Preparation of Stable 2,3-Dihydroindolizines by the Reactions of Pyridinium Methylides with Various Acrylates

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Pyridinium methoxycarbonylmethylides(**5**—**8**), readily obtainable from their corresponding salts(**1**—**4**), reacted with various acrylates to afford dimethyl 2,3-*trans*-dihydroindolizine-1,3-dicarboxylate derivatives(**9**—**20**) in moderate yields. These dihydroindolizines were very stable and were not aromatized by heating. However, treatment with lead tetraacetate gave the corresponding indolizine derivatives(**21**—**32**) in good yields. The configuration at C-2 and C-3 positions in these dihydroindolizines was assigned to *trans* from their NMR and by comparison with an authentic specimen(**12**).

Cycloaddition and cyclization of various pyridinium ylides are useful methods for synthesizing nitrogen-bridged heteroaromatics such as indolizines and pyrazolopyridines. However, because of their sensitiveness to air, hardly any reports have appeared on the isolation of primary dihydroadducts formed.

Sasaki *et al.*,[1] and Tamura *et al.*[2] have reported that 1,5-dipolar cyclization of pyridinium allylides gave only their aromatized indolizine derivatives. Pohjala[3] reported on the isolation of the primary dihydroadducts, 1,8a-dihydroindolizines by similar cyclization reactions.

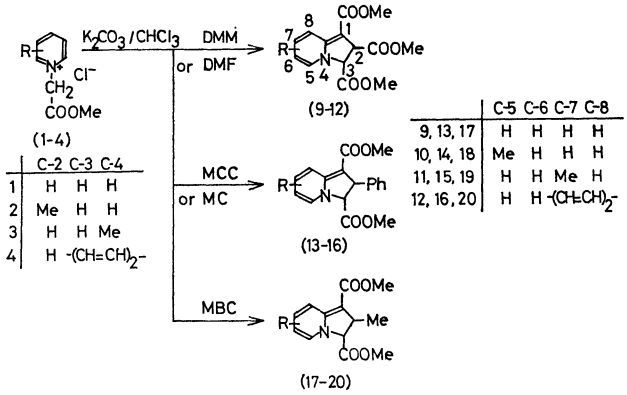
Kabayashi *et al.*[4] obtained 2,3- and 3,8a-dihydro isomers from the 1,3-dipolar cycloaddition of isoquinolinium disubstituted methylides with dimethyl acetylenedicarboxylate.

This paper deals with 1,3-dipolar cycloaddition of pyridinium methoxycarbonylmethylides with various acrylates, and the isolation of the resulting stable 2,3-dihydroindolizines.

Results and Discussion

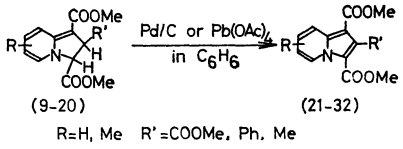
*Reactions of Pyridinium Salts(**1**)–(**4**) with Various Acrylates in the Presence of Alkali.* An equimolar mixture each of pyridinium salt(**1**)—(**4**) and dimethyl maleate (DMM) were stirred with excess potassium carbonate in chloroform at room temperature for 2—3 days to afford 2,3-dihydroindolizine derivatives(**9**)—(**12**) in 20—50% yields respectively. The same products(**9**) and (**10**) were obtained in 29 and 35% yields, respectively, when dimethyl fumarate(DMF) was used in place of DMM for the reactions with salts(**1**) and (**2**). Similar treatments of the salts(**1**)—(**4**) with methyl α-chlorocinnamate (MCC) and methyl α-bromocrotonate(MBC) also afforded the corresponding 2,3-dihydroindolizines(**13**)—(**20**). Compound (**13**) was also prepared from salt(**1**) and methyl cinnamate(MC), but the yield was low (6%). In these reactions, no product generated through the Micheal-type reaction of the pyridinium methylides(**5**)—(**8**) with the acrylates, such as observed in the reaction of *N*-ethoxycarbonyliminopyridinium ylide,[5] was detected. The results are shown in Scheme 1.

In contrast with the instability of the known 1,8a- and 3,8a-dihydroindolizine derivatives, 2,3-dihydroindolizines (**9**)—(**20**) were very stable. Compounds (**9**)—(**20**) remained unchanged on being put to stand for a few months on contact with air or when their benzene solutions were refluxed. However, treatment with dehydrogenating agents gave the corresponding indolizine derivatives (**21**)—(**32**).



Scheme 1.

*Aromatization of Dihydroindolizines(**9**)—(**20**).* Dihydroindolizines(**9**)—(**20**) were treated with palladium on carbon in benzene at reflux temperature to afford the corresponding indolizine derivatives(**21**)—(**32**) in only 10—20% yields. However, increased yields were observed when lead tetraacetate was used as a dehydrogenating agent(Scheme 2).



Scheme 2.

*Structural Elucidation of 2,3-Dihydroindolizines(**9**)—(**20**).* Structures of products(**9**)—(**20**) were established mainly by their physical and spectral data and by comparison with the authentic specimen(**12**) reported by Kobayashi.[4] The elemental analyses of the products (**9**), (**10**), (**12**)—(**14**), (**16**)—(**18**) and (**20**) were in good accordance with their proposed structures. The analyses of products(**11**), (**15**) and (**19**) were not performed, since the compounds were amorphous and preparation of the samples for analyses was unsuccessful. The spectral patterns of products (**9**)—(**20**), were extremely similar to each other. The NMR spectra, in particular, strongly supported the presence of the 2,3-dihydroindolizine skeleton; for example, compound(**9**) exhibited signals at δ 5.95, 6.99, 7.03 and

Table 1. NMR spectral data of 2,3-dihydroindolizines

Compd.[a]	Substituent													
	C-2		C-3		C-5		C-6		C-7		C-8		COOMe		R′(C-2)
9	4.18 d		5.01 d		7.03 dd		5.95 bt		6.99 bt		7.35 dd		3.67 s	3.75 s	3.80 s
	$J_{2,3}$=3.5,				$J_{5,6}$=7.0,				$J_{6,7}$=7.0,				$J_{7,8}$=9.0,		$J_{5,7}$=$J_{6,8}$=2.0
10	4.07 d		5.14 d		2.13 s		5.80 bd		6.93 q		7.31 dd		3.68 s	3.75 s	3.86 s
	$J_{2,3}$=3.0,				$J_{6,7}$=7.0,				$J_{7,8}$=9.0,				$J_{6,8}$=2.5		
11	4.13 d		4.99 d		7.03 d		5.84 dd		2.13 s		7.17 bs		3.66 s	3.72 s	3.78 s
	$J_{2,3}$=3.0,				$J_{5,6}$=7.0,				$J_{6,8}$=2.0						
12	4.29 d		4.83 d		6.74 d		6.22 d		7.1—7.6 m[b]				3.67 s	3.71 s	3.76 s
	$J_{2,3}$=3.5,				$J_{5,6}$=7.0										
13	4.52 s				6.87 bd		5.90 t		6.95 q		7.44 bd		3.53 s	3.83 s	7.0—7.4 m
	$J_{2,3}$=0,				$J_{5,6}$=6.0,				$J_{6,7}$=6.0,				$J_{7,8}$=9.0		
14	4.41 d		4.65 d		2.01 s		5.76 d		6.91 q[c]				3.55 s	3.84 s	7.0—7.3 m
	$J_{2,3}$=2.5,				$J_{6,7}$=6.0,				$J_{7,8}$=9.0						
15	4.44 s				6.76 d		5.75 d		2.10 s[c]				3.48 s	3.77 s	7.0—7.3 m
	$J_{2,3}$=0,				$J_{5,6}$=6.0										
16	4.42 d		4.55 d		6.62 d		6.17 d		7.0—7.5 m[d]				3.47 s	3.77 s	7.0—7.5 m
	$J_{2,3}$=2.5,				$J_{5,6}$=7.5										
17	3.35 m		4.19 d		6.84 bd		5.68 bt		6.80 bt		7.26 bd		3.62 s	3.72 s	1.29 d
	$J_{2,3}$=3.5,				$J_{2,Me}$=7.0,				$J_{5,6}$=6.0,				$J_{6,7}$=6.0,		$J_{7,8}$=8.0
18	3.28 m		4.33 d		2.03 s		5.67 d		6.80 q		7.20 dd		3.62 s	3.71 s	1.26 d
	$J_{2,3}$=2.5,				$J_{2,Me}$=7.0,				$J_{6,7}$=6.5,				$J_{7,8}$=8.0,		$J_{6,8}$=1.5
19	3.34 m		4.23 d		6.86 d		5.71 dd		2.05 s		7.10 d		3.60 s	3.69 s	1.27 d
	$J_{2,3}$=3.5,				$J_{2,Me}$=7.0,				$J_{5,6}$=7.0,				$J_{6,8}$=1.5		
20	3.45 m		4.14 d		6.65 d		6.13 d		7.1—7.5 m[e]				3.67 s	3.68 s	1.31 d
	$J_{2,3}$=2.5,				$J_{2,Me}$=7.0,				$J_{5,6}$=7.0						

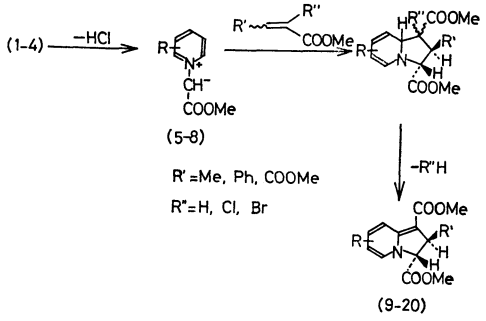
a) All compounds were measured in deuteriochloroform. b) Plus 9.74(1H, d, J=8.0). c) Overlapped with phenyl protons. d) Plus 9.78(1H, d, J=7.5). e) Plus 9.81(1H, d, J=7.5).

7.35 due to the four protons on the six-membered ring, and at δ 4.18 and 5.01 attributable to the two protons on the five-membered ring, together with three methoxycarbonyl proton signals at δ 3.67, 3.75 and 3.80. The latter signals at δ 4.18 and 5.01 coupled with 3.5 Hz, which is indicative of its *trans* configuration. In the cases of compounds(**17**)—(**20**) the proposed structure, 2,3-dihydroindolizine, was verified by the presence of the coupling(J=7.0 Hz) between a proton and a methyl group at C-2 position. The NMR data of compounds (**9**)—(**20**) are listed in Table 1. Compound (**12**) was entirely in accord with an authentic specimen prepared by the alkali-methanolysis of the corresponding adduct of isoquinolinium bis(methoxycarbonyl)methylide and dimethyl acetylenedicarboxylate.[4]

From the results, products(**9**)—(**20**) were concluded to be dimethyl 2,3-*trans*-dihydroindolizine-1,3-dicarboxylate derivatives.

*Structural Elucidation of Indolizines(**21**)—(**32**).* The structures of the indolizine derivatives(**21**)—(**32**) were determined by their unequivocal syntheses(**21**)—(**28**) and by comparison with authentic specimens(**21**) and (**24**). Compounds(**21**)—(**28**) were in accord with the indolizines obtained from the 1,3-dipolar cycloaddition of pyridinium methoxycarbonylmethylides(**5**)—(**8**) with dimethyl acetylenedicarboxylate and methyl phenylpropiolate respectively.[6]

Reaction Mechanism. The formation of 2,3-dihydroindolizines (**9**)—(**20**) seems to proceed *via* the well-known 1,3-dipolar cycloaddition of pyridinium methoxycarbonylmethylides(**5**)—(**8**) with acrylates, followed by elimination of two hydrogen atoms or a hydrogen halide from C-1 and C-8a positions of the resulting tetrahydroindolizine derivatives(Scheme 3).



Scheme 3.

In these reactions, the appearance of the only *trans*-adducts at C-2 and C-3 positions may be considered as the result of the approach from each less hindered site of the reactants in the transition state, and rapid conversion from 1,2,3,8a-tetrahydro- into 2,3-dihydroindolizine can be ascribed to be parallel with the

instability of 1,8a-dihydroindolizine, which gave smoothly indolizine.[3] Although the primary tetrahydroadducts could not be detected and isolated, the pyridinium methylides reacted with various acrylates to afford the corresponding cycloadducts. 1,3-Dipolar cycloaddition of pyridinium ylides with such olefinic dipolarophiles has not been reported.

Experimental

Mps were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 Elemental Analyser. The NMR spectra were determined with a JEOL JNM-4H-100 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO DS-301 spectrophotometer.

*Preparation of Pyridinium Salts(**1**)—(**4**).* A mixture of a pyridine base and methyl chloroacetate was kept at room temperature without any solvent and the resulting mass of pyridinium salt was filtered and washed 3—4 times with ether. The corresponding pyridinium salts (pyridinium, α-, γ-picolinium and isoquinolinium salt, **1**—**4**) were obtained as very hygroscopic colorless crystals almost quantitatively. The salts were used for subsequent reactions without further purification.

*Reactions of Salts(**1**)—(**4**) with Various Acrylates in the Presence of Alkali.* A solution of the salt(4 mmol) and an acrylic derivative(4 mmol) in chloroform(50 ml) was stirred with potassium carbonate(10 g) at room temperature for 2—4 days. The reaction mixture was filtered to remove inorganic substances and the filtrate was concentrated under reduced pressure. The resulting yellowish or reddish oil was then separated by column chromatography (alumina) using ether as an eluent. Recrystallization from chloroform-ether-*n*-hexane gave the corresponding 2,3-dihydroindolizine derivatives(**9**)—(**20**) as yellow or red crystals, but not compounds (**11**), (**15**) and (**19**). The results and properties of 2,3-dihydroindolizines are listed in Table 2.

*Aromatization of 2,3-Dihydroindolizines(**9**)—(**20**).* A benzene solution of 2,3-dihydroindolizine was stirred with an equimolar amount of lead tetraacetate at room temperature for 6—12 hrs, the reaction mixture then being filtered.

Table 2. Data of 2,3-dihydroinodolizines

Compd.	Reactant		React. time (day)	Yield (%)	$\nu_{C=O}^{KBr}$ (cm^{-1})		Mp (°C)	Formula	Calcd%			Found%		
	Salt	Acrylate							C	H	N	C	H	N
9	**1**	DMM	2	35	1748	1762	103—106	$C_{14}H_{15}NO_6$	57.33	5.16	4.78	57.16	5.17	4.71
	1	DMF	2	29										
10	**2**	DMM	3	48	1734	1746	182—185	$C_{15}H_{17}NO_6$	58.63	5.58	4.56	58.36	5.67	4.32
	2	DMF	3	35										
11	**3**	DMM	3	33[a]	amorphous substance									
12	**4**	DMM	2	28	1725	1747	156—157[b]	$C_{18}H_{17}NO_6$	62.97	4.99	4.08	62.95	4.97	3.99
13	**1**	MCC	3	10	1740		137—140	$C_{18}H_{17}NO_4$	69.44	5.50	4.50	69.68	5.62	4.37
	1	MC	4	6										
14	**2**	MCC	3	27	1745		156—159	$C_{19}H_{19}NO_4$	70.14	5.89	4.31	70.25	6.01	4.32
15	**3**	MCC	4	15[a]	amorphous substance									
16	**4**	MCC	2	31	1737		205—208	$C_{22}H_{19}NO_4$	73.11	5.30	3.88	73.10	5.22	3.77
17	**1**	MBC	3	56	1751		124—126	$C_{13}H_{15}NO_4$	62.64	6.07	5.62	62.90	6.03	5.60
18	**2**	MBC	3	78	1750		79— 81	$C_{14}H_{17}NO_4$	63.86	6.51	5.32	63.89	6.47	5.19
19	**3**	MBC	3	57[a]	amorphous substance									
20	**4**	MBC	4	59	1745		106—108	$C_{17}H_{17}NO_4$	68.21	5.73	4.68	68.29	5.70	4.61

a) Crude yield. b) Lit[4] 155—156.

Table 3. Data of indolizines

Compd.	Reactant	Yield (%)	Mp (°C)	$\nu_{C=O}^{KBr}$ (cm^{-1})		Formula	Calcd%			Found%		
							C	H	N	C	H	N
21	**9**	85	145—147[a]	1696	1738							
22	**10**	70	113—115	1687	1741							
23	**11**	65	141—142	1692	1743							
24	**12**	75	149—150[b]	1706	1730							
25	**13**	75	139—142	1675								
26	**14**	60	115—118	1690	1710							
27	**15**	60	172—175	1680								
28	**16**	85	143—145	1695								
29	**17**	80	122—123	1680		$C_{13}H_{13}NO_4$	63.15	5.30	5.67	62.98	5.36	5.51
30	**18**	80	80— 82	1690		$C_{14}H_{15}NO_4$	64.36	5.79	5.36	64.26	5.80	5.14
31	**19**	85	117—119	1685	1708	$C_{14}H_{15}NO_4$	64.36	5.79	5.36	64.11	5.77	5.10
32	**20**	80	115—117	1685		$C_{17}H_{15}NO_4$	68.67	5.08	4.71	68.59	5.22	4.86

a) Lit.[4] 148—149 °C. b) Lit.[4] 150—151 °C.

The filtrate was concentrated under reduced pressure and the residue was separated by column chromatography (silica gel) using benzene as an eluent. Recrystallization from ether-*n*-hexane or methanol gave the corresponding indolizine derivative as colorless crystals. The results and properties of indolizines(**21**)—(**32**) are listed in Table 3. Compounds (**21**)—(**28**) were in accord with the products prepared from the 1,3-dipolar cycloaddition of the pyridinium salts(**1**)—(**4**) with dimethyl acetylenedicarboxylate and methyl phenylpropiolate in the presence of potassium carbonate. Compounds (**21**) and (**24**) were also in accord with the products reported by Kobayashi.[4]

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