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One-step Synthesis of 3-(Dialkylamino)indolizines by the Palladium-catalyzed Reaction of α-Bromopyridine, Propargyl Alcohol, and Secondary Amine[1]

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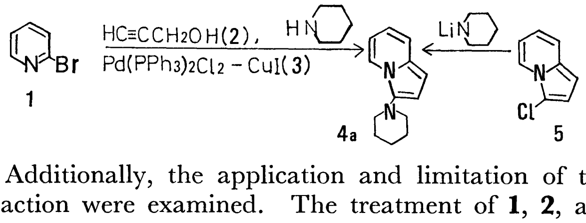
3-(Dialkylamino)indolizines were synthesized in one step by the reaction of 2-bromopyridine, propargyl alcohol, and secondary amines in the presence of $Pd(PPh_3)_2Cl_2$–CuI as a catalyst. 3-(2-Pyridyl)-2-propyn-1-ol and 3-(2-pyridyl)acrylaldehyde were suggested to be intermediates of the reaction. 3-Dialkylamino derivatives of pyrrolo[1,2-*a*]quinoline, pyrrolo[2,1-*a*]isoquinoline, and pyrrolo[1,2-*b*]pyridazine were obtained from the corresponding α-haloazaaromatics in a similar way.

Since the first preparation[2] of indolizine from α-picoline and acetic anhydride, various types of its derivatives have been synthesized by a number of methods undertaken from chemical,[3] pharmaceutical,[4] and physical[5] points of view.

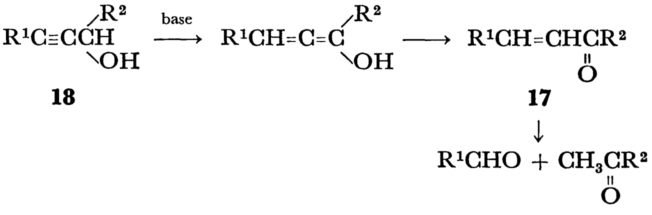
As for aminoindolizines, Hurst *et al.* prepared some of them in several steps in order to evaluate them biologically.[6] Nevertheless, a general synthetic method for aminoindolizine derivatives has not been established. During an examination of the alkynylation of α-haloazaaromatics with propargyl alcohol according to Sonogashira's method,[7] it was found that indolizine derivatives are unexpectedly formed instead of alkynylated products. In this paper, we describe a one-step synthesis of 3-(dialkylamino)indolizines by the reaction of α-haloazaaromatics, propargyl alcohol, and secondary amines, using $Pd(PPh_3)_2Cl_2$–CuI as a catalyst.

Results and Discussion

When 2-bromopyridine (**1**) and propargyl alcohol (**2**) were heated in piperidine with $Pd(PPh_3)_2Cl_2$–CuI (**3**), a somewhat air-sensitive yellow compound (**4a**) was obtained. Its NMR spectrum indicated the presence of a piperidino group and showed signals which were assigned to the protons on the indolizine-ring carbons. The maximum of its UV spectrum appeared at 241 nm ($\varepsilon = 2.4 \times 10^4$), similarly to that of indolizine.[8] On the basis of the elemental analysis and the above data, its structure was assumed to be piperidinoindolizine. Moreover, the position of the piperidino group in **4a** was synthetically confirmed. The product obtained from the reaction of 3-chloroindolizine(**5**)[9] with lithium piperidide was identical with **4a**, and the structure of **4a** was determined to be 3-piperidinoindolizine.



Additionally, the application and limitation of this reaction were examined. The treatment of **1**, **2**, and piperidine in the absence of the catalyst(**3**) did not afford **4a**. The reaction of **1** and **2** in the presence of **3** with other secondary amines, such as morpholine and diethylamine, afforded 3-morpholinoindolizine(**4b**) and 3-(diethylamino)indolizine(**4c**) respectively. However, the use of primary amines (*e.g.*, butylamine) did not afford the corresponding indolizines. The similar treatment of other α-haloazaaromatics, such as 2-chloroquinoline(**6**) and 1-chloroisoquinoline(**7**), in diethylamine afforded 3-(diethylamino)pyrrolo[1,2-*a*]quinoline(**8**) and 3-(diethylamino)pyrrolo[2,1-*a*]isoquinoline(**9**) respectively. Similarly, the reaction of 3-chloropyridazines (**10**—**12**), which have substituents at the 6-positions, in secondary amines afforded 2-substituted 7-(dialkylamino)pyrrolo[1,2-*b*]pyridazines (**13a**—**c**, **14**, and **15**). These results are shown in Table 1.



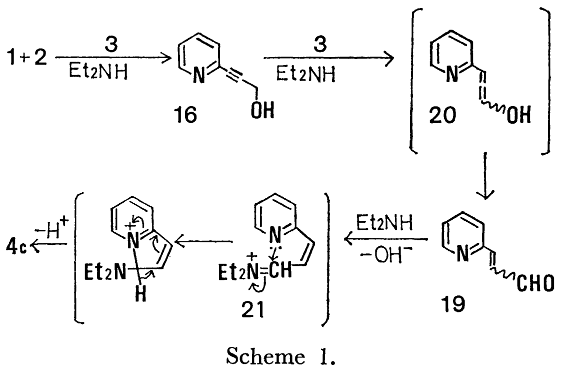
$$R^1C{\equiv}C\overset{R^2}{\underset{OH}{C}}H \xrightarrow{\text{base}} R^1CH{=}C{=}\overset{R^2}{\underset{OH}{C}} \longrightarrow R^1CH{=}CH\underset{O}{\overset{}{\underset{\|}{C}}}R^2$$

18 17

$$\downarrow$$

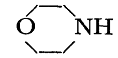
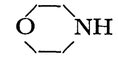
$$R^1CHO + CH_3\underset{O}{\underset{\|}{C}}R^2$$

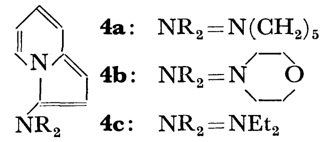
The mechanism of the formation of **4c** was investigated. It has been known that the halogen atoms of some haloazaaromatics are substituted with alkynyl groups by means of reactions with monosubstituted acetylenes, in the presence of amines and $Pd(PPh_3)_2Cl_2$–CuI (**3**) as catalysts.[7,10,11] Actually, the reaction of **1** with **2**, Et_2NH, and **3** under mild conditions (30 °C, for 16 h) afforded the 2-alkynylated pyridine, *i.e.*, 3-(2-pyridyl)-2-propyn-1-ol (**16**), in an 89% yield, although it was not obtained in the absence of **3**. When **16** was heated (80 °C, 16 h) in Et_2NH with **3**, the expected indolizine (**4c**) was obtained in a 15% yield, although heating **16** in Et_2NH in the absence of the catalyst did not give **4c** and the starting material was recovered.



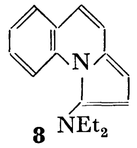
Scheme 1.

TABLE 1. SYNTHESIS OF 3-(DIALKYLAMINO)INDOLIZINE DERIVATIVES

	Halide	Amine	Conditions		Products	Yield (%)
			Temp/°C	Time/h		
1	2-Br-pyridine	$(CH_2)_5NH$	80	16	**4a**	36
			80	16	**4b**	12
		Et_2NH	70	3	**4c**	11
6	2-Cl-quinoline	Et_2NH	70	16	**8**	17
7	1-Cl-isoquinoline	Et_2NH	70	16	**9**	18
10	3-Cl-6-Me-pyridazine	Et_2NH	70	16	**13a**	49
		$(CH_2)_5NH$	70	16	**13b**	26
			70	16	**13c**	30
11	3-Cl-6-Ph-pyridazine	Et_2NH	70	16	**14**	13
12	3,6-Cl_2-pyridazine	Et_2NH	70	16	**15**	14



4a: $NR_2=N(CH_2)_5$
4b: $NR_2=N$
4c: $NR_2=NEt_2$



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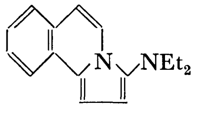

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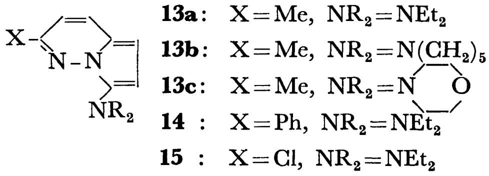

13a: X=Me, $NR_2=NEt_2$
13b: X=Me, $NR_2=N(CH_2)_5$
13c: X=Me, $NR_2=N$
14 : X=Ph, $NR_2=NEt_2$
15 : X=Cl, $NR_2=NEt_2$

TABLE 2. PROPERTIES OF 3-(DIALKYLAMINO)INDOLIZINE DERIVATIVES

4	Mp (°C) or bp (°C/mm)	Found (Calcd) (%)			NMR (δ, J in Hz)
		C	H	N	
4a	58	77.45 (77.96	8.19 8.05	13.78 13.99)	1.4—2.0(6H, brm), 2.7—3.1(4H, brm), 6.2—6.7(4H, m), 7.1—7.4(1H, m), 7.7—8.0(1H, m)
4b	85	71.48 (71.26	7.07 6.98	13.65 13.85)	2.8—3.1(4H, m), 3.7—4.0(4H, m), 6.2—6.7(4H, m), 7.1—7.4(1H, m), 7.7—8.0(1H, m)
4c	50/3	76.25 (76.55	8.41 8.57	14.69 14.88)	0.94(6H, t, J=6.9), 2.98(4H, q, J=6.9), 6.2—6.7(4H, m), 7.1—7.4(1H, m), 7.9—8.2(1H, m)
8	140/2	80.44 (80.63	7.66 7.61	11.50 11.76)	1.02(6H, t, J=6.9), 3.06(4H, q, J=6.9), 6.42(2H, s), 6.78(1H, d, J=9.3), 7.18(1H, d, J=9.3), 7.1—7.7(3H, m), 9.4—9.7(1H, m)
9	210/3	80.64 (80.63	7.82 7.61	11.74 11.76)	0.96(6H, t, J=6.3), 3.00(4H, q, J=6.3), 6.36(1H, d, J=4.5), 6.64(1H, d, J=7.5), 6.86(1H, d, J=4.5), 7.1—7.6(3H, m), 7.94(2H, m)
13a	100/1	70.40 (70.90	8.41 8.43	20.67 20.67)	1.00(6H, t, J=7.5), 2.38(3H, s), 3.24(4H, q, J=7.5), 6.10(1H, d, J=9.0), 6.30(2H, s), 7.40(1H, d, J=9.0)
13b	54—55	72.66 (72.52	7.80 7.96	19.37 19.52)	1.4—2.0(6H, brm), 2.40(3H, s), 3.0—3.3(4H, brm), 6.0—6.4(3H, m), 7.46(1H, d, J=9.0)
13c	53—54	66.64 (66.34	6.91 6.96	19.63 19.34)	2.40(3H, s), 3.0—3.4(4H, m), 3.7—4.0(4H, m), 6.14(1H, d, J=8.4), 6.1—6.4(2H, m), 7.45(1H, d, J=8.4)
14	oil[a)]	76.91 (76.94	7.36 7.22	15.63 15.84)	1.08(6H, t, J=7.2). 3.36(4H, q, J=7.2), 6.40(2H, s), 6.76(1H, d, J=9.0), 7.3—7.6(3H, m), 7.64(1H, d, J=9.0), 7.8—8.1(2H, m)
15	150/2	59.96 (59.06	6.52 6.31	18.86[b)] 18.78)	1.02(6H, t, J=7.2), 3.26(4H, q, J=7.2), 6.30(1H, J=9.0), 6.3—6.6(2H, m), 7.50(1H, d, J=9.0)

a) The compound could not be distilled at 200 °C under 0.01 mm. b) Because elemental analyses of this compound did not give satisfactory data, it was derived into **13a**. See Experimental.

Lappin[12)] has assumed that the conjugated ketones (**17**) were the intermediates in the degradation of β-acetylenic alcohols (**18**) with alkali to give aldehydes and methylketones.

Therefore, 3-(2-pyridyl)acrylaldehyde (**19**) was postulated as the intermediate of the reaction from **16** to **4c**; in fact, the alternatively available **19** gave **4c** (56%) on treatment with Et_2NH at room temperature.

On the basis of these observations, we propose that the reaction proceeds as is shown in Scheme 1.

The cross-coupling between **1** and propargyl alcohol in the presence of an amine and $Pd(PPh_3)_2Cl_2$–CuI might occur to give **16**, which is then transformed into **19** through the 1,3-migration of a hydrogen atom, followed by the ketonization of the allenic alcohol (**20**). The condensation of **19** and Et_2NH then affords the iminium ion (**21**), and an intramolecular cyclization of **21** gives **4c**.

Thus, we have established a one-step synthesis of novel types of indolizines, which are difficult to obtain, using easily available starting materials.

Experimental

The properties of the products are listed in Table 2. All the melting points are uncorrected. All the boiling points are represented by the bath temperature. The NMR spectra were recorded on Hitachi R-20 and R-22 instruments.

General Procedure of One-step Synthesis. A mixture of α-haloazaaromatic (5 mmol), propargyl alcohol (0.6 g, 11 mmol), $Pd(PPh_3)_2Cl_2$ (73 mg, 0.1 mmol), CuI (5 mg), and secondary amine (3 ml) was heated at 60—70 °C for 3—16 h with stirring under a nitrogen atmosphere. The solution was then evaporated to remove the excess amine. The residue was chromatographed over basic Al_2O_3 to give a yellow oil or crystals, and the material was purified by distillation or recrystallization (from pentane or MeOH) to give 3-(dialkylamino)indolizine.

3-Piperidinoindolizine (4a): 2-Bromopyridine (0.8 g, 5 mmol), propargyl alcohol (0.6 g, 11 mmol), $Pd(PPh_3)_2Cl_2$ (73 mg, 0.1 mmol), and CuI (5 mg) were heated in piperidine (3 ml) at 80 °C for 16 h with stirring under a nitrogen atmosphere. The solution was then evaporated, and the residue was chromatographed over basic Al_2O_3 with hexane–ether (50:1) to give yellow crystals (**4a**); yield, 0.36 g (36%); mp 58 °C (pentane).

*2-Chloro-7-(diethylamino)pyrrolo[1,2-*b*]pyridazine (15)*: 3,6-Dichloropyridazine (0.75 g, 5 mmol), propargyl alcohol (0.6 g, 11 mmol), $Pd(PPh_3)_2Cl_2$ (73 mg, 0.1 mmol), and CuI (5 mg) were heated in Et_2NH (3 ml) at 70 °C for 16 h. A work-up similar to that used before afforded 2-chloro-7-(diethylamino)pyrrolo[1,2-*b*]pyridazine (**15**) as a yellow oil [bp 150 °C (2 mmHg)] in a yield of 0.16 g (14%).

*Synthesis of 2-Methyl-7-(diethylamino)pyrrolo[1,2-*b*]pyridazine (13a) from 15*: Ni(dppp)Cl_2 (3 mg) was added to a solution of MeMgI prepared from Mg (28 mg) and MeI (150 mg) in ether (3 ml). A solution of **15** (112 mg) was stirred, drop by drop, into the reaction mixture under a nitrogen atmosphere. The oil obtained by the usual work-up[13] was found to be identical with 2-methyl-7-(diethylamino)pyrrolo-[1,2-*b*]pyridazine (**13a**) by TLC, IR, and NMR.

Reaction of 3-Chloroindolizine (5) and Lithium Piperidide. Ten ml of a solution containing BuLi (15% in hexane) was added dropwise into a solution of piperidine (0.85 g in 10 ml of THF) under a nitrogen atmosphere, with cooling in a Dry Ice–acetone bath. The mixture was allowed to stand at room temperature for 30 min and then cooled again in a Dry Ice–acetone bath. A solution of 3-chloroindolizine (**5**, 0.75 g in 10 ml of THF) was then stirred in, drop by drop. Then the mixture was allowed to stand at room temperature for 16 h, and H_2O (0.5 ml) was added dropwise to the mixture. After filtration and evaporation, the residue was purified by basic Al_2O_3 column chromatography with hexane–ether (20:1), followed by silica-gel chromatography (hexane), to give a compound which was found to be identical with **4a** by means of its NMR and IR spectra and melting point.

Reaction of 3-Chloro-6-methylpyridazine with $BuNH_2$. A mixture of 3-chloro-6-methylpyridazine (0.65 g), propargyl alcohol (0.6 g), $Pd(PPh_3)_2Cl_2$ (73 mg), CuI (5 mg), and $BuNH_2$ (3 ml) was heated at 70 °C for 16 h with stirring under nitrogen. The solution was then evaporated to give a tar. Attempts to isolate products failed.

Reaction of 2-Bromopyridine and Propargyl Alcohol in Et_2NH at 30 °C. A mixture of 2-bromopyridine (1.6 g), propargyl alcohol (1.2 g), $Pd(PPh_3)_2Cl_2$ (146 mg), CuI (10 mg), and Et_2NH (30 ml) was stirred at 30 °C for 16 h under nitrogen. After the filtration of crystals (diethylamine hydrobromide), the filtrate was evaporated and the residue was chromatographed on silica gel with CH_2Cl_2 to give crystals. Recrystallization from ether gave 3-(2-pyridyl)-2-propyn-1-ol; mp 82—83 °C (lit,[14] 82—82.5 °C); yield, 1.2 g (89%). When either $Pd(PPh_3)_2Cl_2$ or CuI was absent, the reaction did not proceed.

Reaction of 3-(2-Pyridyl)-2-propyn-1-ol and Et_2NH. A mixture of 3-(2-pyridyl)-2-propyn-1-ol (0.65 g), Et_2NH (3 ml), $Pd(PPh_3)_2Cl_2$ (73 mg), and CuI (5 mg) was heated at 80 °C for 4 h with stirring under nitrogen. The solution was evaporated, and the residue was chromatographed over basic Al_2O_3 with hexane–ether (50:1) to give 3-(diethylamino)indolizine (**4c**); yield, 0.14 g (15%). A similar operation in the absence of $Pd(PPh_3)_2Cl_2$ and CuI did not give **4c**; rather the starting material was recovered.

Reaction of 3-(2-Pyridyl)acrylaldehyde and Et_2NH. A solution of 3-(2-pyridyl)acrylaldehyde (230 mg) in Et_2NH was allowed to stand at room temperature (26 °C) for 30 min under nitrogen. The solution was then evaporated below 35 °C, and the residue was chromatographed over basic Al_2O_3 with hexane to give 170 mg (56%) of **4c**.

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