

## Preparation of New Nitrogen - bridged Heterocycles. 12.<sup>1)</sup> Reaction of 2-(Acylmethoxy)-3-vinylindolizines in the Presence of a Base

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Reactions of 2-(aroylmethoxy)-3-vinylindolizines (11-18) with diazabicyclo[5.4.0]-7-undecene (DBU) or diazabicyclo[4.3.0]-5-nonene (DBN) and of 2-(ethoxycarbonylmethoxy)-3-vinylindolizines (19 and 20) with DBN were investigated mechanistically from the standpoint of preparation. 11-18 react with DBU or DBN in chloroform, with elimination of a methylene compound, to give 2-arylfuro-[2,3-*b*]indolizine derivatives in good to excellent yields. In contrast, 19 and 20 react with DBN in ethanol to form devinylated compounds, 2-(ethoxycarbonylmethoxy)indolizines, in low yields, with simultaneous formation of considerable amounts of polymeric substances. A discussion is made with respect to the effect of substituents on the 3-vinyl group upon the transformations observed and possible reaction mechanisms.

In our previous papers<sup>3-5)</sup> we reported a convenient method for synthesizing functionalized 2-alkoxy-3-vinylindolizines and allowing them to transform to fused heterocycles such as furo[2,3-*b*]indolizines and pyrano[2,3-*b*]indolizines. In order to obtain further information on the reactivity, we have examined the behavior of these 2-(acylmethoxy)-3-vinylindolizine derivatives under carbanion-generating conditions. In this paper we report on a new preparative method for 2-arylfuro[2,3-*b*]indolizine derivatives and a devinylation of 3-vinylindolizine derivatives.

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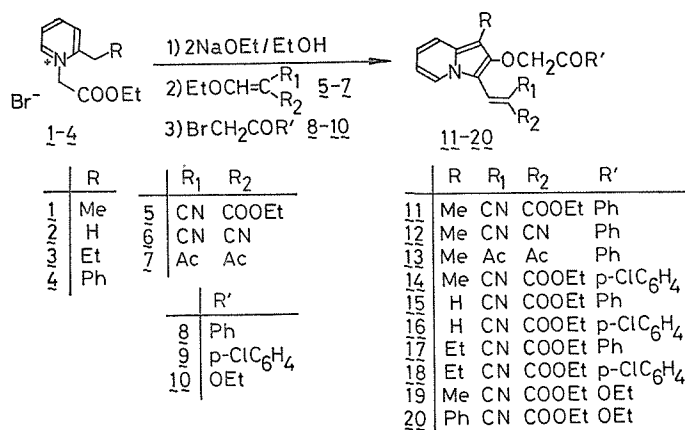
\*\* Professor

\*\*\* Student of master course

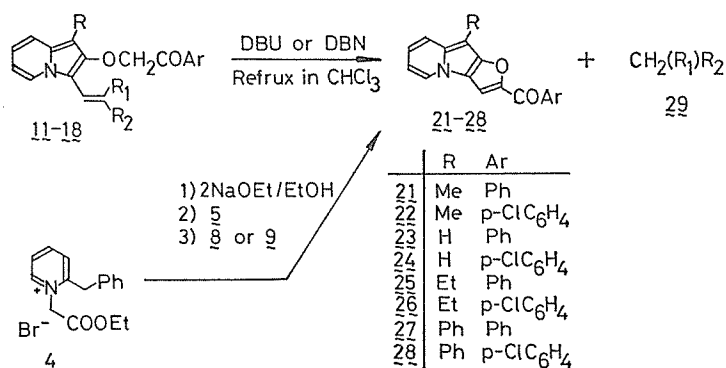
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## Results and Discussion

A treatment of 2-(benzoylmethoxy)-3-[2-cyano-2-(ethoxycarbonyl)vinyl]-1-methylindolizine (11), readily obtainable through a reaction of 1-(ethoxycarbonylmethyl)-2-ethylpyridinium bromide (1) with a base, ethyl (ethoxymethylene)cynoacetate (5), and phenacyl bromide (8) (see Scheme 1), with DBU in chloroform at the refluxing temperature, afforded smoothly a reddish crystalline compound 21, mp 120-121°C, in 92% yield. The same compound 21 could also be obtained through reactions of 2-(benzoylmethoxy)-3-(2,2-dicyanovinyl)-1-methylindolizine (12) or 2-(benzoylmethoxy)-3-(2,2-diacetylvinyl)-1-methylindolizine (13) with DBU in 50 or 41%, respectively. The 2-cyano-2-(ethoxycarbonyl)vinyl group in the indolizine 11 is more effective for this transformation than the 2,2-dicyanovinyl group in 12 and the 2,2-diacetylvinyl group in 13. A reaction of indolizine 11 with DBN afforded also a furoindolizine derivative 21 in 91% yield, but those with organic amines such as triethylamine and pyridine gave no product. A similar treatment of 2-(aroylmethoxy)-3-[2-cyano-2-(ethoxycarbonyl)vinyl]indolizines 14-18 with DBU gave the corresponding products 22-26 in 58-93% yields. In the case of 3-vinylindolines 11 and 14-18 with DBU, a formation of ethyl cyanoacetate 29 ( $R_1=CN$ ,  $R_2=COOEt$ ) was detected by GLC analysis of reaction mixtures. Interestingly, compound 27 or 28 could be obtained directly through reactions of 2-benzyl-1-(ethoxycarbonylmethyl)pyridinium bromide (4) with a base, 5, and phe-



Scheme 1.



Scheme 2.

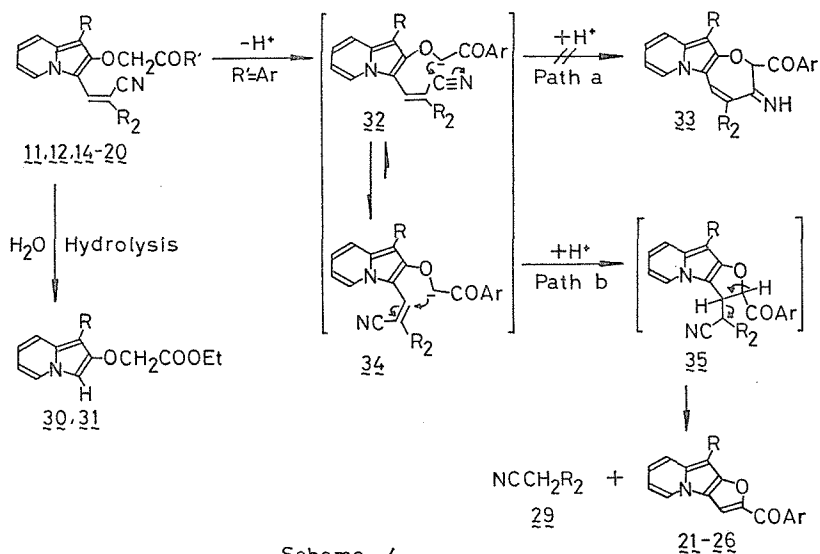


Scheme 3.

nacyl bromide (8) or *p*-chlorophenacyl bromide (9) in 40 or 49% yields, respectively.

Reactions of 2-(ethoxycarbonylmethoxy)-3-[2-cyano-2-(ethoxycarbonyl)-vinyl]indolizine derivatives 19 or 20 with DBN in ethanol gave a strongly fluorescent, pale yellow substance 30 or 31 in low yield, respectively, but that in chloroform afforded only a trace amount of the same product 30 or 31. In these reactions considerable amounts of polymeric substances were always formed.

From these experimental results and related physical and spectral inspections, it is derived that crystalline compounds 21-28 are 2-arylfuro[2,3-*b*]indolizine derivatives and not any conceivable alternatives such as oxepino[2,3-*b*]indolizines 33 (see Scheme 4). Of course, these compounds 21-28 were completely in accord with the authentic samples prepared earlier by us.<sup>4)</sup> The structures of products 30 and 31 were determined mainly on the basis of the presence of the 3-proton ( $\delta$  near 7.0) and the absence of the 2-cyano-2-(ethoxycarbonyl)vinyl group in their proton NMR spectra.



Mechanistically, the formation of 2-arylfuro[2,3-*b*]indolizine derivatives 21-26 can be interpreted in terms of the intramolecular Michael addition of anionic species 34 generated by the proton abstraction from the active methylene group of 2-(arylmethoxy)-3-vinylindolizines 11-18, followed by the aromatization of the resulting tricyclic adducts 35 along with the elimination of a methylene compound 29 (Path b); the other route (Path a) leading to oxepino[2,3-*b*]indolizines 33 seems not to proceed because of the more hindered conformation of intermediate carbanion 32. Furthermore, the route<sup>4)</sup> *via* the hydrolysis of the 3-vinyl group of 11-18 followed by the condensation between the 3-formyl group and the active methylene group, may also be neglected because no conversion of such vinyl groups to a formyl group occurs under the reaction conditions employed here.<sup>6)</sup> The direct formation of 2-aryl-9-phenylfuro[2,3-*b*]indolizines 27 and 28 must have resulted from the high reactivity of intermediate 2-(arylmethoxy)-1-phenyl-3-[2-(ethoxycarbonyl)vinyl]indolizines once formed.

The formation of 2-(ethoxycarbonylmethoxy)indolizine derivatives 30 and 31 may be a result of retro-vinylation since the vinylation of 3-unsubstituted indolizines with some active ethoxymethylene compounds in the presence of a base is well known.<sup>3,7)</sup>

This method in which 2-(arylmethoxy)-3-[2-cyano-2-(ethoxycarbonyl)vinyl]indolizines are used for the preparation of 2-arylfuro[2,3-*b*]indolizines, has a high utility because of its manageability including the

easy handling of indolizines 11 and 14-18.

### Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240 elemental analyzer. The NMR spectra were obtained with a Varian EM360A spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Chemical shifts are expressed in  $\delta$  values. IR spectra were taken with a Hitachi 260-10 infrared spectrophotometer.

*Preparations of 2-(Acylmethoxy)-3-vinylindolizines 11-20 and 2-Aroyl-9-phenylfuro[2,3-*b*]indolizines 27 and 28.* These 2-(acylmethoxy)-3-vinylindolizine derivatives 11-20 were synthesized through reactions of 1-(ethoxycarbonylmethyl)pyridinium salts 1-4 according to the procedure reported earlier by us<sup>3,4</sup> and recrystallized from ethanol. Similar reactions of 2-benzyl-1-(ethoxycarbonylmethyl)pyridinium bromide (4), with a base, ethyl (ethoxymethylene)cyanoacetate (5), and phenacyl bromide (8) or *p*-chlorophenacyl bromide (9) did not give expected 2-(aroylmethoxy)-1-phenyl-3-vinylindolizines, but afforded 2-benzoyl- (27) (mp 186-188°C from ethanol) and 2-(*p*-chlorobenzoyl)-9-phenylfuro[2,3-*b*]indolizine (28) (mp 227-229°C from ethanol) in 40 and 49% yields, respectively. Compounds 12, 19, and 20 were completely in accord with the authentic samples.<sup>3,4</sup> Some physical and spectral data of the new compounds are as follows. 11: 97%, orange needles, mp 191-192°C,  $\nu$  (KBr) 2202 (CN) and 1681  $\text{cm}^{-1}$  (CO). Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4$ : C, 71.12; H, 5.19; N, 7.21%. Found: C, 70.89; H, 5.22; N, 7.12%. 13: 29%, orange prisms, mp 200-201°C,  $\nu$  (KBr) 1687  $\text{cm}^{-1}$  (CO). Anal. Calcd for  $\text{C}_{23}\text{H}_{21}\text{NO}_4$ : C, 73.58; H, 5.64; N, 3.73%. Found: C, 73.42; H, 5.62; N, 3.90%. 14: 63%, orange needles, mp 203-205°C,  $\nu$  (KBr) 2210 (CN), 1693 (CO), and 1686  $\text{cm}^{-1}$  (CO). Anal. Calcd for  $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_4\text{Cl}$ : C, 65.33; H, 4.53; N, 6.62%. Found: C, 65.33; H, 4.38; N, 6.77%. 15: 24%, orange needles, mp 165-167°C,  $\nu$  (KBr) 2208 (CN), 1680 (CO), and 1670  $\text{cm}^{-1}$  (CO). Anal. Calcd for  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_4$ : C, 70.58; H, 4.85; N, 7.48%. Found: C, 70.66; H, 4.94; N, 7.30%. 16: 22%, orange needles, mp 169-171°C,  $\nu$  (KBr) 2209 (CN), 1689 (CO), and 1682  $\text{cm}^{-1}$  (CO). Anal. Calcd for  $\text{C}_{22}\text{H}_{17}\text{N}_2\text{O}_4\text{Cl}$ : C, 64.63; H, 4.19; N, 6.85%. Found: C, 64.90; H, 4.20; N, 6.57%. 17: 87%, orange needles, mp 166-168°C,  $\nu$  (KBr) 2201 (CN) and 1690  $\text{cm}^{-1}$  (CO). Anal. Calcd for  $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_4$ : C, 71.63; H, 5.51; N, 6.96%. Found: C, 71.51; H, 5.30; N, 6.89%. 18: 58%, orange needles, mp 198-200°C,  $\nu$  (KBr) 2201 (CN) and

1687  $\text{cm}^{-1}$  (CO). Anal. Calcd for  $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_4\text{Cl}$ : C, 65.98; H, 4.85; N, 6.41%. Found: C, 66.17; H, 4.72; N, 6.15%.

*Preparations of 2-Aroylfuro[2,3-*b*]indolizines 21-26.* General Method: A mixture of 2-(aroylmethoxy)-3-vinylindolizine (1 mmol), DBU or DBN (0.5g), and chloroform (50ml) was heated under reflux in a water bath until the disappearance of the starting indolizine was completely confirmed by TLC. The resulting reddish solution was concentrated under reduced pressure, and the residue was separated by column chromatography on alumina using hexane, ether, and chloroform as eluents. The ether and chloroform layers were concentrated under reduced pressure and the crude product was collected. A recrystallization from ethanol gave red needles of 2-aroylfuro[2,3-*b*]indolizine.

In the reactions of 2-(aroylmethoxy)-3-[2-cyano-2-(ethoxycarbonyl)vinyl]-indolizines 11 and 14-18 with DBU, ethyl cyanoacetate could be detected by GLC analyses of reaction mixtures. No use of triethylamine or pyridine as a base caused such reactions. These furo[2,3-*b*]indolizines 21-26 thus obtained were completely in accord with the samples synthesized earlier by us.<sup>4)</sup> Some data of these reactions are shown in Table 1.

*Preparations of 3-Unsubstituted 2-(Ethoxycarbonylmethoxy)indolizines 30 and 31.* General Method: An ethanolic solution (50 ml) of 2-(ethoxycarbonylmethoxy)-3-vinylindolizine (1 mmol) and DBN (0.5g) was heated at the reflux temperature until the starting indolizine was disappeared (as confirmed by

Table 1. Some Data of 2-Aroylfuro[2,3-*b*]indolizines

Compd	Reactant	Reaction time	Base	Yield/%	mp/°C
21	11	30 min	DBU	92	120-121
	11	2 h	DBN	91	
	11	10 h	TEA <sup>a)</sup>	0	
	11	10 h	PY <sup>b)</sup>	0	
	12	30 min	DBU	50	
	13	42 h	DBU	41 <sup>c)</sup>	
22	14	20 min	DBU	74	197-199
23	15	35 min	DBU	58	124-127
24	16	30 min	DBU	87	185-187
25	17	30 min	DBU	93	117-119
26	18	25 min	DBU	72	188-190

a) Triethylamine.

b) Pyridine.

c) The 2-(benzoylmethoxy)-3-(2,2-diacetylvinyl)-1-methylindolizine (13) was recovered in 54%.

TLC). The solution was then concentrated under reduced pressure, and the residual oil was separated by column chromatography on alumina using hexane and ether. The evaporation of the solvent from the ether layer afforded 2-(ethoxycarbonylmethoxy)indolizine derivative.

The reactions of 3-vinylindolizines 19 and 20 under the same conditions with the preparations of furoindolizines 21-26 always gave considerable amounts of polymeric tars, and only a trace amount of devinylated compounds 30 and 31 could be isolated. Furthermore, similar treatment of 19 and 20 with DBU in ethanol afforded the same products 30 and 31 in very low yields (1-3%).

Some data of products 30 and 31 are as follows. 30: 40% (reaction time 8h), pale yellow oil (its picrate, mp 137-138°C (dec)),  $\nu$  (KBr) 1751  $\text{cm}^{-1}$  (CO),<sup>8)</sup>  $\delta$  ( $\text{CDCl}_3$ ) 1.31 (3H, t,  $J=7.0$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.27 (3H, s, 1-Me), 4.30 (2H, q,  $J=7.0$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.61 (2H, s,  $\text{OCH}_2$ ), 6.39 (1H, br t,  $J=7.0$  and 7.0 Hz, 6-H), 6.65 (1H, br t,  $J=9.0$  and 7.0 Hz, 7-H), 6.93 (1H, s, 3-H), 7.25 (1H, br d,  $J=9.0$  Hz, 8-H), and 7.81 (1H, br d,  $J=7.0$  Hz, 5-H). Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_{10}$ : C, 49.36; H, 3.92; N, 12.12%. Found: C, 49.19; H, 3.87; N, 11.89%.<sup>8)</sup> 31:28% (reaction time 9h), pale yellow oil,  $\nu$  (neat) 1751  $\text{cm}^{-1}$  (CO),  $\delta$  ( $\text{CDCl}_3$ ) 1.30 (3H, t,  $J=7.0$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.31 (2H, q,  $J=7.0$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.63 (2H, s,  $\text{OCH}_2$ ), 6.68 (1H, br t,  $J=7.0$  and 7.0 Hz, 6-H), 6.80 (1H, br t,  $J=9.0$  and 7.0 Hz, 7-H), 7.04 (1H, s, 3-H), and 7.1-8.3 (7H, m, 5-H, 8-H, and phenyl protons).<sup>9)</sup>

#### References and Notes

- 1) For Part 11 of this series, see A. Kakehi, S. Ito, M. Ito, T. Yotsuya, and K. Nagata, *Bull. Chem. Soc. Jpn.*, **58**, 1432 (1985).
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- 7) Y. Yamashita, D. Suzuki, and M. Masumura, *Heterocycles*, **16**, 1499 (1981).
- 8) Picrate.
- 9) The preparation of the analytical sample of 2-(ethoxycarbonylmethoxy)-1-phenylindolizine (31) was unsuccessful because of its instability and non-availability of its picrate.