–6d; (2) DDQ/rt/0.5 h	68:14	[5]
46	Benzo		2,2,6,6-tetramethylpiperidine, n-BuLi, PhBr/THF/−78 °C/1 h	6.6	[66]

Tominaga showed that indolizines **47a**,**b** having annelated benzene ring across the bond C7–C8 underwent [8+2] cycloaddition forming benzo[g]cycl[3.2.2]azines [29,67], Scheme 22.



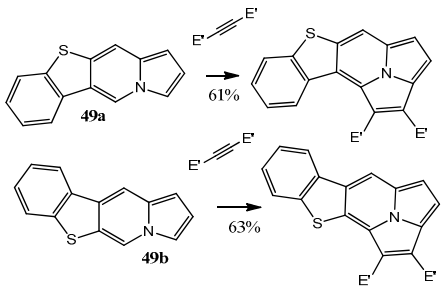
Scheme 22. Pd-C/PhMe/Δ/30h. **47a** R^2 = H (33%), **47b** R^2 = MeS (27%).

In another paper [68], he demonstrated a similar reaction of dibenzoindolizine **48** with DMAD leading to dibenzo[a,h]cycl[3.2.2]azine, Scheme 23.



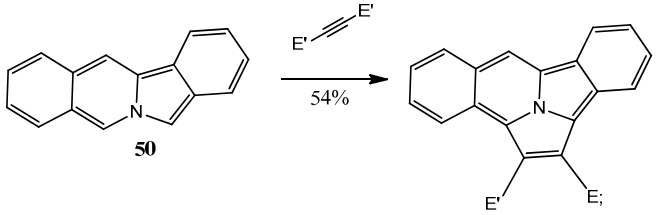
Scheme 23. MePh + HOAc/Δ/20 h.

Isomeric indolizines **49a**,**b** annelated across the bond C6–C7 with benzothiophene underwent cycloaddition with DEAD (PhMe/Δ/6h) without any catalyst [69], Scheme 24.



Scheme 24. Example of cycloaddition to fused indolizines.

The last example is 1,2,5,6-dibenzocycl[2,2,3]azine obtained with a yield of 54% from dibenzoindolizine and DEAD in presence of Pd-C [70], Scheme 25.



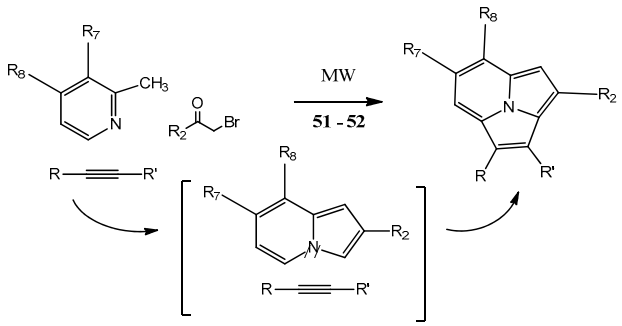
Scheme 25. Pd-C/PhMe/Δ/14 h.

This reaction is featured, firstly, because it was the first cycloaddition in the history of indolizines that even made an influence on Boekelheide. Second, is that the structure of

dibenzoindolizine is extremely polyenic (annelation in indolizine appears across two single bonds), and therefore, the process could be better treated as [2+16] rather than [2+8] cycloaddition.

6. Cycloadditions Where Indolizines Are Intermediates

There are many examples of cyclazine synthesis where the intermediates are indolizines. First, there are so-called 3 component reactions: picoline and bromoketone in the presence of a base (Chichibabin combination to obtain indolizine) and alkyne. Two examples of such combination were reported in microwave conditions [71,72], Scheme 26, Table 12.



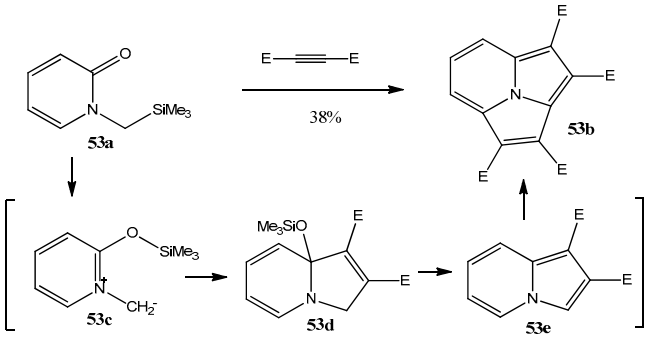
Scheme 26. Microwave three-component synthesis of cyclazines (see Table 12).

Table 12. Substituents and yields of microwave three-component synthesis of cyclazines (Scheme 26).

N	R	R′	R2	R7	R8	Yield, %	Ref.
51a	E	E	Ph	H	H	90	[71] [a]
51b	E	E	4-Me-Ph	H	H	92	[71]
51c	E	E	4-Cl-Ph	H	H	60	[71]
51d	E	E	4-NO2-Ph	H	H	20	[71]
51e	E	E	Polycyclic R	H	H	78	[71]
51f	E	E	1-Cyclohexenyl	H	H	74	[71]
51g *	H	E′	Ph	H	H	78	[71]
51h *	H	E′	Ph	Me	H	80	[71]
51i *	H	E′	4-Me-Ph	Me	H	74	[71]
51j *	H	E′	4-Cl-Ph	H	Me	65	[71]
51k *	H	E′	4-NO2-Ph	H	Me	22	[71]
52a	E	E	Ph	H	H	37	[72] [b]
52b	E	E	4-NO_2Ph	H	H	78	[72]
52c	E	E	4-ClPh	H	H	46	[72]
52d	E	E	4-MeOPh	H	H	23	[72]
52e	E	E	4-MePh	H	H	39	[72]
52f	E	E	4-OHPh	H	H	36	[72]
52g	E	E	4-BrPh	H	H	49	[72]
52h	E	E	4-FPh	H	H	42	[72]

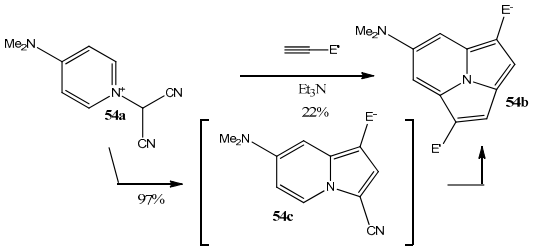
[a]: K_2CO_3, water MW, 100 °C 2–5 min; [b]: Alumina, 300 W, 2 min; * Attention: unexpected products, place of R and R′ groups should be reversed. Probably mistake made by the authors.

Another example is given by cycloaddition to pyridone **53a** giving cyclazine **53b** [73], Scheme 27. Evidently, intermediates are (partially isolated) indolizine **55e** which is obtained by sequence **55c–55d**.



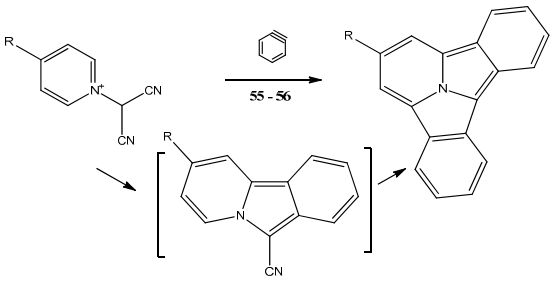
Scheme 27. PhMe/Δ/30 h.

Another example of cyclazine **54b** synthesis from pyridine **54a** with ethyl propiolate via indolizine **54c** [74] is illustrated in Scheme 28. Indolizine **54c** could be isolated.



Scheme 28. TEA (1.2 eq), ethyl propiolate (1.5 eq), CH_3CN + DMF, rt, 24 h.

A similar reaction is between the same pyridine and benzyne [75–77] forming dibenzoindolizine, Scheme 29, Table 13.



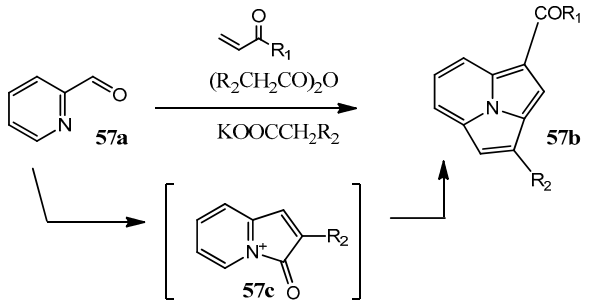
Scheme 29. Synthesis of benzocyclazines from pyridinium ylides (Table 13).

Table 13. Substituents and yields of benzocyclazines from pyridinium ylide (Scheme 29).

N	R	A, Yield, %	B, Yield, %	C, Yield, %	Ref.
55a	H	11 (20)	4 (35)	39	[76]
55b	Me	5 (22)	2 (12)	33	[76]
55c	Ph	3 (44)	2 (10)	38	[76]
55d	PhCO	0.5 (21)	17 (24)	25	[76]
55e	MeOCO	3 (33)	32	-	[76]
55f	MeCO	Trace (27)	18	-	[76]
56a	1,2-Me	12	-	-	[77]
56b	1,3-Me	5	-	-	[77]

In brackets—yield of benzoindolizine. A—diphenyliodonium-2-carboxylate monohydrate 200 °C; B—anthranilic acid and isopentyl nitrite in refluxing chloroform-acetone; C—6-cyanobenzo[a]indolizine diphenyliodonium-2-carboxylatem monohydrate in DME 200 °C. 3 h

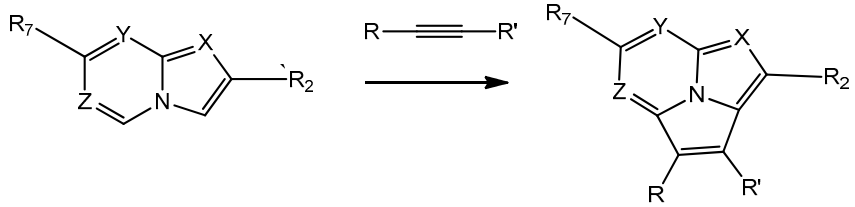
Interesting multistep reaction starting from pyridine **57a** and finishing with cyclazine **57b** with the yields 15–70% was observed independently by Acheson and Pohjala [51,78–82], Scheme 30. The mechanism of this process included Perkin reaction and intermediate formation of indolizine skeleton **57c**.



Scheme 30. Multistep reaction ending with cyclazines.

7. Cycloaddition to Azacyclazines and Their Benzo-Derivatives

The first cycloaddition to aza-analogs of indolizine was observed by Boekelheide [83] in the reaction of imidazo[1,2-a]pyridine **58** with DMAD in presence of Pd-C, Scheme 31 and Table 14. It was also shown that 6-azaindolizine **59** [84] (but not 7-aza-derivative [25]) can be involved in a similar process. Soon it was proved also for 8-aza-indolizine **60a** and its 7-oxo-analog **61b** [85]. 1-Azaindolizine bearing 2-SO_2Me group failed to go in such cycloaddition [86], whereas the same structures with 2-SMe group **61a**,**b** [87] and their [h]-benzannelated derivatives **62** [88] formed the desired azacyclazines with DMAD. In our recent work, we proved that MAC could react with 1-azaindolizine **63** giving azacyclazine in the open air [36]. Diphenylacetylene was capable to transform imidazopyridine **64** to azacyclazine under the action of $Pd(OAc)_2/Cu(OAc)_2$ [89].

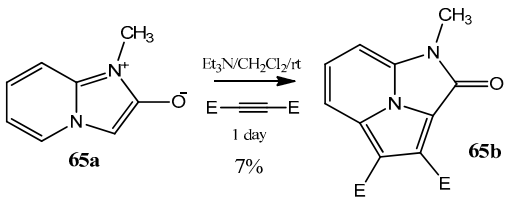


Scheme 31. Synthesis of azacyclazines from azaindolizines (Table 14).

Table 14. Substituents, conditions and yields of azacyclazines from azaindolizines (Scheme 31).

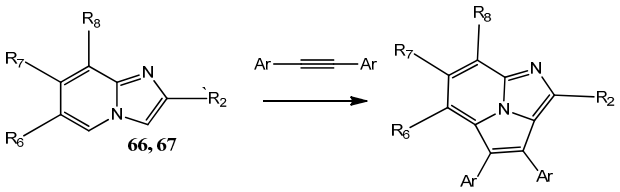
N	R/R′	X	R2	Z	R7	Y	Cat/Solv/T°/Time	Yield, %	Ref.
58	E/E	N	Ph	H	H	H	Pd-C/MePh/Δ/25 h	29	[83]
59	E/E	H	Ph	N	Me	H	Pd-C/MePh/Δ/21 h	28	[84]
60a	E/E	H	Me	H	Me	N	Pd-C/MePh/Δ/	66	[85]
60b	E/E	H	Me	H	O=	NMe	Pd-C/MePh/Δ/	59	[85]
61	E/E	NSMe		H	(CH=CH)2		Pd-C/MePh/Δ/30 h	6	[88]
62a	E/E	NSMe		H	H	H	Pd-C/MePh/Δ/30 h	36	[87]
62b	E/E	NSMe	MeC	H	MeC		Pd-C/MePh/Δ/30 h	40	[87]
63	E/H	Nt-Bu		H	H	H	O_2/MePh/Δ/4 h	75	[36]
64	Ph/PhN	H		H	H	H	$Pd(OAc)_2/Cu(OAc)_2$ LiOAc/DMAc/120°/8 h	49	[89]

Mesoionic structure **65a** underwent cycloaddition with DMAD giving fully covalent structure **65b** proved by X-ray [55], Scheme 32.



Scheme 32. Synthesis of azacyclazinone from mesoionic structure.

Imidazopyridines **66** are transformed to azacyclazines under the action of $Pd(OAc)_2/Cu(OAc)_2$ [90] and [91], Scheme 33, Table 15.



Scheme 33. $Pd(OAc)_2$, $Cu(OAc)_2$, DMSO, 110 °C, 12 h [90]. Pd-Se complex $Cu(OAc)_2$, KOtBu, DMAC, 120 °C, 16 h [91].

Table 15. Substituents and yields of reaction of 2-arylimidazopiridines and diarylacetylenes (Scheme 33).

N	Ar	R2	R6	R7	R8	Yield, %	Ref.
66a	Ph	Ph	H	H	H	78	[90]
66b	Ph	Ph	H	H	Me	76	[90]
66c	Ph	Ph	H	Me	H	75	[90]
66d	Ph	Ph	Cl	H	H	68	[90]
66e	Ph	4-MePh	H	H	H	79	[90]
66f	Ph	4-FPh	H	H	H	75	[90]
66g	Ph	4-ClPh	H	H	Me	73	[90]
66h	Ph	4-CNPh	H	H	H	71	[90]
66i	Ph	4-NO_2Ph	H	H	H	67	[90]
66j	Ph	CF_3	H	H	H	64	[90]
66k	Ph	i-Bu	H	H	H	63	[90]
66l	4-MePh	Ph	H	H	H	77	[90]
66m	4-MePh	Ph	H	Me	H	74	[90]
66n	4-MeOPh	Ph	H	H	H	70	[90]
66o	4-MeOPh	Ph	H	Me	H	69	[90]
66p	4-MeOPh	i-Bu	H	H	H	61	[90]
67a	Ph	Ph	H	H	H	68	[91]
67b	Ph	1-Naphtyl	H	H	H	69	[91]
67c	Ph	Ph	H	Cl	Cl	57	[91]
67d	Ph	Ph	H	Br	Br	51	[91]
67e	Ph	Ph	Me	H	H	76	[91]
67f	Ph	4-CN-Ph	H	H	H	64	[91]
67g	Ph	4-F-Ph	H	H	H	68	[91]
67h	Ph	4-Br-Ph	H	H	H	66	[91]
67i	Ph	4-MeO-Ph	H	H	H	73	[91]
67j	Ph	4-F-Ph	Me	H	H	61	[91]
67k	Ph	2-Tienyl	H	H	H	67	[91]
67l	Ph	Ph	H	H	H	63	[91]
67m	4-Br-Ph	Ph	H	H	H	78	[91]
67n	E′	Ph	H	H	H	31	[91]

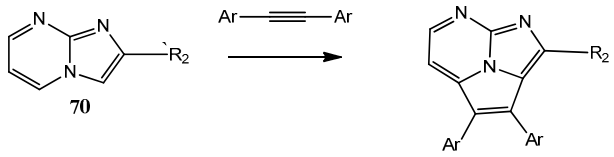
Imidazo[1,2-a]pyridines and imidazo[1,2-a]pyrimidines readily reacted with diaryl acetylenes in presence of catalyst [92], Scheme 34, Table 16.

Scheme 34. Pd-NHC complex, $Cu(OAc)_2$, TBAB, DMA, 90 °C, 12 h.

Table 16. Substituents and yields of reaction of 2-arylimidazopiridines and diarylacetylenes (Scheme 34).

N	Ar/Ar	R2	R8	Yield, %	Ref.
69a	Ph	Me	H	67	[92]
69b	4-Me-Ph	Me	H	71	[92]
69c	2-Me-Ph	Me	H	60	[92]
69e	4-MeO-Ph	Me	H	63	[92]
69f	4-F-Ph	Me	H	68	[92]
69g	4-Cl-Ph	Me	H	68	[92]
69h	4-Br-Ph	Me	H	63	[92]
69i	Ph	t-Bu	H	78	[92]
69j	4-Me-Ph	t-Bu	H	75	[92]
69k	4-F-Ph	t-Bu	H	74	[92]
69l	4-Cl-Ph	t-Bu	H	80	[92]
69m	4-Br-Ph	t-Bu	H	66	[92]
69n	Ph	t-Bu	N	63	[92]
69o	4-Cl-Ph	t-Bu	N	68	[92]
69p	Ph	Me	Me	61	[92]
69q	4-F-Ph	Me	Me	59	[92]
69r	Ph	Mes	H	66	[92]
69s	4-Cl-Ph	Me	H	72	[92]

Separate catalyzed reaction of imidazopyrimidines **70** with diaryl acetylenes gave library of compounds with anti-inflammatory activity [11], Scheme 35, Table 17.



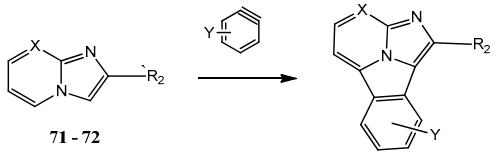
Scheme 35. DMF, PEG-1500, sealed tube $Pd(OAc)_2$, $Cu(OAc)_2$, TBAB 90 °C, 12 h.

Table 17. Substituents and yields of reaction of imidazopyrimidines and diarylacetylenes (Scheme 35).

N	Ar	R2	Yield, %	Ref.
70a	Ph	Ph	76	[11]
70b	Ph	2-MeOPh	72	[11]
70c	4-FPh	2-MeOPh	78	[11]
70d	E	2-MeOPh	74	[11]
70e	E	4-MeOPh	70	[11]
70f	4-FPh	3-CNPh	61	[11]
70g	Ph	3-CNPh	82	[11]
70h	2-Pyridyl	3-CNPh	65	[11]
70i	4-MePh	4-CNPh	68	[11]

70j	Ph	2-NO2Ph	64	[11]
70k	Ph	4-MeOPh	74	[11]
70l	4-MePh	4-MeOPh	65	[11]

The new class of excited-state intramolecular proton transfer-capable molecules, benzo[a]cyclazines, bearing the 2-hydroxyphenyl substituent were prepared in a straightforward manner from imidazo[1,2-a]pyridines **71** via a tandem [8+2] cycloaddition–[2+6+2] dehydrogenation reaction using microwave [6], and similar reaction also involved imidazopyrimidine derivatives **72** [93], Scheme 36, Table 18.



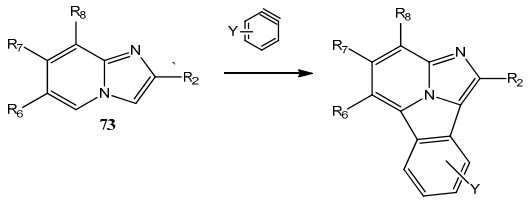
Scheme 36. Reaction of azaindolizines with benzynes (Table 18).

Table 18. Substituents and yields of reaction of azaindolizines and benzynes (Scheme 36).

N	R2	X	Y *	Yield, %	Ref.
71a	2-HOPh	H	A	23	[6]
71b	2-HO-4-MeOPh	H	A	21	[6]
71c	2-HO-5-FPh	H	A	19	[6]
71d	2-HO-5-MePh	H	A	21	[6]
72a	Ph	H	B	74	[93]
72b	4-MeOPh	H	B	39	[93]
72c	4-FPh	H	B	49	[93]
72d	4-NO2Ph	H	B	51	[93]
72e	3,5-(BnO)2Ph	H	B	49	[93]
72f	Ph	N	B	58	[93]
72g	4-MeOPh	N	B	54	[93]
72h	4-FPh	N	B	38	[93]
72i	4-MeOPh	H	C	43 (3′)	[93]
72j	4-MeOPh	N	C	34 (3′)	[93]
72k	4-MeOPh	H	D	39 (4′)	[93]
72l	4-MeOPh	H	D	18 (5′)	[93]
72m	E′	H	B	51	[93]

A—1-TMS-2-OSO_2CF_3-benzene, CsF, 18-Crown-6, MW (25 min, 160 °C); B—1-TMS-2-OSO_2CF_3-benzene, CsF, 18-Crown-6, MW (90 W, 40 psi, 15 min, 80 °C); C—1-TMS-2-OSO_2CF_3-3-MeO-benzene, CsF, 18-Crown-6, MW (90 W, 50 psi, 15 min, 80 °C); D—1-TMS-2-OSO_2CF_3-4-MeO-benzene, CsF, 18-Crown-6, MW (90 W, 50 psi, 15 min, 80 °C)

A base promoted protocol for the synthesis of benzo[a]cyclazines from imidazopyridines and benzyne precursors under metal-free conditions was developed [94], Scheme 37, Table 19.



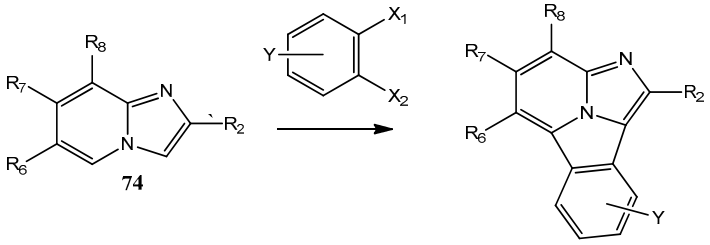
Scheme 37. Reaction of imidazopyridines with benzynes (Table 19).

Table 19. Substituents and yields of reaction of imidazopiridines and benzynes (Scheme 37).

N	R2	R6	R7	R8	Method *	Reagent	Yield, %	Ref.
73a	Ph	H	H	H	A	[Benzyne]	75	[94]
73b	4-MeO-Ph	H	H	H	A	[Benzyne]	72	[94]
73c	4-Et-Ph	H	H	H	A	[Benzyne]	81	[94]
73d	4-F-Ph	H	H	H	A	[Benzyne]	69	[94]
73e	4-CN-Ph	H	H	H	A	[Benzyne]	82	[94]
73f	2-F-Ph	H	H	H	A	[Benzyne]	70	[94]
73g	2-Cl-Ph	H	H	H	A	[Benzyne]	66	[94]
73h	2-Me-Ph	H	H	H	A	[Benzyne]	71	[94]
73i	2-Br-Ph *	H	H	H	A	[Benzyne]	55 (de-brom)	[94]
73j	4-Cl-Ph	Me	H	H	A	[Benzyne]	83	[94]
73k	2-Cl-Ph	H	H	Me	A	[Benzyne]	63	[94]
73l	Ph	Me	H	H	A	[Benzyne]	71	[94]
73m	4-Et-Ph	H	H	Me	A	[Benzyne]	65	[94]
73n	4-Et-Ph	Me	H	H	A	[Benzyne]	60	[94]
73o	4-MeO-Ph	Me	H	H	A	[Benzyne]	72	[94]
73p	2-F-Ph	H	H	Me	A	[Benzyne]	60	[94]
73q	Ph	H	H	Me	A	[Benzyne]	75	[94]
73r	4-Cl-Ph	H	Me	H	A	[Benzyne]	32	[94]
73s	4-Et-Ph	Br *	H	H	A	[Benzyne]	54 (de-brom)	[94]
73t	H	H	CO2Me	H	A	[Benzyne]	50	[94]
73u	H	Cl	H	H	A	[Benzyne]	78	[94]
73v	H	H	H	H	A	[Benzyne]	45	[94]
73x	H	H	H	H	B	[1-MeO-benzyne-2]	70	[94]
73y	H	H	H	H	C	[1-Me-benzyne-3]	65 (2 isom.)	[94]
73	4-Et-Ph	H	H	H	C	[1-Me-benzyne-3]	72 (2 isom.)	[94]
73z	4-Cl-Ph	H	H	H	C	[1-Me-benzyne-3]	69 (2 isom.)	[94]
73a1	4-CN-Ph	H	H	H	D	[1-MeO-benzyne-2]	80 (3′)	[94]
73b1	4-CN-Ph	H	H	H	E	[1-Me-benzyne-3]	75 (2 isom.)	[94]
73c1	4-Et-Ph	H	H	H	F	[1-MeO-benzyne-2]	73	[94]
73d1	t-Bu	H	H	H	G	[Benzyne]	62	[94]

* A—1-TMS-2-OSO_2CF_3-benzene 18-crown-6-ether, K_2CO_3; acetone, 45 °C, 24 h; B—1-TMS-2-OSO_2CF_3-3-MeO-benzene; C—1-TMS-2-OSO_2CF_3-4-Me-benzene; D—1-TMS-2-OSO_2CF_3-3-MeO-benzene; E—1-TMS-2-OSO_2CF_3-4-Me-benzene; F—1-TMS-2-OSO_2CF_3-3-MeO-benzene; G—1-TMS-2-OSO_2CF_3-benzene.

An interesting reaction that formally fit the [8+2] cycloaddition was developed for interaction of imidazopyridines **74** and 1,2-dihalobenzenes in presence of Pd-catalyst [95], Scheme 38. Table 20.



Scheme 38. Pd/xphos, K_2CO_3, DMF, 160 °C, 24 h.

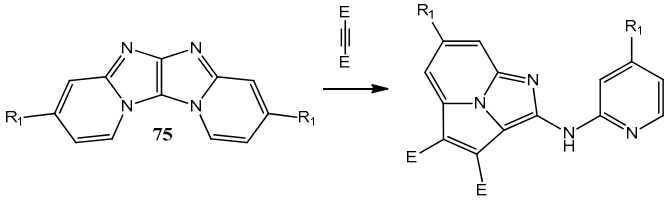
Table 20. Substituents and yields of reaction of imidazopyridines and 1,2-dihalobenzenes (Scheme 38).

N	R2	R6	R7	R8	Yield, %	Benzene *	Ref
74a	Ph	H	H	H	77	A	[95]
74b	4-Me-Ph	H	H	H	79	A	[95]
74c	4-MeOPh	H	H	H	54	A	[95]
74d	4-ClPh	H	H	H	45	A	[95]
74e	4-CF3Ph	H	H	H	74	A	[95]

74f	3-MeOPh	H	H	H	83	A	[95]
74g	2-MePh	H	H	H	60	A	[95]
74h	2-Naphtyl	H	H	H	52	A	[95]
74i	Ph	H	H	Me	83	A	[95]
74j	Ph	H	Me	H	87	A	[95]
74k	Ph	H	Cl	H	27	A	[95]
74l	Ph	Me	H	H	73	A	[95]
74m	Ph	H	H	N	95	A	[95]
74n	Ph	H	H	H	80	B	[95]
74o	Ph	H	H	H	69	C	[95]
74p	Ph	H	H	H	82	D	[95]
74q	Ph	H	H	H	86	E	[95]

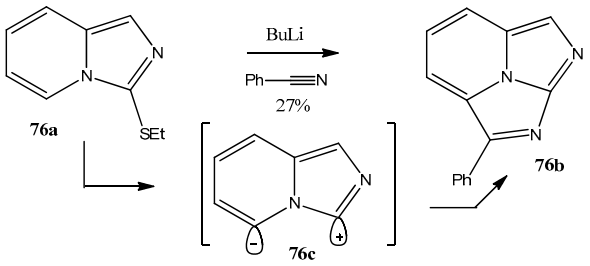
* Benzene: A 1,2-Br_2, B 1-Br-2-Cl, 1-I-2-Br, D 1,2-Br_2-4,5-Me_2, E 1-Br-2-Cl-4-Me.

The system containing two fused imidazopyridines **75** was placed in reaction with DMAD [96], Scheme 39. One ring of imidazopyridine entered into [8+2] cycloaddition with the yields 22–30% on heating in benzene.



Scheme 39. Cycloaddition of tetraazapentalene derivatives.

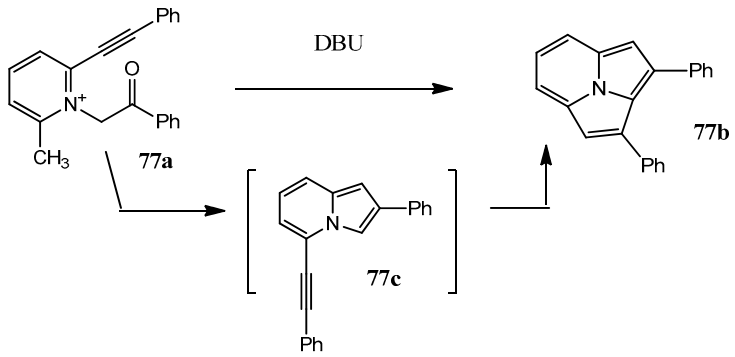
A rare example of benzonitrile entered into [8+2] cycloaddition to produce diazacyclazine **76b** was reported [97], Scheme 40. Azaindolizine **76a** reacted with BuLi giving dipolar structure **76c** which underwent cyclization.



Scheme 40. Synthesis of diazacyclazine.

8. Concerted One-Step 1,10 Processes

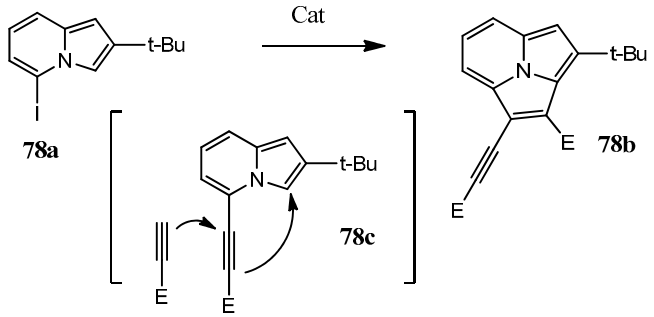
If one adds a multiple bond to the end of the tetraene fragment of indolizine, the ring closure becomes possible. A multiple bond can be alkene, alkyne or arene, and the "end" of the tetraene can be position 3 or 5. However, no such reactions exist for 3-vinyl/ethynyl derivatives and for 5-vinyl indolizines. The first example of such cyclization was reported for 5-ethynyl indolizine **77c** [98,99] which is postulated to be intermediate, Scheme 41.



Scheme 41. Cyclization of 6-ethynylpyridinium salts.

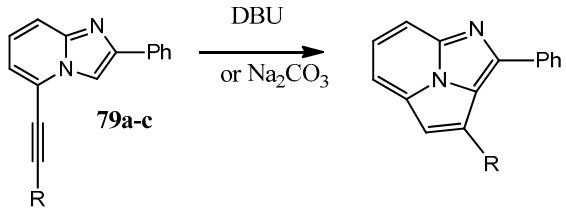
According to [98] reaction **77a–77b** proceeded with a yield of 10–15%, later result [99] was 7%. The main product was 5-Me-3-benzoyl indolizine which could not be converted to **77b**. However, we showed that 5-ethynyl indolizine **77c** obtained by Sonogashira coupling [100] could not be converted to cyclazine **77b** under thermal or acidic conditions.

5-Iodo-indolizine **78a** in conditions of Sonogashira reaction with 2 eq of ethoxycarbonyl acetylene gave cyclazine **78b** [36], Scheme 42. We supposed that the reaction started from nucleophilic attack of acetylenide anion on **78c**.



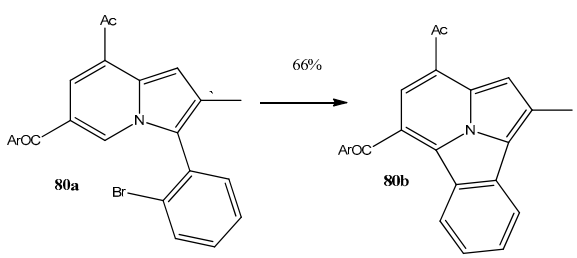
Scheme 42. $Pd(PPh_3)_2Cl_2/CuI/MeCN/Et_3N/rt$.

5-Ethynyl derivatives of imidazopyridines **79a–c** behaved in an expected way [99], Scheme 43.



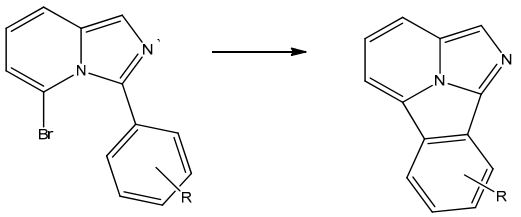
Scheme 43. 79a–c Me, n-Bu, Ph (70–80%).

In one case the double bond of benzene ring at position 3 of indolizine **80a** underwent catalytic ring closure to benzocyclazine **80b** [35], Scheme 44.



Scheme 44. $Pd(OAc)_2$ 10 mol %. PPh_3, K_2CO_3. PhMe/115 °C/60 h.

A similar process was employed to obtain highly fluorescent benzo derivatives of azacyclazine starting from Br-substituted 3-aryl imidazopyridines **81**, Scheme 45, Table 20 [8,101].



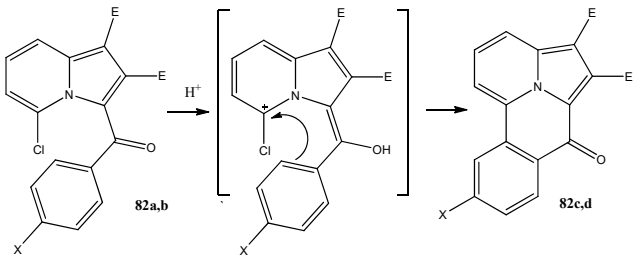
Scheme 45. Cyclization of Br-substituted 3-arylimidazopyridines (Table 21).

Table 21. Substituents and yields of the ring closure reaction on Scheme 45.

N	Ar	R8	Yield, %	Ref.
81a	Ph	H	100	[8] **, [101] *
81b	4-(Ph)-Ph	H	100	[8]
81c	4-t-Bu-Ph	H	89	[8]
81d	4-BnO-Ph	H	90	[8]
81e	4-$(O(CH_2)_2OBz)$-Ph	H	89	[8]
81f	4-NMe_2-Ph	H	98	[8]
81g	4-F-Ph	H	98	[8]
81i	4-Cl-Ph	H	94	[8]
81j	4-CO_2Me-Ph	H	95	[8]
81k	4-CN-Ph	H	99	[8]
81l	3,4,5-$(Me)_3$-Ph	H	93	[8]
81m	2-EtO-4-NO_2-Ph	H	92	[8]
81n	2,3,4,5-$(F)_4$-Ph	H	66	[8]
81o	2-MeO-Ph	H	98	[8]
81p	1-Naphtyl	H	97	[8]
81q	2-Fluorenonyl	H	61	[8]
81r	2-Furyl	H	40	[8]
81s	2-Tienyl	H	65	[8]
81t	2-Propenyl	H	87	[8]
81u	2-Styryl	H	28	[8]

* $Pd_2(dba)_3$, $HP(t\text{-}Bu)_3BF_4$, DMF, 90 °C, 16 h. ** $Pd_2(dba)_3$, $HP(t\text{-}Bu)_3BF_4$, K_2CO_3, DMF 120 °C, 2.5 h.

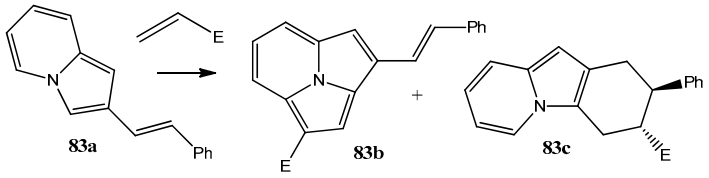
We found that 5-chloro-3-benzoyl indolizines **82a**,**b** in acidic conditions closed the ring [102,103], Scheme 46, forming benzocyclazine derivatives **82c**,**d** (X = Cl 83%, X = NO_2 90%). Here the protonation opened direct link to 1,10-polyene which underwent ring closure.



Scheme 46. Unusual ring closure of 5-chlorindolizines.

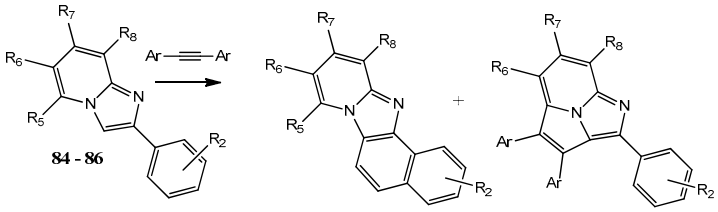
9. Concurrence of [8+2] and [4+2] Cycloadditions

2-Styrylindolizine **83a** reacted with methyl acrylate (Scheme 47) giving the usual product of oxidative [8+2] cycloaddition—cyclazine **83b** together with [4+2] cycloadduct **83c** without catalyst [38]. After more prolonged heating (from 122 h to 288 h) the ratio **83b:83c** changed from 3:68 to 38:10. A somewhat similar result was obtained in reaction with N-ethylmaleimide where [4+2] adduct (33%) was formed together with isomeric dihydrocyclazines (43%).



Scheme 47. Example of concurrence between [8+2] and [8+2] cycloaddition.

Possibility of concurrence between [8+2] and [4+2] cycloaddition appeared in the case of 2-aryl substituted azaindolizines, Scheme 48. At least three papers appeared on this topic [7,104,105] and the data are summarized in Table 22.



Scheme 48. Concurrence in cycloaddition for 2-arylimidazopyridines (Table 22).

Table 22. Substituents, yields and ratio of isomers in concurrent 2+4 and 2+8 cycloadditions of 2-arylazaindolizines and acetylenes (Scheme 48).

N	Ar	Ar	R2	R5	R6	R7	R8	Yield, % (4+2/8+2)	Ref.
84a	Ph	Ph	H	H	H	H	H	85 (82/18)	[104] [a]
84b	4-FPh	4-FPh	H	H	H	H	H	79 (68/32)	[104]
84c	4-Me-Ph	4-Me-Ph	H	H	H	H	H	89 (60/40)	[104]
84d	Ph	Ph	H	H	H	H	Me	88 (46/54)	[104]
84e	Ph	Ph	H	Me	H	H	H	74 (100/0)	[104]
85a	Ph	Ph	H	H	H	H	H	65/18	[105] [b]
85b	Ph	Ph	4-Me	H	H	H	H	72/15	[105]
85c	Ph	Ph	4-MeO	H	H	H	H	75/13	[105]
85d	Ph	Ph	4-F	H	H	H	H	50/33	[105]
85e	Ph	Ph	4-CF3	H	H	H	H	39/42	[105]
85f	Ph	Ph	2-Me	H	H	H	H	40/45	[105]
85g	Ph	Ph	2-Tienyl	H	H	H	H	80/9	[105]
85h	Ph	Ph	1-Naphtyl	H	H	H	H	43/35	[105]
85i	Ph	Ph	H	H	H	Me	H	55/29	[105]
85j	Ph	Ph	H	H	H	H	Me	60/26	[105]
85k	Ph	Ph	H	H	Cl	H	H	69/7	[105]
85l	Ph	Ph	H	H	CF_3	H	H	77/0	[105]
85m	4-MeO-Ph	4-MeO-Ph	H	H	H	H	H	61/16	[105]
85n	4-Cl-Ph	4-Cl-Ph	H	H	H	H	H	60/20	[105]
85o	4-CF_3-Ph	4-CF_3-Ph	H	H	H	H	H	63/15	[105]
85p	2-Me-Ph	2-Me-Ph	Ph	H	H	H	H	66/20	[105]
85q	E′	E′	H	H	H	H	H	51/14	[105]
85r	Ph	Me	Ph	H	H	H	H	56/14	[105]
85s	Ph	n-Pr	Ph	H	H	H	H	47/16	[105]

85t	Ph	Ph	Ph	Me	H	H	H	60/0	[105]
85u	Ph	Ph	4-Me	Me	H	H	H	65/0	[105]
85v	Ph	Ph	4-CF_3	Me	H	H	H	51/0	[105]
85w	Ph	Ph	4-F	Me	H	H	H	56/0	[105]
85x	Ph	Ph	2-Me	Me	H	H	H	52/0	[105]
85y	Ph	Ph	3-Me	Me	H	H	H	68/0 2 isomers	[105]
85z	Ph	Ph	Mes	H	H	H	H	0/77	[105]
85a1	Ph	Ph	Mes	H	H	H	Me	0/81	[105]
85b1	Ph	Ph	Mes	H	H	Me	H	0/79	[105]
85c1	Ph	Ph	Mes	H	Me	H	H	0/77	[105]
85d1	Ph	Ph	Mes	H	H	MeO	H	0/86	[105]
85e1	Ph	Ph	Mes	H	Cl	H	H	0/65	[105]
86a	4-BrPh	4-BrPh	Ph	H	H	H	H	22/27	[7]
86b	4-BrPh	4-BrPh	4-CNPh	H	H	H	H	22/35	[7]

[a]: Pd-cat NHC complex $Cu(OAc)_2$, TBAB, DMA, 90 °C, 12 h; [b]: $Pd(OAc)_2$, $Cu(OAc)_2$, O_2, TBAB, DMF, 100 °C; [c]: $Pd(OAc)_2$, $Cu(OAc)_2$, TBAB, DMAC, 90 °C.

10. Understanding the Mechanism: Michael Adducts, Hydrogenated Structures and Others

Reactions of [8+2] type of indolizines and their aza/benzo derivatives with acetylenes and alkenes are regioselective due to pronounced polarization of indolizine and (if any) of a multiple bond. Thus, the positive end of the double/triple bond (e.g., in E-C≡CH or in ECH=CH_2) would be definitely attached to π-excessive pyrrole carbon C-3 without any exception, as is evident from all the tables. If the alkene/acetylene bears an electron-donating group and indolizine is appropriately polarized (e.g., by additional 6(8)-NO_2 group), then regioselectivity is again preserved, and electronegative end of the multiple bond would be attached to π-deficient pyridine carbon C-5.

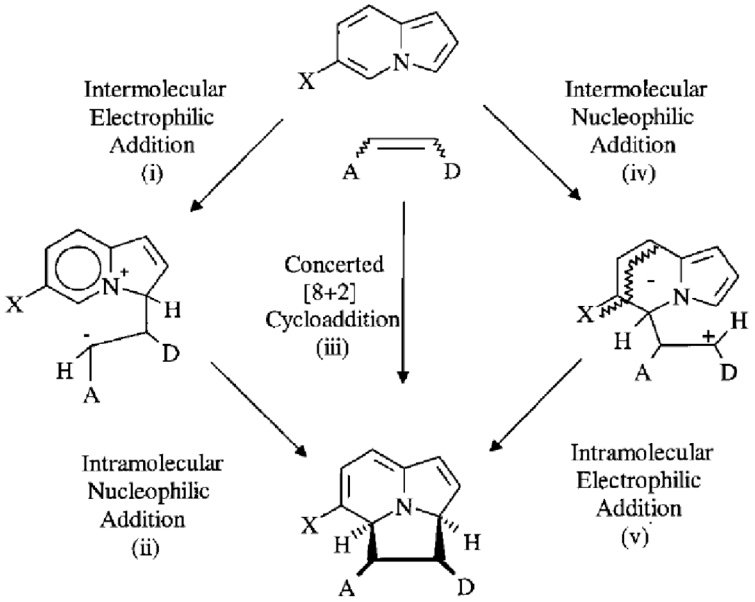
10.1. Theory

There are theoretical quantum chemical calculations on [8+2] cycloaddition of alkenes to indolizines [106,107] with a variation of the polar nature of substituents in alkenes and comparing indolizine and 6-nitroindolizine. An ab initio and semiempirical (AM1 and SINDO1) calculations clearly confirm the possibility of three different mechanisms (Scheme 49). The concerted one-step mechanism (iii) is preferable, if there are no polar groups in a dienophile and indolizine. Another type of stepwise cycloaddition (electrophilic addition (i)—nucleophilic ring closure (ii)) should be realized for the case of nitroethylene. The last type of dipolar cycloaddition (nucleophilic addition (iv)—electrophilic ring closure (v)) would be expected for the reaction of 6-nitroindolizine with aminoethylene, Table 23.

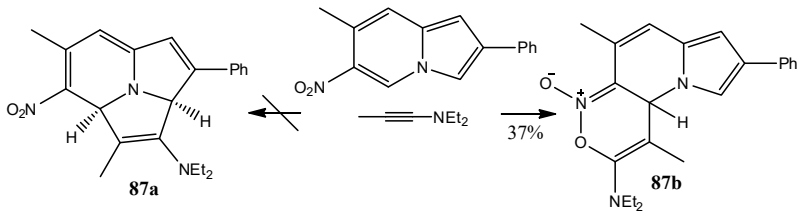
Table 23. Possible mechanisms of [8+2] cycloaddition depending on the nature of groups in alkene and indolizne as shown on Scheme 49.

Substituent in Alkene	Indolizine	6-Nitroindolizine
Nitroethylene	(i), (ii)	(i), (ii)
Methyl acrylate	(iii)	(iii)
Acrylonitrile	(iii)	(iii)
Ethylene	(iii)	(iii)
N,N-Dimethylaminoethylene	(iii)	(iv), (v)

However, indolizines (even activated by 6- or 8-NO_2-group) failed to react with enamines or enols [107], although reaction with dialkylaminoacetylene is possible, Scheme 50. Although the 1:1 adduct was definitely not the product of [8+2] cycloaddition **87a,** rather it was [4+2] adduct of acetylene across the nitroethylene **87b**, its structure confirmed the regioselectivity of attack of aminnoacetylene to the position C-5 of indolizine.

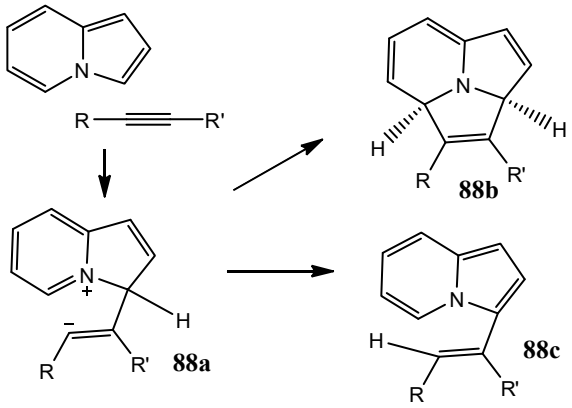


Scheme 49. Theoretically possible mechanisms of [8+2] cycloaddition to indolizines.



Scheme 50. Abnormal cycloadditon to 6-nitroindolizine.

After the addition of alkyne to position C-3 of indolizine, the initially formed zwitter-ion **88a** could be transformed to a covalent structure either forming the cycloadduct **88b** (i.e., dihydrocyclazine) or underwent shift of H-3 from acidic position C-3 to vinyl anion thus forming 3-vynyl derivative **88c**. Scheme 51.

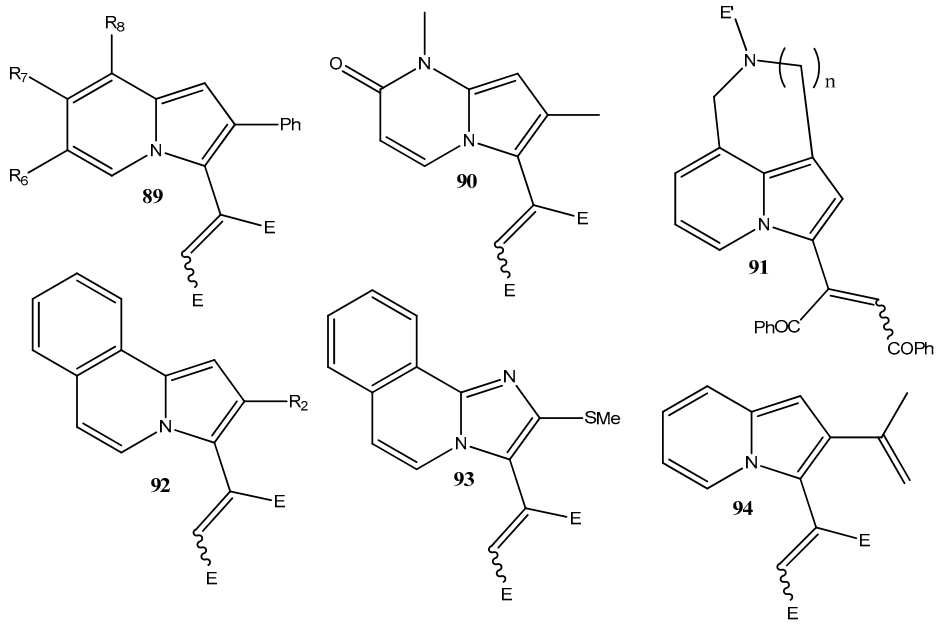


Scheme 51. Possible channels of transformation of initially formed zwitter-ion.

10.2. 3-Vinyl Derivatives

In few cases, 3-vinyl substituted intermediates were isolated and characterized from reactions of indolizines and acetylenes, Scheme 52, Table 24. In the first experiment of reaction of indolizines with DMAD without any catalyst, the cis- and trans-adducts **89** were formed [108]. Cis- and trans-derivatives of pyrrolopyrimidone **90** and DMAD did not undergo further cyclization to azacyclazine in presence of Pd-C [85]. 1.8-Annelatyed

indolizines gave purple 3-vinyl adducts **91** with DBZA [46] which underwent further dehydrogenation without cyclization (see Scheme 9). Benzoindolizines **92** [29] and their aza-derivative **93** [88] even in presence of catalysis gave the adducts together with cyclazines. 2-Isopropenyl indolizine **94** after prolonged heating with DMAD gave the mixture of isomeric 3-vinyl derivatives [109].



Scheme 52. 3-Vinyl derivatives of aza/benzo/indolizines isolated as intermediates (see Table 24).

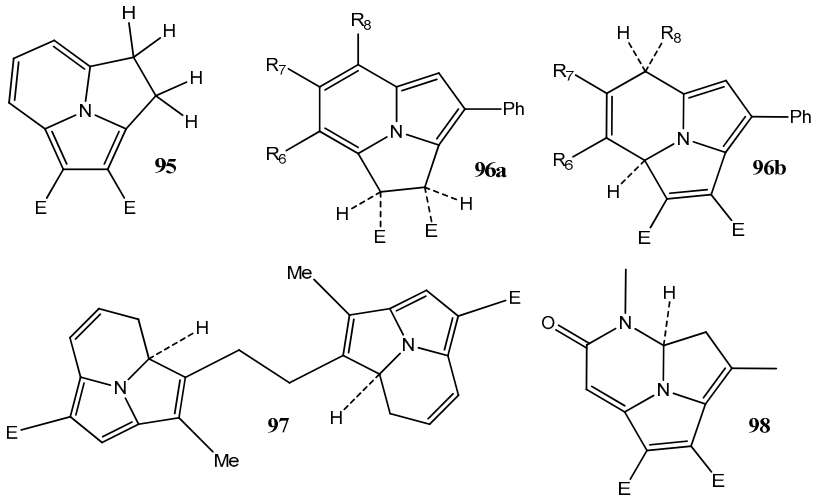
Table 24. Stereochemistry, conditions and yields of synthesis of vinyl indolisines on Scheme 52.

N	R	Yield (trans/cis), %	Conditions	Ref.
89a	R = H	13:4	No/Me_2CO/rt/15 h	[108]
89b	R6 = Me	11:5		[108]
89c	R7 = Me	16:0		[108]
89d	R8 = Me	20:0		[108]
90		18:13	Pd/PhMe/Δ/21 h	[85]
91a	n = 1	62 *	No/0°/THF	[46]
91b	n = 2	62 *	No/0°/THF	[46]
92a	R2 = SMe	26:17	Pd-C/PhMe/Δ/30 h	[29]
92b	R2 = H	0:11	Pd-C/PhMe/Δ/30 h	[29]
93		4 *	Pd-C/PhMe/Δ/30 h	[88]
94		14 *	No/PhMe/rt/120 h	[109]

* Not determined, ** In a mixture.

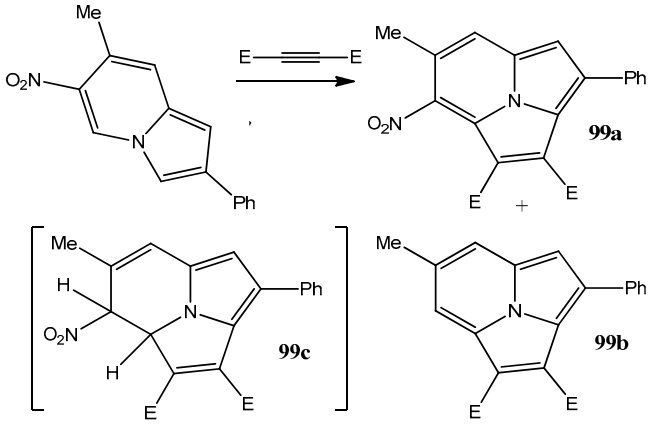
10.3. Dihydrocyclazines

First, dihydrocyclazine was obtained by Boekelheide [23] with a yield of 15% together with cyclazine. He tried to prove the position of protons by chemical tools and finally assigned the protons to be located as in **95** (Scheme 53), i.e., far from the attached DMAD. In 1984 Japanese chemists tried to prove the structure of all intermediated in the reaction of indolizines with DMAD in the absence of catalyst [108]. They proved two types of structures **96a** and **96b** (together with 3-vinyl adducts **89**) obtained with the yields 4–27% for **96a** and 5–6% for **96b**. Bis-(indolizinyl)etane formed the bis-dihydrocyclazine derivative **97** with a yield of 26% [39]. Azaindolizinone reacted with DMAD in presence of Pd-C giving about 4% of dihydro-compound **98** [85].



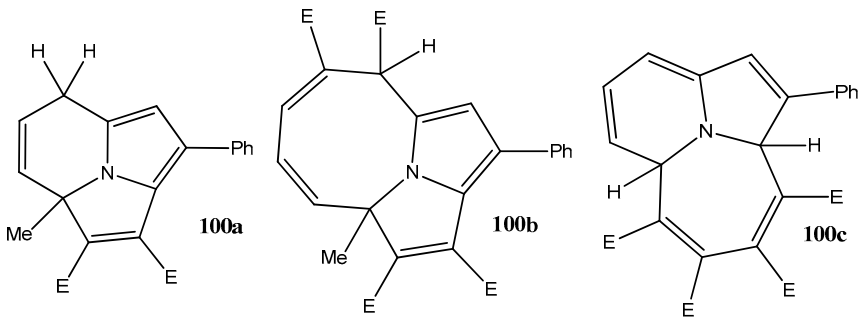
Scheme 53. Dihydrocyclazines obtained in the synthesis.

The structure of dihydrocyclazine depends on the nature of substituents in the ring. Thus, in our early work [110] we found that 6-nitroindolizine reacted with DMAD (PhMe/Δ/3h) giving the expected nitrocyclazine **99a** (Scheme 54) together with the cyclazine **99b** without NO_2 group (31%:7%), which is formed presumably by elimination of HNO_2 from dihydrocyclazine **99c**.



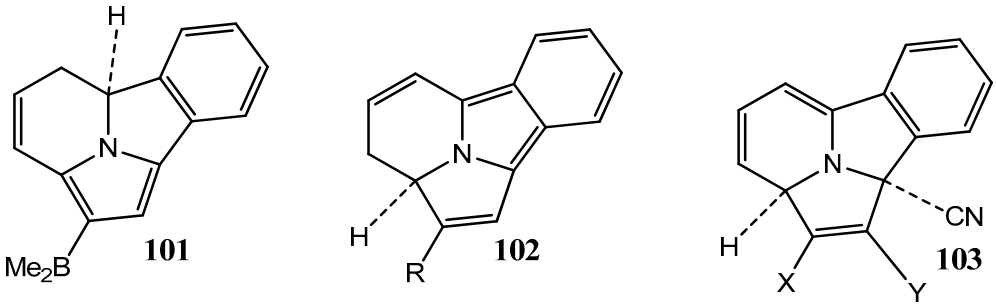
Scheme 54. Unusual cycloaddion to 6-nitroindolizine with the loss of NO_2 group.

In the paper [111] it was shown that 5-Me-indolizine derivative under the action of DMAD (PhH, rt) gave dihydrocyclazine **100a** with a yield of 54%, Scheme 55. Further reaction with the excess of DMAD give the macrocyclic cyclazine derivative **100b** [111] with the structure proved by X-ray, and it was not the structure of the 1:2 adduct (**100c**) postulated in [108].



Scheme 55. 1:1 and 1:2 cycloadducts of 5-methylindolizine and DMAD.

The reaction of Mes_2B-substituted acetylene with benzoindolizine at rt gave dihydrocyclazine **101** with 90% yield [37] (Scheme 56) which can be further aromatized. The same structure underwent cycloaddition with hetearyl acetylenes [66] ($CH_2ClCH_2Cl/\Delta/6$ h) giving another type of dihydrocyclazines **102** (R = 2-pyridyl, 54% and R = 2-quinoline, 42%) which were converted to benzocyclazines under the action of sulfur (PhCl/Δ/10 h with the yields 59% and 42%). 3-CN substituted benzo[a]indolizine with DMAD (Pd-C/PhMe/Δ/2 h) gave 7% of the adduct of the structure **103** (together with benzocyclazine) and with di-t-BuOCO-acetylene the yield of cycloadduct is higher (42%) [65].



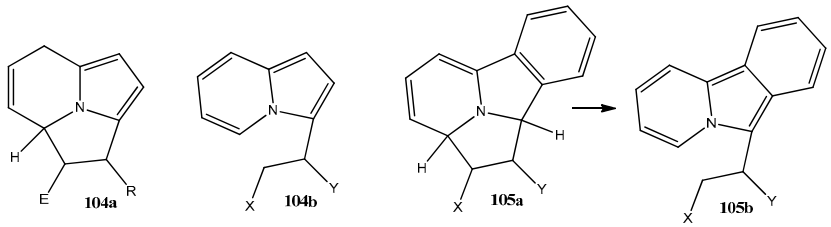
Scheme 56. Different cycloadducts obtained from benzoindolizine.

10.4. Alkenes

The reaction of indolizines with alkenes has attracted a lot of attention. The following potential dienophiles were used as 2π-components for potential [8+2] cycloaddition: nitroolefins, acrylonitrile, benzoquinone, methylvinylketone, alkyl acrylates, alkyl maleate, alkyl fumarate, maleic acid, maleic anhydride, N-substituted maleimide, 4-substituted-1,2,4-triazoline-3,5-dione, dialkyl azodicarboxylates, nitrile oxide, 1.2-dicyanocyclobutene and some other [38,53,112–115].

In most reactions, two types of products are observed: first from proton shifts in an intermediate zwitter-ion leading ultimately to the isolated Michael addition product at the position 3 of the indolizine or, second, deriving from hydrogen loss or shifts in the primary adduct giving [2+8] cycloadducts of tetrahydro-, dihydro- or (in rarest cases) aromatic cyclazines.

In particular, indolizines reacted with maleates and acrylates giving [8+2] cycloadducts with the subsequent 1,5-hydrogen shift as in **104a**, Scheme 57 [112]. In most other cases Michael adducts at C-3 **104b** were formed. Benzo[a]indolizines with some dipolarophiles produced kinetically controlled cycloadducts **105a** which isomerized to Michael adducts **105b** [113]. For further discussion on the mechanism see ref. [116].



Scheme 57. Structure of some adducts and cycloadducts of indoliznes and alkenes.

11. Conclusions

As is evident from all the schemes and tables, [8+2] cycloaddition of indolizines, their aza- and benzo derivatives leading to (aza/benzo) cyclazines is a big portion of modern organic chemistry, its concrete and powerful tool with its own achievements and secrets. There are a lot of catalyst and oxidants proposed to make the final aromatic structure,

starting from oxygen, sulfur, Pd-C, $Pd(OAc)_2$ and Pd complexes, $Cu(OAc)_2$, MnO_2, quinones (DDQ, benzoquinone), new tools appeared to stimulate reaction (blue LED, microwaves, etc.). The dependence of the process on the nature of substituents in the benzo/aza-substituted indolizines and alkynes/alkenes, the intermediacy of open chains cyclic derivatives made clearer the entire mechanism. Even 60 years after its first discovery, [8+2] cycloadditions continue to play an important part in organic synthesis.

Author Contributions: E.V.B. formulated the goals, managed performance of all work and wrote the review. I.A.S. prepared all tables with the yields. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Flitsch, W. Pyrroles with fused six-membered heterocyclic rings: A-fused. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C.W., Eds.; Pergamon Press: Oxford, UK, 1984; Volume 4, pp. 443–496.
2. Tominaga, Y.; Komiya, K.; Kataoka, S.; Shigemitsu, Y.; Hirota, T.; Sasaki, K. Synthesis of a Luminescent Compound: 8-Dimethylaminopyridazino[4,5-a][2.2.3]cyclazine-1,4(2H,3H)-diones. *Heterocycles* **1988**, *48*, 1985–1988. doi:10.3987/COM-98-8249.
3. Shen, Y.-M.; Grampp, G.; Leesakul, N.; Hu, H.-W.; Xu, J.-H. Synthesis and Emitting Properties of the Blue-Light Fluorophores Indolizino[3,4,5-ab]isoindole Derivatives. *Eur. J. Org. Chem.* **2007**, *22*, 3718–3726. doi:10.1002/ejoc.200700250.
4. Granger, D.B. Acenes, Heteroacenes and Analogous Molecules for Organic Photovoltaic and Field Effect Transistor Applications. Ph.D. Thesis, University of Kentucky, Lexington, KY, USA, 2017. doi:10.13023/ETD.2017.202.
5. Zeng, C.; Yuan, K.; Wang, N.; Peng, T.; Wu, G.; Wang, S. The opposite and amplifying effect of B ← N coordination on photophysical properties of regioisomers with an unsymmetrical backbone. *Chem. Sci.* **2019**, *10*, 1724–1734. doi:10.1039/C8SC04210A.
6. Stasyuk, A.J.; Banasiewicz, M.; Ventura, B.; Cyrański, M.K.; Gryko, D.T. Benzo[a]imidazo[5,1,2-cd]indolizines – a new class of molecules displaying excited state intramolecular proton transfer. *New J. Chem.* **2014**, *38*, 189–197. doi:10.1039/c3nj00842h.
7. Maitra, R.; Chen, J.-H.; Hu, C.-H.; Lee, H.M. Synthesis and Optical Properties of Push-Push-Pull Chromophores Based on Imidazo[5,1,2-cd]indolizines and Naphtho[1′,2′:4,5]imidazo[1,2-a]pyridines. *Eur. J. Org. Chem.* **2017**, *40*, 5975–5985. doi:10.1002/ejoc.201701109.
8. Lévesque, É.; Bechara, W.S.; Constantineau-Forget, L.; Pelletier, G.; Rachel, N.M.; Pelletier, J.N.; Charette, A.B. General C–H Arylation Strategy for the Synthesis of Tunable Visible Light-Emitting Benzo[a]imidazo[2,1,5-c,d]indolizine Fluorophores. *J. Org. Chem.* **2017**, *82*, 5046–5067. doi:10.1021/acs.joc.6b02928.
9. Jørgensen, A.S.; Jacobsen, P.; Christiansen, L.B.; Bury, P.S.; Kanstrup, A.; Thorpe, S.M.; Narum L.; Wassermann, K. Synthesis and estrogen receptor binding affinities of novel pyrrolo[2,1,5-cd]indolizine derivatives. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2383–2386.
10. Jørgensen, A.S.; Jacobsen, P.; Christiansen, L.B.; Bury, P.S.; Kanstrup, A.; Thorpe, S.; Bain, S.; Narum L.; Wassermann, K. Synthesis and pharmacology of a novel pyrrolo[2,1,5-cd]indolizine (NNC 45-0095), a high affinity non-steroidal agonist for the estrogen receptor. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 399–402. doi:10.1016/S0960-894X(00)00015-9.
11. Sanivarapu, S.; Vaddiraju, N.; Velide, L. Synthesis and anti-inflammatory activity of 1,2-3-substituted 2a1,4,5-triazacyclopenta[cd]indene derivatives. *Med. Chem. Res.* **2019**, *28*, 1461–1470. doi:10.1007/s00044-019-02386-6.
12. Acheson, R.M. Reactions of Acetylenecarboxylic Acids and Their Esters with Nitrogen-Containing Heterocyclic Compounds. *Adv. Heterocycl. Chem.* **1963**, *1*, 125–165. doi:10.1016/S0065-2725(08)60524-3.
13. Taurins, A. *Special Topics in Heterocyclic Chemistry*; Wiley: Chichester, UK, 1977; Volume 30, pp. 245–270. doi:10.1002/9780470187005.ch4.
14. Matsumoto, K.; Uchida, T.; Yamaguchi, J. The Chemistry of Cyclazines. *J. Syn. Org. Chem.* **1977**, *35*, 739–749. doi:10.5059/yukigoseikyokaishi.35.739.
15. Flitsch, W.; Kramer, U. Cyclazines and Related N-Bridged Annulenes. *Adv. Heterocycl. Chem.* **1978**, *22*, 321–365. doi:10.1016/S0065-2725(08)60106-3.
16. Tominaga, Y.; Shiroshita, Y.; Hosom, A. Synthesis of [2.2.3]Cyclazines, Aza[2.2.3]cyclazines and Their Related Compounds. *Heterocycles* **1988**, *27*, 2251–2288. doi:10.3987/REV-88-395.
17. Beusker, P.H.; Scheeren, H.W. Intermolecular cyclization reactions to form carbocycles. In *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed.; John Wiley & Sons: Hoboken, NJ, USA, 2000; Volume 2, pp. 329–480.
18. Matsuda, Y. The Chemistry of Cyclazines. *J. Pharm. Soc. Jpn.* [*Yakugaku Zasshi]* **2001**, *121*, 971–988. doi:10.1248/yakushi.121.971.
19. Tominaga, Y. *Science of Synthesis. Houben-Weyl Methods of Molecular Transformations*; Thieme: New York, NY, USA, 2004; Volume 17, pp. 1025–1078. doi:10.1055/sos-SD-017-01619.
20. Nair, V.; Abhilash, K. [8+2] Cycloaddition Reactions in Organic Synthesis. *Synlett* **2008**, *3*, 301–312. doi:10.1055/s-2008-1032058.
21. Nair, V.; Abhilash, K.G. [8+2] Cycloaddition Reactions in the Construction of Heterocycles. *Top. Heterocycl. Chem.* **2008**, *13*, 173–200. doi:10.1007/7081_2007_105.

22. Windgassen, R.J.; Saunders, W.H.; Boekelheide, V. Cyclazines. A New Class of Aromatic Heterocycles. *J. Am. Chem. Soc.* **1959**, *81*, 1459–1465. doi:10.1021/ja01515a045.
23. Galbraith, A.; Small, T.; Barnes, R.A.; Boekelheide, V. The Formation of Cycl[3.2.2]azine Derivatives via the Reaction of Pyrrocoline with Dimethyl Acetylenedicarboxylate. *J. Am. Chem. Soc.* **1961**, *83*, 453–458. doi:10.1021/ja01463a046.
24. Boekelheide, V.; Small, T. A Correlation of Some Electrophilic Substitution Reactions of Cycl[3.2.2]azine1. *J. Am. Chem. Soc.* **1961**, *83*, 462–463. doi:10.1021/ja01463a048.
25. Boekelheide, V.; Fahrenholtz, K. The Formation of Pyrrocolines by the Reaction of Dimethyl Acetylenedicarboxylate with Heterocyclic Zwitterions. *J. Am. Chem. Soc.* **1961**, *83*, 458–462. doi:10.1021/ja01463a047.
26. Starikov, A.S.; Kalashnikov, V.V.; Tarakanov, P.A.; Simakov, A.O.; Simonov, S.V.; Tkachev, V.V.; Yarkov, A.V.; Kazachenko, V.P.; Chernyak, A.V.; Zhurkin, F.E.; et al. Synthesis of 1,2-Dicyano-3-arylcycl[3.2.2]azines—First 1,2-Dicarbonitriles Based on Cyclazine Heterocycle. *Eur. J. Org. Chem.* **2020**, 5852–5856. doi:10.1002/ejoc.202000958.
27. Jackman, L.; Porter, Q.; Underwood, G. Studies of aromaticity by nuclear magnetic resonance spectroscopy. IV. The proton chemical shifts in Cycl[2,2,3]azine. *Aust. J. Chem.* **1965**, *18*, 1221–1226. doi:10.1071/CH9651221.
28. Smith, J.O.; Mandal, B.K. A convenient synthesis of 8-substituted indolizines as precursors to 5-substituted cycl{3.2.2}azine derivatives. *J. Heterocycl. Chem.* **1997**, *34*, 5, 1441–1446. doi:10.1002/jhet.5570340511.
29. Tominaga, Y.; Shiroshita, Y.; Kurokawa, T.; Gotou, H.; Matsuda, Y.; Hosomi, A. Synthesis of cycl[3.2.2]azine and benzo[g]cycl[3.2.2]azine derivatives by use of the [2+8] cycloaddition reaction of indolizines and dimethyl acetylenedicarboxylate. *J. Heterocycl. Chem.* **1989**, *26*, 477–487. doi:10.1002/jhet.5570260243.
30. Maseda, C.; Sone, M.; Tominaga, Y.; Natsuki, R.; Matsuda, Y. Synthesis of Indolizine Derivatives and Their Reactions. *J. Pharm. Soc. Jpn.* [*Yakugaku Zasshi]* **1974**, *94*, 839–843. doi:10.1248/yakushi1947.94.7_839.
31. Matsuda, Y.; Gotou, H.; Katou, K.; Matsumoto, H.; Yamashita, M.; Takahashi, K.; Ide, I. A New Synthesis of 2,12-Dithia[3.3](1,4)cycl[3.2.2]azinophanes. *Heterocycles* **1990**, *31*, 6, 983–986. doi:10.3987/COM-90-5368.
32. Matsuda, Y.; Katou, K.; Matsumoto, H.; Nishiyori, T.; Uemura, T.; Urakami, M. Synthesis of 2,12-Dithia[3](2,6)pyridino[3](1,4)cycl[3.2.2]azinophane and It's Barrier to Methylene Twist. *Heterocycles* **1996**, *43*, 1633–1640. doi:10.3987/COM-96-7462.
33. Babaev, E.V. Fluorinated Indolizines. In *Fluorine in Heterocyclic Chemistry*; Nenajdenko, V., Ed.; Springer: Wien, Austria, 2014; Volume 1, pp. 157–180, ISBN 978-3-7091-0689-1.
34. Motornov, V.; Tabolin, A.; Nelyubina, Y.V.; Nenajdenko, V.; Ioffe, S. Copper-mediated oxidative [3+2]-annulation of nitroalkenes and pyridinium ylides: A general access to functionalized indolizines. Efficient synthesis of 1-fluoroindolizines. *Org. Biomol. Chem.* **2019**, *17*, 1442–1454. doi:10.1039/C8OB03126F.
35. Lepitre, T.; Le Biannic, R.; Othman, M.; Lawson, A.M.; Daïch, A. Metal-Free Cascade Approach toward Polysubstituted Indolizines from Chromone-Based Michael Acceptors. *Org. Lett.* **2017**, *19*, 1978–1981. doi:10.1021/acs.orglett.7b00309.
36. Babaev, E.V.; Shadrin, I.A.; Rybakov V.B. (Aza)indolizines and ethyl propiolate: [8+2] and [1,10] cyclizations. *Chem. Heterocycl. Comp.* **2018**, *54*, 339–343. doi:10.1007/s10593-018-2270-6.
37. Yang, D.-T.; Radtke, J.; Mellerup, S.K.; Yuan, K.; Wang, X.; Wagner, M.; Wang, S. One-Pot Synthesis of Brightly Fluorescent Mes2B-Functionalized Indolizine Derivatives via Cycloaddition Reactions. *Org. Lett.* **2015**, *17*, 10, 2486–2489. doi:10.1021/acs.orglett.5b00994.
38. Siberdt, F.; Nasielski, J. Indolizines. 2. The reaction of 2-β-styrylindolizine with dienophiles. *Bull. Soc. Chim. Belg.* **1997**, *106*, 29–38.
39. Goto, H.; Kurata, K.; Awaya, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. Studies on Indolizine Derivatives. VI. Synthesis of Cycl[3.2.2]azinophane Derivative. *Heterocycles* **1982**, *17*, 325–329. doi:10.3987/S-1982-01-0325.
40. Matsuda, Y.; Kohra, S.; Katou, K.; Itou, T.; Uemura, T. Synthesis of a New Annulenoannulene, Cycl[3.2.2]azino[1,2-a]cycl[3.2.2]azine. *Heterocycles* **1997**, *45*, 2223–2228. doi:10.3987/COM-97-7960.
41. Matsuda, Y.; Kohra, S.; Katou, K.; Itou, T.; Uemura, T. Synthesis of a New Annulenoannulenone, 3H-Cycl[3.2.2]azino[2,1-e]cycl[3.3.2]azin-3-one. *Heterocycles* **1998**, *48*, 2573–2579. doi:10.3987/COM-98-8331.
42. Noguchi, M.; Tanigawa, N.; Kajigaeshi, S. Preparation of cyclohepta and benzo[ef]cycl[3.2.2]azines. *J. Heterocycl. Chem.* **1985**, *22*, 1049–1053. doi:10.1002/jhet.5570220425.
43. Noguchi, M.; Tamai, R.; Tanigawa, N.; Okumura, H.; Kajigaeshi, S. Synthesis and properties of cyclohepta[hi]pyrrolo-[2,1,5-cd]indolizines. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 969–975. doi:10.1246/bcsj.60.969.
44. Noguchi, M.; Yamamoto, T.; Kajigaeshi, S.; Saito, K.; Arai, T. Synthesis and Properties of 4H-Benzo[hi]pyrrolo[2,1,5-cd]indolizin-4-ones. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 423–429. doi:10.1246/bcsj.61.423.
45. Noguchi, M.; Yamamoto, T.; Kajigaeshi, S. Synthesis and Properties of 6H-Benzo[hi]pyrrolo[2,1,5-cd]indolizin-6-ones. *Heterocycles* **1990**, *31*, 563–568. doi:10.3987/COM-89-5291.
46. Noguchi, M.; Tanigawa, N.; Kajigaeshi, S. Preparation of Pyrido- and Azepino-fused Cycl[3.2.2]azines. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3444–3447. doi:10.1246/bcsj.58.3444.
47. Hu, H.; Li, G.; Hu, W.; Liu, Y.; Wang, X.; Kan, Y.; Ji, M. Synthesis of Pyrrolo[2,1,5-cd]indolizines through Dehydrogenative Heck Annelation of Indolizines with Diaryl Acetylenes Using Dioxygen as an Oxidant. *Org. Lett.* **2015**, *17*, 1114–1117. doi:10.1021/ol503681n.

48. Zhang, Y.; Yu, Y.; Liang, B.; Pei, Y.; Liu, X.; Yao, H.-G.; Cao, H. Synthesis of Pyrrolo[2,1,5-cd]indolizine Rings via Visible-Light-Induced Intermolecular [3+2] Cycloaddition of Indolizines and Alkynes. *J. Org. Chem.* **2020**, *85*, 10719–10727. doi:10.1021/acs.joc.0c01253.
49. Liang, Y.; Teng, L.; Wang, Y.; He, Q.; Cao, H. Visible-Light-Induced Intermolecular [3+2] Alkenylation–Cyclization Strategy: Metal-Free Construction of Pyrrolo[2,1,5-cd]indolizine Rings. *Green Chem.* **2019**, *21*, 4025–4029. doi:10.1039/C9GC01766F.
50. Yang, Y.; Chen, L.; Zhang, Z.; Zhang, Y. Palladium-Catalyzed Oxidative C−H Bond and C=C Double Bond Cleavage: C-3 Acylation of Indolizines with α,β-Unsaturated Carboxylic Acids. *Org. Lett.* **2011**, *13*, 1342–1345. doi:10.1021/ol200025k.
51. Pohjala, E.K. Indolizine derivatives. IX. Preparation of 1-acylpyrrolo[2,1,5-cd]indolizinesviacycloaddition of 3-acyloxyindolizines to active ethylenes and acetylenes. *J. Heterocycl. Chem.* **1978**, *15*, 955–960. doi:10.1002/jhet.5570150611.
52. Kojima, H.; Kinoshita, Y.; Matsumura, N.; Inoue, H. Reaction of tris(alkylthio)cyclopropenyl cations with 2-pyridylmagnesium bromide as a new route to indolizines. *J. Heterocycl. Chem.* **1991**, *28*, 2059–2060. doi:10.1002/jhet.5570280848.
53. Flitsch, W.; Heinrich, J. 1,2-Dialkoxycarbonylhydrazine derivatives of pyrroles and indolizines. A new synthesis of cycl[3.2.2]azines. *Tetrahedron Lett.* **1980**, *21*, 3673–3676. doi:10.1016/S0040-4039(00)78741-7.
54. Yerxa, B.R.; Moore, H.W. Synthesis of indolizine-5,8-diones and [3.2.2]cyclazines. *Tetrahedron Lett.* **1992**, *33*, 7811–7814. doi:10.1016/S0040-4039(00)74750-2.
55. Babaev, E.V. *Novel Synthetic Strategies in the Chemistry of Indolizine and Its Heteroanalogs*; Lambert Academic Publishing: Saarbrucken, Germany, 2016; ISBN 978-3-659-95107-7. (In Russian)
56. Kuznetsov, A.G.; Bush, A.A.; Babaev, E.V. Synthesis and reactivity of 5-Br(I)-indolizines and their parallel cross-coupling reactions. *Tetrahedron* **2008**, *64*, 749–756. doi:10.1016/j.tet.2007.11.017.
57. Matsumoto, K.; Ikemi-Kono, Y.; Uchida, T.; Paquette, L.A. Synthesis and Cycloadditian Reactions of 3-Cyanoindolizines. *Heterocycles* **1980**, *14*, 103. doi:10.3987/R-1980-01-0103.
58. Uchida, T.; Matsumoto, K. Cycloaddition reaction of 3-cyanoindolizines with dimethyl acetylenedicarboxylate—Formation of cycl[3.2.2]azines and 1:2 adducts. *Chem. Lett.* **1980**, *9*, 149–150. doi:10.1246/cl.1980.149.
59. Tominaga, Y.; Shiroshita, Y.; Hosomi, A. Synthesis of 2-methylthioindolizine-3-carbonitriles using nitro ketene dithioacetal. *J. Heterocycl. Chem.* **1988**, *25*, 1745–1749. doi:10.1002/jhet.5570250627.
60. Matsumoto, K.; Uchida, T.; Yoshida, H.; Toda, M.; Kakehi, A. Cycloadditions of indolizine-3-carbonitriles with dimethyl acetylenedicarboxylate: Formation of [2.2.3]cyclazines and 1:2 adducts. *J. Chem. Soc. Perkin Trans. 1* **1992**, *18*, 2437–2441.doi:10.1039/P19920002437.
61. Matsumoto, K.; Kabuto, C.; Uchida, T.; Yoshida, H.; Ogata, T.; Iwaizumi, M. Formation of an extremely unusual 1:2 adduct from 3-cyanoindolizines and dimethyl acetylenedicarboxylate. *Tetrahedron Lett.* **1987**, *28*, 5707–5708. doi:10.1016/s0040-4039(00)96819-9.
62. Matsumoto, K.; Uchida, T.; Sugi, T.; Kobayashi, T. Syntheses and Cycloadditions of 1,2-Aromatic Ring-fused 3-Cyanoindolizines. *Heterocycles* **1983**, *20*, 1525–1529. doi:10.3987/R-1983-08-1525.
63. Matsumoto, K.; Uchida, T.; Aoyama, K.; Nishikawa, M.; Kuroda, T.; Okamoto, T. Synthesis and reactions of 1,2-fused 3-cyanoindolizines. *J. Heterocycl. Chem.* **1988**, *25*, 1793–1801. doi:10.1002/jhet.5570250637.
64. Tominaga, Y.; Shiroshita, Y.; Gotou, H.; Matsuda, Y. Synthesis of Benzannelated Cycl[3.2.2]azine: Benzo[a]cycl[3.2.2]azine. *Heterocycles* **1986**, *24*, 3071–3074. doi:10.3987/R-1986-11-3071.
65. Matsumoto, K.; Uchida, T.; Kato, T.; Toda, M.; Aoyama, K.; Konishi, H. Cycloaddition Reactions of 6-Cyanobenz[a]indolizines with Activated Alkynes. Formation of Benzo[2.2.3]- and [2.3.4]cyclazines. *Heterocycles* **1990**, *31*, 593–596. doi:10.3987/COM-90-5331.
66. Mitsumori, T.; Bendikov, M.; Dautel, O.; Wudl, F.; Shioya, T.; Sato, H.; Sato, Y. Synthesis and Properties of Highly Fluorescent Indolizino[3,4,5-ab]isoindoles. *J. Am. Chem. Soc.* **2004**, *126*, 16793–16803. doi:10.1021/ja049214x.
67. Tominaga, Y.; Gotou, H.; Oniyama, Y.; Nishimura, Y.; Matsuda, Y. Synthesis of benzannelated cycl[3.2.2]azine: Benzo[g]cycl [3.2.2]azine. *Chem. Pharm. Bull.* **1985**, *33*, 3038–3041. doi:10.1248/cpb.33.3038.
68. Tominaga, Y.; Shiroshita, Y.; Matsuda, Y.; Hosomi, A. The Effect of Benzannelation toward Cycl[3.2.2]azine. Synthesis and Physical Properties of Dibenzo[a,h]cycl[3.2.2]azine. *Heterocycles* **1987**, *26*, 2073–2075. doi:10.3987/R-1987-08-2073.
69. Ohier, P.; Daïch, A.; Decroix, B. Pyrrolo[1,4]diazepines, via thermolyse of carbonylazides, and [2,2,3]cyclazines, via Diels-Alder reaction of [f]indolizines, annelated to [1]benzothiophene. *Tetrahedron* **1996**, *52*, 13547–13556. doi:10.1016/0040-4020(96)00828-9.
70. Godfry, J. Communications-Novel Synthesis of a 1,2,5,6-Dibenzocycl[2,2,3]azine. *J. Org. Chem.* **1959**, *24*, 581. doi:10.1021/jo01086a618.
71. Gogoi, S.; Dutta, M.; Gogoi, J.; Boruah, R.C. Microwave promoted synthesis of cycl[3.2.2]azines in water via a new three-component reaction. *Tetrahedron Lett.* **2011**, *52*, 813–816. doi:10.1016/j.tetlet.2010.12.036.
72. Sheela Gopal, M.; Anitha, I. Microwave Synthesis and Characterisation of Some Cycl[2,2,3]Azine Derivatives. *Int. J. Sci. Res.* **2016**, *5*, 960–963.
73. Komatsu, M.; Kasano, Y.; Yamaoka, S.; Minakata, S. Novel Generation of Pyridinium Ylides from N-(Silylmethyl)pyridone Analogs via 1,4-Silatropy and their 1,3-Dipolar Cycloadditions Leading to N-Heteropolycycles. *Synthesis* **2003**, *9*, 1398–1402. doi:10.1055/s-2003-40188.
74. Moise, I.-M.; Ghinet, A.; Shova, S.; Bîcu, E. Switching the reactivity of cyanomethylpyridinium salts in the 1,3-cycloaddition conditions with alkyl propiolates to cyanoindolizines or cyanoazaindolizinyl-indolizines. *Tetrahedron* **2020**, *76*, 131502–131512. doi:10.1016/j.tet.2020.131502.

75. Matsumoto, K.; Uchida, T.; Sugi, T.; Yagi, Y. Consecutive 1,3-dipolar cycloadditions of cycloimmonium ylides to benzyne: Formation of novel 18π benzo[a]isoindolo[1,2,3-cd]indolizines. *Chem. Lett.* **1982**, *11*, 869–870. doi:10.1246/cl.1982.869.
76. Matsumoto, K.; Katsura, H.; Uchida, T.; Aoyama, K.; Machiguchi, T. Formation of 1,2,3,4-dibenzocycl[2.2.3]azines by a novel consecutive 1,3-dipolar cycloaddition of pyridinium dicyanomethylides to benzyne. *J. Chem. Soc. Perkin Trans. 1* **1996**, *21*, 2599–2602. doi:10.1039/p19960002599.
77. Matsumoto, K.; Iida, H.; Mimori, S.; Hamana, H.; Uchida, T. Nitrogen 14 NMR CP and Correlations of Oxidation Potentials of Dibenzo[a,d]cycl[2.2.3]azines with the Corresponding HOMOs: Further Evidence for Peripheral Conjugate System. *Heterocycles* **2007**, *73*, 883–889. doi:10.3987/COM-07-S(U)53.
78. Acheson, R.M.; Robinson, D.A. The formation of cycl[2,2,3]azines from pyridines and methyl propiolate. *Chem. Commun.* **1967**, *4*, 175–176. doi:10.1039/C19670000175.
79. Acheson, R.M.; Woollard, J.M. Addition reactions of heterocyclic compounds. Part XLVI. Reactions of acetylenic esters with pyridines in the presence of proton donors, and with alkyl 3-(2-pyridyl)-trans-acrylates. *J. Chem. Soc. C Org.* **1971**, 3296–3305. doi:10.1039/J39710003296.
80. Pohjala, E.K. Indolizine Derivatives. V. The Perkin Reaction of 2-Pyridinecarbaldehyde. Disproportionation of 3-(2-Pyridyl)acrylic Acid. *Acta Chem. Scand. B* **1976**, *30*, 198–202. doi:10.3891/acta.chem.scand.30b-0198.
81. Pohjala, E.K. Indolizine Derivatives. VIII. 3-Acyloxyindolizines via Cyclization of Diethyl 2-Pyridylmethylenemalonate. *Acta Chem. Scand. B* **1977**, *31*, 321–324. doi:10.3891/acta.chem.scand.31b-0321.
82. Pohjala, E.K. Indolizine Derivatives. I. A Novel One-step Synthesis of Pyrrolo[2,1,5-cd]-indolizines. The Mechanism of the Acylative Cyclization of 2-Pyridinecarbaldehyde and Unsaturated Carbonyl Compounds. *Acta Chem. Scand. B* **1974**, *28*, 582–583. doi:10.3891/acta.chem.scand.28b-0582.
83. Boekelheide, V.; Miller, A. Synthesis of 2-Phenyl-1-azacyl[3.2.2]azine. *J. Org. Chem.* **1961**, *26*, 431–432. doi:10.1021/jo01061a038.
84. Boekelheide, V.; Kertelj, S.S. A Synthesis of 6-Methyl-2-phenyl-5-azacycl[3.2.2]azine and Related Compounds1,2. *J. Org. Chem.* **1963**, *28*, 3212–3213. doi:10.1021/jo01046a507.
85. Buchan, R.; Fraser, M.; Shand, C. Azaindolizines. 4. Synthesis and formylation of 8-azaindolizines. *J. Org. Chem.* **1977**, *42*, 2448–2454. doi:10.1021/jo00434a022.
86. Kurata, K.; Awaya, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. Synthesis of Indolizine Derivatives and Their Reactions. II. *J. Pharm. Soc. Jpn. [Yakugaku Zasshi]* **1978**, *98*, 631–635. doi:10.1248/yakushi1947.98.5_631.
87. Tominaga, Y.; Shiroshita, Y.; Kurokawa, T.; Matsuda, Y.; Hosomi, A. Synthesis of 1-azacycl[3.2.2]azine and 1-azabenzo[h]cycl[3.2.2]azine. *J. Heterocycl. Chem.* **1988**, *25*, 185–189. doi:10.1002/jhet.5570250127.
88. Tominaga, Y.; Shiroshita, Y.; Kawabe, M.; Goto, H.; Oniyama, Y.; Matsuda, Y. Synthesis of Benzannelated 1-Azacycl[3.2.2]azine: 1-Azabenzo[h]cycl[3.2.2]azine. *Heterocycles* **1985**, *23*, 2531–2534. doi:10.3987/R-1985-10-2531.
89. Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. Fused Ring Construction around Pyrrole, Indole, and Related Compounds via Palladium-Catalyzed Oxidative Coupling with Alkynes. *J. Org. Chem.* **2009**, *74*, 7481–7488. doi:10.1021/jo9016698.
90. Ghosh, M.; Naskar, A.; Mishra, S.; Hajra, A. Palladium-catalyzed dehydrogenative annulation of imidazo[1,2-a]pyridines with diarylalkynes. *Tetrahedron Lett.* **2015**, *56*, 4101–4104. doi:10.1016/j.tetlet.2015.05.028.
91. Joshi, H.; Meena, N.; Sharma, S.; Bhatt, R.; Shinde, V.N.; Sunda, A.P.; Bhuvanesh, N.; Kumar, A. Selenium coordinated palladium(II) trans-dichloride molecular rotor as catalyst for site selective annulation of 2-arylimidazo[1,2-a]pyridines. *Chem. Commun*. **2020**, *56*, 10223–10226. doi:10.1039/D0CC03599H.
92. Ghosh, S.K.; Ghosh, D.; Maitra, R.; Kuo, Y.-T.; Lee, H.M. Palladium-Catalyzed Oxidative Cyclization for the Synthesis of 2-Alkylimidazo[5,1,2-cd]indolizines. *Eur. J. Org. Chem.* **2016**, *34*, 5722–5731. doi:10.1002/ejoc.201601019.
93. Aginagalde, M.; Vara, Y.; Arrieta, A.; Zangi, R.; Cebolla, V.L.; Delgado-Camón, A.; Cossío, F.P. Tandem [8+2] Cycloaddition–[2+6+2] Dehydrogenation Reactions Involving Imidazo[1,2-a]pyridines and Imidazo[1,2-a]pyrimidines. *J. Org. Chem.* **2010**, *75*, 2776–2784. doi:10.1021/jo9022815.
94. Subbarayappa, A.; Semwal, R.; Joshi, A.; Kumar, R. Annulation of Imidazo[1,2-a]pyridines Under Metal-free Conditions. *New J. Chem.* **2020**, *44*, 20530–20534. doi:10.1039/d0nj04521g.
95. Peng, J.; Wang, H.; Chen, C.; Huang, Z.; Yao, L.; Li, B. Palladium-Catalyzed Double C–H Arylation Reaction: Tandem Synthesis of Benzo[a]imidazo[5,1,2-cd]indolizines from Imidazo[1,2-a]pyridines and o-Dihaloarenes. *Synthesis* **2015**, *47*, 2457–2466. doi:10.1055/s-0034-1380865.
96. Pereira, D.E.; Leonard, N.J. A masked [π8+π2] cycloaddition reaction involving the 1,3,4,6-tetraazapentalene ring system. *Tetrahedron Lett.* **1986**, *27*, 4129–4132. doi:10.1016/S0040-4039(00)84928-X.
97. Blatcher, P.; Middlemiss, D.; Murray-Rust, P.; Murray-Rust, J. 1-Phenyl-2,3-diazacycl[2,2,3]azine, a new 10-π electron system. Involvement of 3,5-didehydroimidazo[1,5-a]pyridine? *Tetrahedron Lett.* **1980**, *21*, 4193–4196. doi:10.1016/s0040-4039(00)93686-4.
98. Tsuchiya, T.; Kato, M.; Sashida, H. Thermal intramolecular cyclization of 2-ethynylpyridine N-ylides to indolizines and cyclazines. *Chem. Pharm. Bull.* **1984**, *32*, 4666–4669. doi:10.1248/cpb.32.4666.
99. Sashida, H.; Kato, M.; Tsuchiya, T. Thermal rearrangements of cyclic amine ylides. VIII. Intramolecular cyclization of 2-ethynylpyridine N-ylides into indolizines and cycl(3.2.2)azines. *Chem. Pharm. Bull.* **1988**, *36*, 3826–3832. doi:10.1248/cpb.36.3826.
100. Shadrin, I.A.; Rzhevskii, S.A.; Rybakov, V.B.; Babaev E.V. Sonogashira Reaction of the Indolizine Ring. *Synthesis* **2015**, *47*, 2961–2964. doi:10.1055/s-0034-1378861.

101. Pelletier, G.; Charette, A.B. Triflic Anhydride Mediated Synthesis of Imidazo[1,5-a]azines. *Org. Lett.* **2013**, *15*, 2290–2293. doi:10.1021/ol400870b.
102. Babaev, E.V.; Pasichnichenko, K.Y.; Rybakov, V.B. Heterocyclic Compounds with a Bridge Nitrogen Atom. 14. Cycloaddition of Acetylenedicarboxylic Acid Ester to 2-Chloro-N-phenacylpyridinium Ylide. Crystal Structure of Dimethyl Ester of 5-Chloro-3-(p-nitrobenzoyl)indolizine-1,2-dicarboxylic Acid. *Chem. Heterocycl. Compd.* **2000**, *36*, 1192–1197. doi:10.1023/A:1002872800920_CHC.
103. Rybakov, V.B.; Babaev, E.V.; Pasichnichenko, K.Y. X-ray mapping in heterocyclic design: VIII. Synthesis and X-ray diffraction study of dimethyl 3-(p-chlorobenzoyl)-5-chloroindolizine-1,2-dicarboxylate and the product of its cyclization 1,2-bis(carbomethoxy)-6-chloro-3H-isoquinolino[1,2,3-d,c]indolizine-3-one. *Crystallogr. Rep.* **2002**, *47*, 622–628. doi:10.1134/1.1496061.
104. Ghosh, S.K.; Kuo, B.-C.; Chen, H.-Y.; Li, J.-Y.; Liu, S.-D.; Lee, H.M. Double C-H Functionalization to Construct Polycyclic Heteroarenes Catalyzed by an Ionic Salt of a Pd Complex with an N-Heterocyclic Carbene Ligand. *Eur. J. Org. Chem.* **2015**, *19*, 4131–4142. doi:10.1002/ejoc.201500417.
105. Li, P.; Zhang, X.; Fan, X. Synthesis of Naphtho[1′,2′:4,5]imidazo[1,2-a]pyridines and Imidazo[5,1,2-cd]indolizines through Pd-Catalyzed Cycloaromatization of 2-Phenylimidazo[1,2-a]pyridines with Alkynes. *J. Org. Chem.* **2015**, *80*, 7508–7518. doi:10.1021/acs.joc.5b01092.
106. Simonyan, V.V.; Zinin, A.I.; Babaev, E.V.; Jug, K. Mechanism of cycloaddition to indolizines. *J. Phys. Org. Chem.* **1998**, *11*, 201–208. doi:10.1002/(SICI)1099-1395(199803)11:3<201::AID-POC980>3.0.CO;2-W.
107. Babaev, E.V.; Simonyan, V.V.; Pasichnichenko, K.Y.; Nosova, V.M.; Kisin, A.V.; Jug, K. Quantum Chemical Analysis and Experimental Study of the Cycloaddition Reaction between Aminoacetylenes and 6-Nitroindolizines. NMR and ab Initio Evidence for the [4+2] Adduct Formation. *J. Org. Chem.* **1999**, *64*, 9057–9062. doi:10.1021/jo990841s.
108. Yamashita, Y.; Suzuki, D.; Masumura M. Addition Reaction of Indolizine Derivatives with Dimethyl Acetylenedicarboxylate. *Heterocycles* **1984**, *22*, 705–708. doi:10.3987/R-1984-04-0705.
109. Siberdt, F.; Nasielski, J. Indolizines 3. The synthesis of 2-vinylindolizines and their reaction with dienophiles. *Bull. Soc. Chim. Belg.* **1997**, *106*, 85–96.
110. Zinin, A.I.; Babaev, E.V. Unexpected reaction of 6-nitroindolizine with dimethyl acetylenedicarboxylate. *Russ. Chem. Bull.* **1997**, *46*, 609–610. doi:10.1007/BF02495432.
111. Blake, A.J.; Dick, J.W.; Leaver, D.; Strachan, P. Heterocyclic Compounds with Bridgehead Nitrogen Atoms. Part 11. I Formation of Azocino[2,1,8-cd]pyrrolizines in the Reactions of lndolizines with Dimethyl Acetylenedicarboxylate. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2991–2997. doi:10.1039/P19910002991.
112. Ikeda, S.; Kajigaeshi, S.; Kanemasa, S. Peripheral conjugate systems 1. Cycloaddition of indolizine to electron-deficient olefin. *Chem. Lett.* **1976**, *5*, 367–372. doi:10.1246/cl.1976.367.
113. Kajigaeshi, S.; Mori, S.; Fujisaki, S.; Kanemasa, S. exo-Selective Peripheral Cycloaddition Reactions of Pyrido[2,1-a]isoindole. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3547–3551. doi:10.1246/bcsj.58.3547.
114. Dick, J.W.; Gibson, W.K.; Leaver, D.; Roff, J.E. Heterocyclic compounds with bridgehead nitrogen atoms. Part 9. Synthesis in the pyrrolo[2,1,5-de]quinolizine ([2.3.3]cyclazine) series starting from indolizines. *J. Chem. Soc. Perkin Trans. 1* **1981**, 3150–3157. doi:10.1039/P19810003150.
115. Batroff, V.; Flitsch, W. Ein neuer Zugang zu [2.3.4]Cyclazinen. *Liebigs Ann. Chem.* **1987**, *7*, 621–628. doi:10.1002/jlac.198719870709.
116. Jasiński, R.; Dresler E. On the Question of Zwitterionic Intermediates in the [3+2] Cycloaddition Reactions: A Critical Review. *Organics* **2020**, *1*, 49–69. doi:10.3390/org1010005.