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1,3-Dipolar Cycloaddition Reaction of Bicyclic Aziridines with Cyclobutene. Synthesis of 1,2-Fused 4,5-Dihydro-1H-azepines

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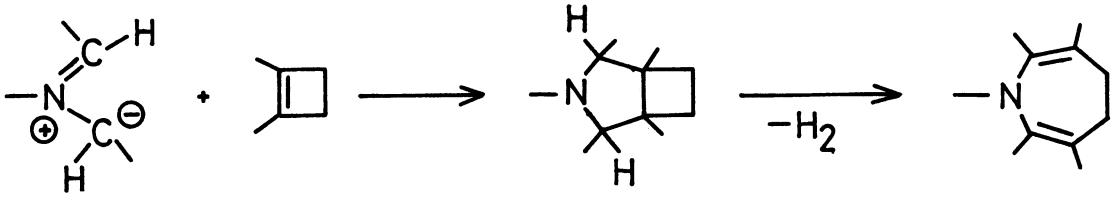
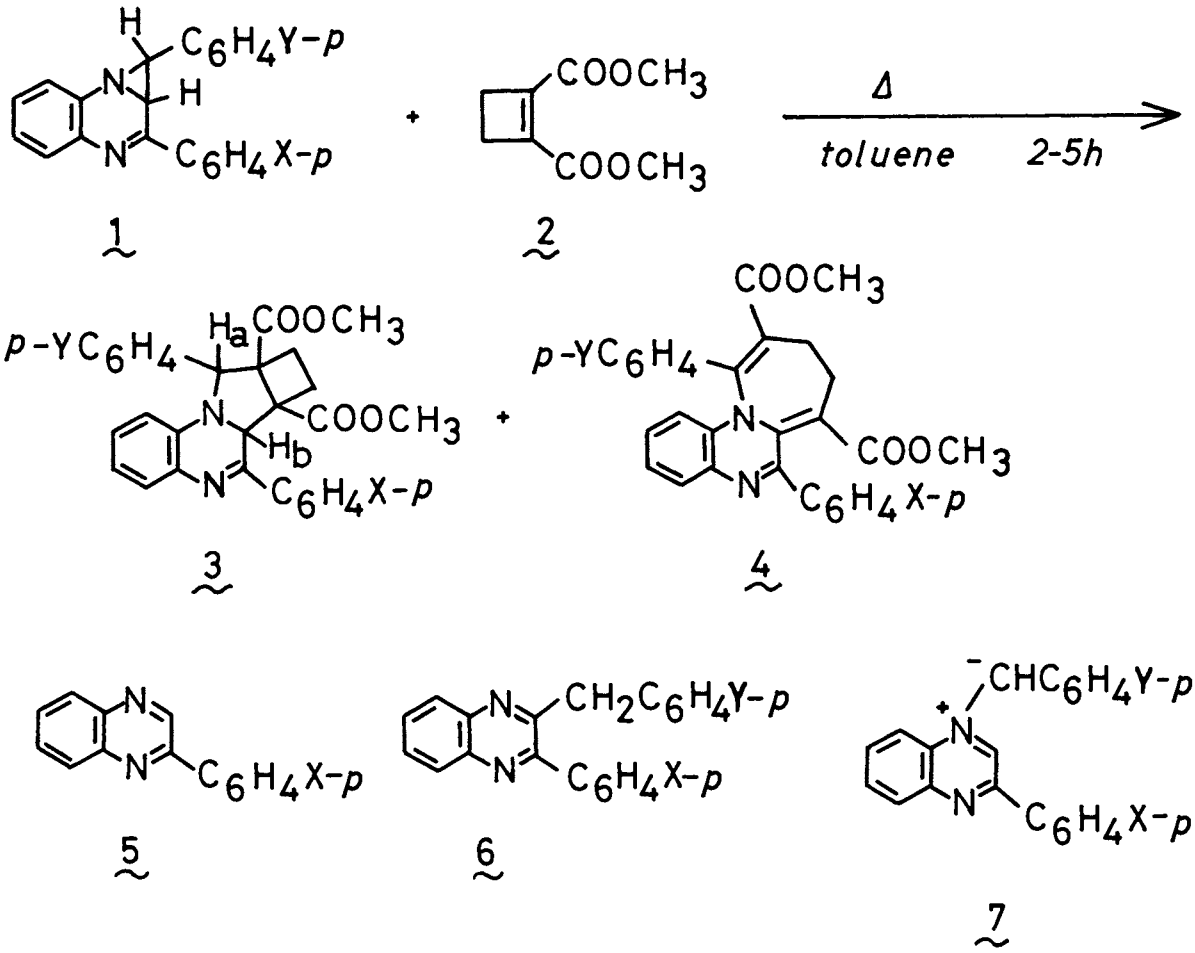
Reactions of 1,1a-dihydro-1,2-diarylazirino[1,2-a]-quinoxalines with dimethyl 1-cyclobutene-1,2-dicarboxylate gave mixtures of the 1,2-fused-4,5-dihydro-1H-azepines along with the 1:1 adducts that were converted to the azepines upon treatment with Pd-C.

4,5-Dihydro-1H-azepines have been of interest as calcium channel blockers.[1] Nevertheless, there are only few reports on their preparations.[2] Although cycloadditions of appropriate 1,3-dipoles such as azomethine ylides[3,4] with cyclobutenes would constitute one of the simplest and most general preparative methods for this type of compounds, only oxazolium 5-oxides have been reported to undergo such conversion.[5] This principle was reduced to practice by us about fifteen years ago,



though the ring opening of a smaller ring in the product was unsuccessful even in the presence of a dehydrogenating reagent such as Pd-C or dichlorodicycanoquinone.[6)]

We expected that employment of more strained bicyclic aziridines would facilitate the ring expansion of the primary cycloadducts. This was indeed the case with 1,1a-dihydro-1,2-diarylazirino[1,2-a]quinoxalines (1). For



1 2 3 4 5 6 7

example, reaction of 1,1a-dihydro-1,2-diphenylazirino[1,2-a]quinoxaline (1a) with dimethyl 1-cyclobutene-1,2-dicarboxylate (2) in refluxing toluene for 2 h gave a mixture of the 1:1 adduct 3a (37%) and 7,10-di(methoxycarbonyl)-6,11-diphenyl-8,9-dihydroazepino[1,2-a]quinoxaline (4a) (56%), which were readily separated by flash chromatography on SiO_2. In certain cases, the quinoxaline 5 was also formed.[7)] The results are summarized in

Table 1. Reactions of azirino[1,2-a]quinoxalines 1 with cyclobutene 2

	1		Yield/%		
	X	Y	3	4	5
a	H	H	37	56	
b	H	F	6	55	
c	H	Cl	22	35	4
d	H	NO_2	3	29	
e	F	H	54	6	3
f	Br	H		63	3
g[a)]	H	H	11	46	

a) 1,1a-Dihydro-6,7-dimethyl-1,2-diphenylazirino[1,2-a]quinoxaline.

Table 2. Typical physical and spectroscopic properties of 3 and 4

3	Mp/°C	^{1}H-NMR		4	Mp/°C	^{1}H-NMR
		H_a and H_b	OCH_3			OCH_3
a	212-213	5.13, 4.94	3.72, 3.74	a	207-208	3.00, 3.54
b	138-141	6.35, 5.06	3.38, 3.69	b	175-177	3.06, 3.63
c	163-165	6.37, 5.24	3.40, 3.67	c	162-163	3.10, 3.67
d	235-236	5.04, 4.94	3.73	d	222-223	3.08, 3.55
e	186-188	6.36, 5.09	3.33, 3.69	e	192-195	3.20, 3.65
				f	201-204	3.33, 3.70
g	214-215	5.04, 4.84	3.69, 3.72	g	206-207	2.95, 3.49

Tables 1 and 2. Although inspection of ^{1}H-NMR data of the 1:1 adducts 3 did not determine their stereochemical structures, 3a, 3d, and 3g are presumably different in stereochemistry from 3b, 3c, and 3e as suggested by the differences of their chemical shifts (H_a, H_b, and OCH_3) (see Table 2). Upon treatment with Pd-C in refluxing toluene, mixtures of 3 and 4 were readily converted to 4 in good yields (80-100%). However, reactions of 1

with 2 in the presence of Pd-C gave 4 in unsatisfactory yields (about 20%) along with the quinoxalines 5 and 6. Thus, the presence of Pd-C facilitated either isomerization or fragmentation rather than cycloaddition. Such catalyzed isomerization of 1e to 6e and thermal conversion of 1e to 5e have been reported.[7)]

Ready ylide generation from the bicyclic aziridines 1 is possibly attributed to the aromatic character of azomethine ylides 7 formed by conrotatory ring opening of 1.[8)]

Since the starting bicyclic aziridines and cyclobutenes are readily available, and particularly because new methods for generation of highly reactive azomethine ylides have extensively been developed,[4)] the present method provides a convenient route to 4,5-dihydro-1H-azepines that are otherwise difficult to obtain.

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