[Chem. Pharm. Bull. 30(3) 881—886 (1982)]

Synthesis of 3-(Dialkylamino)indolizines. Reaction of 3-(2-Pyridyl)-2-propenals with Secondary Amines

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(Received August 3, 1981)

Reaction of 2- or 3-substituted 3-(2-pyridyl)-2-propenals (**3a**—**f**) with secondary amines afforded 2- or 1-substituted 3-(dialkylamino)indolizines (**2a**—**l**) in the presence of metal halides. It was found that titanium tetrachloride was the best catalyst.

Keywords——3-(dialkylamino)indolizine; catalyst; 3-(2-pyridyl)-2-propenal; titanium tetrachloride; metal halide

Several synthetic methods for indolizine derivatives have been reported from chemical,[1] pharmaceutical,[2] and physical[3] points of view. Hurst *et al.*[2b] prepared some aminoindolizines in order to evaluate their biological activity.

In our previous reports,[4] 3-(dialkylamino)indolizines were prepared by the reaction of 2-bromopyridine (**1**) with propargyl alcohol and secondary amines in the presence of $Pd(PPh_3)_2Cl_2$–CuI as a catalyst. 3-(2-Pyridyl)-2-propenal was suggested to be an intermediate of the reaction (Chart 1). However, 1-substituted and 2-substituted 3-(dialkylamino)indolizines (**2**) could not be prepared by this method. In the present report, we describe the synthesis of 1- or 2-substituted 3-(dialkylamino)indolizines by the reaction of substituted 3-(2-pyridyl)-2-propenals (**3**) with secondary amines.

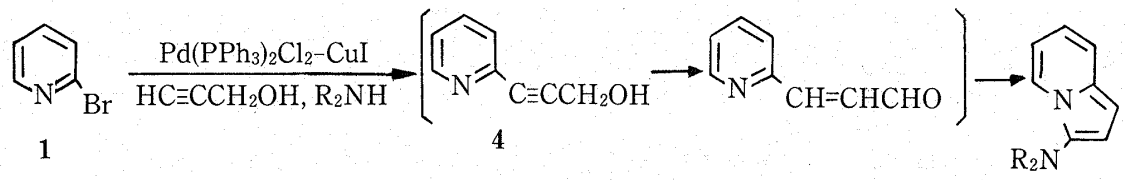

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Chart 1

First, synthesis of substituted 3-(2-pyridyl)-2-propenals (**3a**—**f**) was attempted. The reaction of 3-(2-pyridyl)-2-propyn-1-ol (**4**), prepared by the reaction of **1** and propargyl alcohol,[4b] with Grignard reagents in the presence of CuBr as a catalyst gave 2-substituted 3-(2-pyridyl)-2-propen-1-ols (**5a**—**c**) in yields of 62—74%. On the other hand, **4** was treated with HCl to afford 2-chloro-3-(2-pyridyl)-2-propen-1-ol (**5d**) in 72% yield. The reaction of 2-pyridylketones (**6a**, **b**) with vinylmagnesium bromide afforded 2-(2-pyridyl)-3-buten-2-ol (**7a**) and 1-phenyl-1-(2-pyridyl)-2-propen-1-ol (**7b**) in yields of 66 and 84%, respectively. Treatment of **7a**, **b** with 10% H_2SO_4 afforded 3-substituted 3-(2-pyridyl)-propenols (**5e**, **f**). Oxidation of **5a**—**f** by active MnO_2 afforded the corresponding substituted 3-(2-pyridyl)-2-propenals (**3a**—**f**) in fairly good yields.

As a preliminary experiment, a solution of **3b** and excess morpholine in benzene was heated at 70°C for 16 h. A somewhat air-sensitive yellow compound of mp 78—79°C, 2-ethyl-3-morpholinoindolizine (**2a**), was obtained in 19% yield. Its nuclear magnetic resonance (NMR) spectrum indicated the presence of the morpholino group and the ethyl group, and showed signals which were assigned to the protons on the indolizine ring carbons. The pattern was similar to that of 3-morpholinoindolizine.[4b] It is known that metal halides assist the

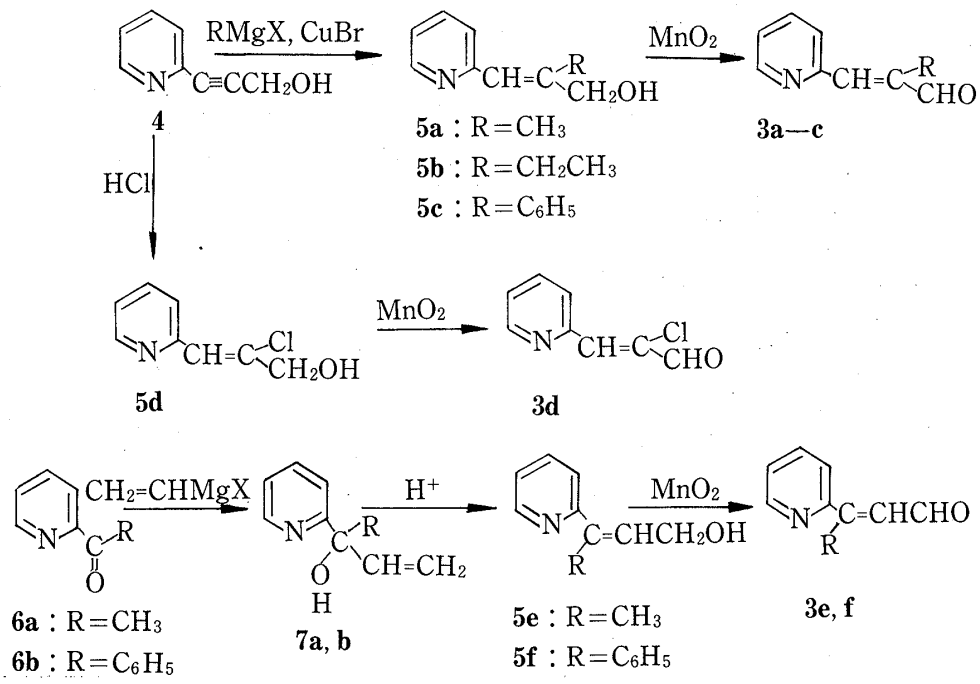
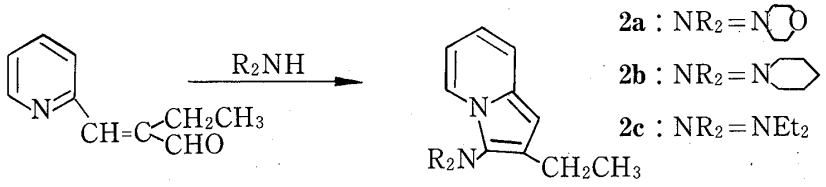


Chart 2

formation of imines from ketones and primary amines[5] and the formation of enamines from ketones and secondary amines.[6]

Hence, the catalytic activity of metal halides in the reaction of **3b** with morpholine was examined, as shown in Table I. The yield was improved when metal halides were used in the reaction and titanium tetrachloride was found to be the best catalyst. Next, the solvent effect on the reaction in the presence of titanium tetrachloride was examined. Use of benzene or methylene chloride resulted in better yields than that of ether or hexane as the solvent. The reaction of **3b** with other secondary amines (piperidine or diethylamine) in the presence of titanium tetrachloride in benzene was examined. The yield of 2-ethyl-3-(diethylamino)-indolizine (**2c**) in CH_2Cl_2 was very low. In the light of these data, the use of benzene as the solvent and titanium tetrachloride as the catalyst was regarded as being optimum.

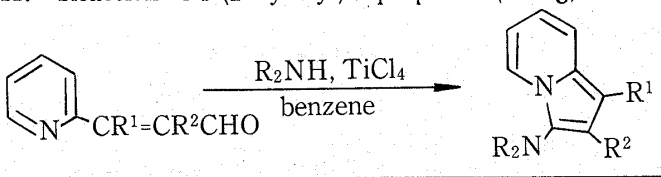
Table I. Reaction of 2-Ethyl-3-(2-pyridyl)-2-propenal(**3b**) with Amines



Amine	Solvent	Catalyst	Product	Yield (%)
Morpholine	Benzene	Absent	**2a**	19
Morpholine	Benzene	$TiCl_4$	**2a**	96
Morpholine	Benzene	$FeCl_3$	**2a**	67
Morpholine	Benzene	$MgCl_2$	**2a**	73
Morpholine	Benzene	$AlCl_3$	**2a**	87
Morpholine	Benzene	$ZnCl_2$	**2a**	74
Morpholine	Benzene	CuBr	**2a**	37
Morpholine	Hexane	$TiCl_4$	**2a**	39
Morpholine	Ether	$TiCl_4$	**2a**	7
Morpholine	CH_2Cl_2	$TiCl_4$	**2a**	95
Piperidine	Benzene	$TiCl_4$	**2b**	96
Diethylamine	Benzene	$TiCl_4$	**2c**	97

Further, the reactions of other 2- or 3-substituted 3-(2-pyridyl)-2-propenals (**3a—f**) with secondary amines were investigated, as shown in Table II. The yields of the products were found to be satisfactory in most cases. In the reaction of 2-phenyl-3-(2-pyridyl)-2-propenal (**3c**) with piperidine, steric hindrance of the phenyl group might be responsible for the poor yield of the product (**2e**).

TABLE II. Reaction of 3-(2-Pyridyl)-2-propenals (**3a—g**) with Amines



3	R_1	R_2	Amine	2	Yield(%)
3a	H	CH_3	Piperidine	**2d**	97
3c	H	C_6H_5	Piperidine	**2e**	39
3e	CH_3	H	Morpholine	**2f**	96
3e	CH_3	H	Piperidine	**2g**	97
3f	C_6H_5	H	Morpholine	**2h**	91
3f	C_6H_5	H	Piperidine	**2i**	93
3f	C_6H_5	H	Diethylamine	**2j**	95
3g	H	H	Diisopropylamine	**2k**	72
3g	H	H	Dibenzylamine	**2l**	80

The mechanism for the formation of **2** is postulated to be as shown in Chart 3. In the reaction without titanium tetrachloride, the iminium ion (**8**) formed by the condensation of aldehyde and amine cyclizes to give an intermediate (**9**), followed by deprotonation to give **2**. To explain the catalytic effect of titanium tetrachloride, three pathways for formation of the intermediate (**9**) might be considered. a) Titanium tetrachloride assists the formation

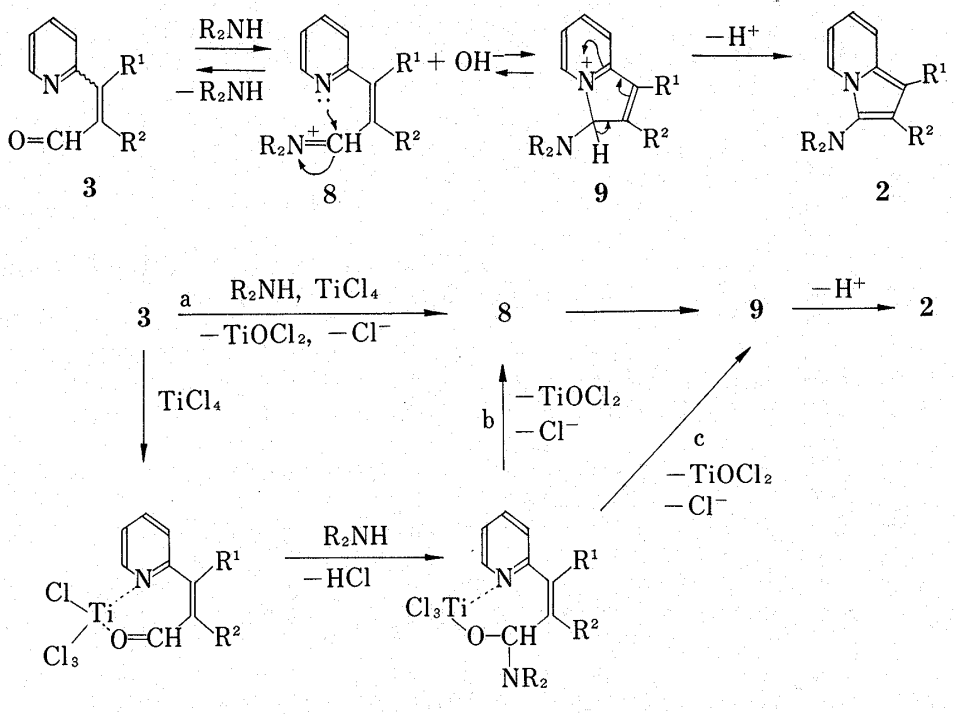


Chart 3

of **8** by changing the reaction (**3**⇄**8**) to an irreversible one, as it is known that titanium tetrachloride assists the formation of enamines from ketones and secondary amines. The iminium ion forms **9** in the same way as without titanium tetrachloride. b) Lone pairs of the oxygen atom in the carbonyl group and the nitrogen atom in the pyridine ring attack the titanium tetrachloride molecule to form a cyclic intermediate (**10**). This intermediate gives **8** and it forms **9**. c) The intermediate (**10**) formed in the same way as in b) gives **9** concertedly without forming **8**.

Experimental

All boiling points and melting points are uncorrected. NMR spectra were recorded on Hitachi R-20 and R-22 instruments. The properties of 3-(2-pyridyl)-2-propen-1-ols (**5a**—**f**) and 3-(2-pyridyl)-2-propenals (**3a**—**f**) are listed in Table III. Properties of 3-(dialkylamino)indolizines (**2a**—**l**) are listed in Table IV.

2-Methyl-3-(2-pyridyl)-2-propen-1-ol (5a)——CuBr (0.05 g) was added to a solution of MeMgI prepared from Mg (0.73 g) and MeI (4.7 g) in ether (50 ml) under a nitrogen atmosphere. Crystals of 3-(2-pyridyl)-2-propyn-1-ol (**4**, 1.43 g) were added to the reaction mixture with stirring. The mixture was refluxed for 16 h, and quenched by adding aq. HCl. After neutralization with K_2CO_3, the ethereal layer was separated and the aqueous layer was extracted with methylene chloride. The extracts were combined, dried over K_2CO_3 and evaporated to dryness. The residue was chromatographed over silica gel (hexane–ether) to give 1.50 g (74%) of **5a**. Further purification was performed by distillation (bp 150°C/0.4 mmHg). Picrate mp 147—149°C (from iso-Pr_2O–MeOH).

Table III. Properties of 3-(2-Pyridyl)-2-propenols (**5a**—**f**) and 3-(2-Pyridyl)-2-propenals (**3a**—**f**)

Compound	Analysis (%) Found (Calcd.) C	H	N	NMR (δ, J in Hz)
5a[a]	47.30	3.60	15.02	2.02 (3H, m, CH_3), 4.10 (1H, br s, OH), 4.20 (2H, s, CH_2), 6.64 (1H, m,
	(47.62	3.73	14.81)	olefin-H), 7.07 (1H, m, 5-H), 7.19 (1H, m, 3-H), 7.60 (1H, m, 4-H), 8.56 (1H, m, 6-H)
5b[a]	49.74	4.11	14.40	1.07 (3H, t, 8, CH_3), 2.49 (2H, q, 8, $C\underline{H}_2CH_3$), 4.25 (2H, m, CH_2), 4.48
	(49.98	4.11	14.28)	(1H, br s, OH), 6.62 (1H, br m, olefin-H), 7.06 (1H, m, 5-H), 7.20 (1H, m, 3-H), 7.60 (1H, m, 4-H), 8.53 (1H, m, 6-H)
5c	79.42	6.13	6.62	4.49 (2H, d, 1.5, CH_2), 4.93 (1H, br s, OH), 6.7—7.6 (9H, m, 3-H, 4-H,
	(79.59	6.20	6.63)	5-H, olefin-H and C_6H_5), 8.47 (1H, m, 6-H)
5d	56.83	4.84	8.05	4.37 (2H, d, 1.5, CH_2), 4.94 (1H, br s, OH), 7.1—7.35 (2H, m, 5-H,
	(56.65	4.75	8.26)	and olefin-H), 7.75 (1H, m, 4-H), 8.0 (1H, m, 3-H), 8.58 (1H, m, 6-H)
5e	71.99	7.65	9.18	2.06 (3H, s, CH_3), 4.28 (1H, br s, OH), 4.39 (2H, d, 7, CH_2)
	(72.48	7.38	9.40)	6.43 (1H, t, 7, olefin-H), 7.07 (1H, m, 5-H), 7.34 (1H, m, 3-H), 7.57 (1H, m, 4-H), 8.48 (1H, m, 6-H)
5f[a]	54.51	3.67	12.55	4.0—4.4 (1H, br s, OH), 4.23 (2H, d, 7, CH_2), 6.8—7.8 (9H, m, 3-H,
	(54.55	3.66	12.72)	4-H, 5-H, olefin-H and C_6H_5), 8.61 (1H, m, 6-H)
3a	73.75	6.08	9.46	2.22 (3H, d, 1.5, CH_3), 7.0—7.2 (2H, m, olefin-H and 5-H), 7.36 (1H,
	(73.45	6.16	9.52)	m, 3-H), 7.61 (1H, m, 4-H), 8.58 (1H, m, 6-H), 9.50 (1H, s, CHO)
3b[a]	49.55	3.60	14.71	1.08 (3H, t, 7, CH_3), 2.78 (2H, q, 7, CH_2), 7.04 (1H, br m, olefin-H),
	(49.23	3.62	14.36)	7.14 (1H, m, 5-H), 7.32 (1H, m, 3-H), 7.60 (1H, m, 4-H), 8.58 (1H, m, 6-H), 9.56 (1H, m, CHO)
3c	80.54	5.32	6.84	6.8—7.8 (9H, m, 3-H, 4-H, 5-H, olefin-H and C_6H_5), 8.60 (1H, m, 6-H),
	(80.36	5.30	6.69)	9.83 (1H, s, CHO)
3d	57.06	3.63	8.43	7.36 (1H, m, 5-H), 7.6—8.1 (2H, m, 4-H and olefin-H), 8.31 (1H, m,
	(57.33	3.97	8.36)	3-H), 8.75 (1H, m, 6-H), 9.58 (1H, s, CHO)
3e	73.34	6.30	9.72	2.61 (3H, d, 1, CH_3), 6.76 (1H, dq, 8, 1, olefin-H), 7.27 (1H, m, 5-H),
	(73.45	6.16	9.52)	7.5—7.9 (2H, m, 4-H and 5-H), 8.63 (1H, m, 6-H), 10.25 (1H, d, 8, CHO)
3f	79.99	5.21	6.84	7.2—7.8 (9H, m, 3-H, 4-H, 5-H, olefin-H and C_6H_5), 8.82 (1H, m, 6-H),
	(80.36	5.30	6.69)	9.71 (1H, d, 8, CHO)

a) In these compounds, elenmental analysis values for the picrates are shown.
b) MS *m/e*: Calcd for M^+: 149.084. Obsd: 149.083; Calcd for $(M-H_2O)^+$: 131.073. Obsd: 131.073.

Table IV. Properties of 3-(Dialkylamino)indolizines (**2a**—**l**)

Compd.	mp (°C) or bp (°C/mmHg)	Analysis (%) Found (Calcd.) C	H	N	NMR (δ, J in Hz)
2a	78-79	72.94 (73.01	7.98 7.88	12.35 12.17)	1.26 (3H, t, 8, CH_3), 2.76 (2H, q, 8, $C\underline{H}_2CH_3$), 2.5—3.5 (4H, br m, NCH_2), 3.5—4.1 (4H, br m, OCH_2), 6.16 (1H, br s, H-1), 6.37 (1H, m, H-6), 6.53 (1H, m, H-7), 7.17 (1H, m, H-8), 7.98 (1H, m, H-5)
2b	190/3	79.03 (78.90	8.92 8.83	11.97 12.27)	1.28 (3H, t, 8, CH_3), 1.2—2.0 (6H, br m, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.77 (2H, q, 8, $C\underline{H}_2CH_3$), 2.9—3.3 (4H, br m, NCH_2), 6.16 (1H, s, H-1), 6.36 (1H, m, H-6), 6.52 (1H, m, H-7), 7.16 (1H, m, H-8), 7.93 (1H, m, H-9)
2c	160/3	77.52 (77.73	9.25 9.32	12.96 12.95)	0.93 (6H, t, 7, $NCH_2C\underline{H}_3$), 1.26 (3H, t, 8, $CCH_2C\underline{H}_3$), 2.67 (2H, q, 8, CCH_2), 3.13 (4H, q, 7, NCH_2), 6.20 (1H, s, H-1), 6.33 (1H, m, H-6), 6.50 (1H, m, H-7), 7.15 (1H, m, H-8), 8.00 (1H, m, H-5)
2d	180/2	78.68 (78.46	8.26 8.47	13.06 13.07)	1.3—2.0 (6H, br m, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.36 (3H, s, CH_3), 2.9—3.4 (4H, br m, NCH_2), 6.13 (1H, s, H-1), 6.40 (1H, m, H-6), 6.56 (1H, m, H-7), 7.18 (1H, m, H-8), 7.98 (1H, m, H-5)
2e	85-86	82.57 (82.57	7.30 7.29	10.09 10.14)	1.64 (6H, br m, $NCH_2C\underline{H}_2C\underline{H}_2$), 3.00 (4H, br m, NCH_2), 6.34 (1H, m, H-1), 6.42 (1H, m, H-6), 6.56 (1H, m, H-7), 7.1—7.6 (6H, m, C_6H_5 and H-8), 7.86 (1H, m, H-5)
2f	107	72.44 (72.19	7.62 7.46	12.89 12.95)	2.35 (3H, s, CH_3), 2.8—3.1 (4H, br m, NCH_2), 3.8—4.0 (4H, br m, OCH_2), 6.28 (1H, s, H-2), 6.3—6.6 (2H, m, H-6 and H-7), 7.24 (1H, m, H-8), 7.80 (1H, m, H-5)
2g	62-64	78.51 (78.46	8.53 8.47	12.93 13.07)	1.4—1.9 (6H, br m, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.30 (3H, s, CH_3), 2.7—3.0 (4H, br m, NCH_2), 6.16 (1H, s, H-2), 6.2—6.5 (2H, m, H-6 and H-7), 7.1—7.3 (1H, m, H-8), 7.6—7.8 (1H, m, H-5)
2h	109-110	77.42 (77.67	6.61 6.52	10.04 10.07)	2.9—3.3 (4H, br m, $NC\underline{H}_2$), 3.8—4.1 (4H, m, $OC\underline{H}_2$), 6.5—6.9 (2H, m, H-6 and H-7), 6.70 (1H, s, H-2), 7.0—8.2 (7H, m, C_6H_5, H-8, and H-5)
2i	95-96	82.32 (82.57	7.36 7.29	9.90 10.04)	1.5—2.0 (6H, br m, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.7—3.4 (4H, br m, NCH_2), 6.4—6.9 (2H, m, H-6 and H-7), 7.64 (1H, s, H-2), 7.1—8.1 (7H, m, C_6H_5, H-8 and H-5)
2j	180/0.001	81.61 (81.78	7.62 7.63	10.49 10.64)	1.04 (6H, t, 8, CH_3), 2.9—3.3 (4H, br m, CH_2), 6.4—6.9 (2H, m, H-6 and H-7), 6.74 (1H, s, H-2), 7.1—8.3 (7H, m, C_6H_5, H-8 and H-5)
2k	250/0.00001	84.44 (84.58	6.44 6.45	9.12 8.97)	4.12 (4H, s, CH_2), 6.2—6.7 (4H, m, H-1, H-2, H-6 and H-7), 7.0—7.5 (11H, m, C_6H_5 and H-8), 7.9—8.1 (1H, m, H-5)
2l	130/3	77.61 (77.73	9.39 9.32	12.93 12.95)	0.97 (12H, d, 7, CH_3), 3.48 (2H, septet, 7, CH), 6.3—6.7 (4H, m, H-1, H-2, H-6 and H-7), 7.1—7.3 (1H, m, H-8), 8.1—8.3 (1H, m, H-5)

2-Ethyl-3-(2-pyridyl)-2-propen-1-ol (**5b**)——Similar treatment with ethyl bromide (3.6 g), Mg (0.73 g) and CuBr (0.05 g) gave 1.34 g (71%) of **5b** (bp 150°C/1 mmHg). Picrate 130—131°C (from iso-Pr_2O–MeOH).

2-Phenyl-3-(2-pyridyl)-2-propen-1-ol (**5c**)——Phenyl bromide (5.2 g), Mg (0.73 g) and CuBr (0.05 g) were treated as above to give 1.40 g (62%) of **5c** as colorless needles. mp 95—96°C (from iso-Pr_2O).

2-Chloro-3-(2-pyridyl)-2-propen-1-ol (**5d**)——A solution of **4** (1.30 g) in conc. HCl (25 ml) was heated at 80°C for 16 h with stirring. After neutralization with K_2CO_3, the aqueous solution was extracted with methylene chloride. The extracts were dried over K_2CO_3 and evaporated to dryness to give 1.43 g (72%) of **5d** as colorless needles of mp 66°C (from ether).

2-(2-Pyridyl)-3-buten-2-ol (**7a**)——A solution of 2-acetylpyridine (**6a**, 4.8 g) dissolved in tetrahydrofuran (THF) (20 ml) was added to a THF solution (50 ml) of Grignard reagent (prepared from 2.0 g of Mg and excess vinyl bromide). The mixture was heated at 45°C for 14 h with stirring. Ice-water was added to the mixture and after removal of the THF by evaporation, aq. HCl was added. The mixture was neutralized with K_2CO_3 and extracted with methylene chloride. The extracts were dried over K_2CO_3 and evaporated to dryness. The residue was chromatographed over aluminum oxide (hexane–ether) to give 3.92 g (66%) of **7a** as a colorless oil. Further purification was performed by distillation (bp 104—106°C/13 mmHg).

NMR ($CDCl_3$) δ: 1.64 (3H, s), 5.0—5.6 (1H, br s), 5.11 (1H, dd, J=10 Hz, J=1.5 Hz), 5.36 (1H, dd, J=17 Hz, J=1.5 Hz), 6.12 (1H, dd, J=17 Hz, J=10 Hz), 7.1—7.5 (2H, m), 7.6—7.8 (1H, m), 8.4—8.65 (1H, m). Picrate mp 138—139°C (from ethyl acetate). *Anal.* Calcd for $C_{15}H_{14}N_4O_8$ (picrate): C, 47.62; H, 3.73; N, 14.81. Found: C, 47.53; H, 3.71; N, 14.71.

1-Phenyl-1-(2-pyridyl)-2-propen-1-ol (**7b**)——A solution of 2-benzoylpyridine (**6b**, 7.32 g) dissolved in THF (20 ml) was added to a THF solution (50 ml) of the Grignard reagent (prepared from 2.0 g of Mg and

excess vinyl bromide). The mixture was worked up as described above to give 6.8 g (84%) of **7b** as a colorless oil of bp 120°C/3 mmHg. NMR ($CDCl_3$) δ: 5.5—6.1 (1H, br s), 5.2—5.5 (2H) and 6.4—6.8 (1H) [ABXm, $J_{AB}=1.5$ Hz, $J_{AX}=17$ Hz, $J_{BX}=10$ Hz], 7.0—7.9 (8H, m), 8.5—8.7 (1H, m). *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.41; H, 6.32; N, 6.52.

3-(2-Pyridyl)-2-buten-1-ol (5e)——A solution of **7a** (3.0 g) dissolved in 10% H_2SO_4 (150 ml) was refluxed for 3 d. The solution was neutralized by adding $NaHCO_3$ and extracted with methylene chloride. The extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was subjected to aluminum oxide column chromatography (hexane–ether) to give 2.01 g (67%) of **5e** as a colorless oil of bp 108°C/1 mmHg.

3-Phenyl-3-(2-pyridyl)-2-propen-1-ol (5f)——A solution of **7b** (4.0 g) dissolved in 10% H_2SO_4 (250 ml) was treated as described above to give 1.8 g (45%) of **5f** as a yellow oil of bp 200°C/0.01 mmHg.

Picrate mp 142—143°C (from ethyl acetate).

2-Methyl-3-(2-pyridyl)-2-propenal (3a)——A mixture of **5a** (1.06 g), active MnO_2[7] (5 g) and chloroform (30 ml) was stirred at room temperature for 2 h. The precipitated materials were filtered off, the filtrate was concentrated and the residue was subjected to chromatography on a short column of silica gel (hexane–ether) to give 0.98 g (90%) of **3a** as colorless needles of mp 39—40°C (from hexane).

2-Ethyl-3-(2-pyridyl)-2-propenal (3b)——A mixture of **5b** (1 g) and MnO_2 (5 g) in chloroform (30 ml) was treated as described above to give 0.90 g (90%) of **3b** as a colorless oil of bp 110°C/0.6 mmHg. Picrate mp 180°C (from ethyl acetate).

2-Phenyl-3-(2-pyridyl)-2-propenal (3c)——A mixture of **5c** (1 g) and MnO_2 (5 g) in chloroform (30 ml) was treated as described above to give 0.95 g (95%) of **3c** as colorless needles. mp 80—81°C (from hexane).

2-Chloro-3-(2-pyridyl)-2-propenal (3d)——A mixture of **5d** (2.78 g) and MnO_2 (25 g) in chloroform (40 ml) was treated as described above to give 1.77 g (64%) of **3d** as colorless needles of mp 56—61°C (from hexane).

3-(2-Pyridyl)-2-butenal (3e)——A mixture of **5e** (1.3 g) and MnO_2 (6 g) in chloroform (50 ml) was treated as described above to give 1.25 g (97%) of **3e** as a colorless oil of bp 120°C/1 mmHg.

3-Phenyl-3-(2-pyridyl)-2-propenal (3f)——A mixture of **5f** (0.82 g) and MnO_2 (4 g) in chloroform (100 ml) was treated as described above to give 0.72 g (88%) of **3f** as colorless needles of mp 75—76°C (from hexane).

General Procedure for the Reaction of 3a—f with Secondary Amine——A solution of titanium tetrachloride (0.05 ml) in benzene (1 ml) was added to a mixture of **3a—f** (0.0005 mol) and secondary amine (0.8 ml) in benzene (3 ml) under a nitrogen atmosphere with cooling. The mixture was heated at 70°C (**3a, b** and **3d—f**) or refluxed (**3c**) for 16 h with stirring. The insoluble materials were filtered off and the filtrate was evaporated to dryness. The residue was subjected to aluminum oxide column chromatography (hexane–ether) to give a somewhat air-sensitive yellow oil or needles. The material was purified by distillation or recrystallization (from MeOH) to give 3-(dialkylamino)indolizines (**2a—k**).

Reaction of 3b with Morpholine——A solution of **3b** (0.08 g) and morpholine (0.8 ml) in benzene (3 ml) was heated at 70°C for 16 h. The solution was evaporated to dryness and the residue was subjected to aluminum oxide column chromatography to give 0.022 g (19%) of 2-ethyl-3-morpholinoindolizine (**2a**) as yellow needles of mp 78—79°C (from MeOH). When $FeCl_3$ (0.081 g), $MgCl_2$ (0.048 g), $AlCl_3$ (0.067 g), $ZnCl_2$ (0.068 g) or CuBr (0.067 g) was present during this operation, the yields of **2a** were 0.077 g, 0.084 g, 0.099 g, 0.085 g and 0.042 g, respectively.

Reaction of 3d with Piperidine——A mixture of **3d** (0.167 g), piperidine (1.6 ml) and titanium tetrachloride (0.1 ml in 2 ml of benzene) in 6 ml of benzene was treated as described in the general procedure to give a tar. Attempts to isolate the product failed.

Acknowledgement This work was supported in part by a Grant-in-Aid (No. 56570729) for Scientific Research from the Ministry of Education, Science and Culture of Japan, which is gratefully acknowledged.

References and Notes

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