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ONE-STEP SYNTHESIS OF 3-DIALKYLAMINOINDOLIZINES

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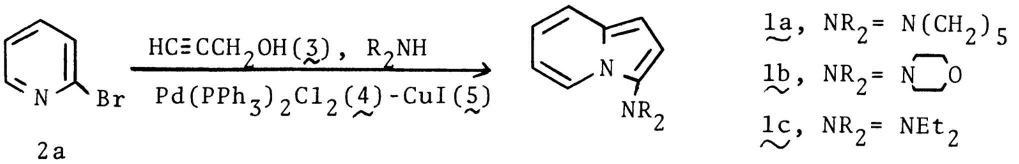
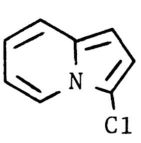
3-Dialkylaminoindolizines, pyrrolo[1,2-*a*]quinoline, pyrrolo[2,1-*a*]isoquinoline, and 2-methyl-pyrrolo[1,2-*b*]pyridazine were obtained from the corresponding α-halo-azaaromatics, propargyl alcohol and secondary amines in the presence of catalytic amounts of $Pd(PPh_3)_2Cl_2$ and CuI.

The general method for the preparation of aminoindolizines has not been established although considerable attention has been given to indolizines and a number of their derivatives have been synthesized in view of physical,$^{1)}$ chemical,$^{2)}$ and biochemical$^{3)}$ interests.

We report here a one-step synthesis of 3-dialkylaminoindolizines (**1a**-**e**) and a 5-aza analogue (**1f**) from α-halo-azaaromatics.



2a



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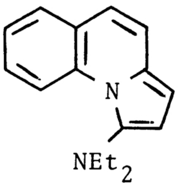
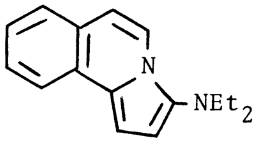
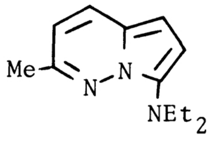


1d



1e



1f

A mixture of 2-bromopyridine (2a, 0.8 g, 5 mmol), propargyl alcohol (3, 0.6 g, 11 mmol), piperidine (3 ml),[4] $Pd(PPh_3)_2Cl_2$ (4, 0.073 g, 0.1 mmol), and CuI (5, 0.005 g, 0.025 mmol) was heated (80°C for 16 h), and purification of the products using chromatography (basic Al_2O_3) gave a somewhat air-sensitive solid (1a, yield 0.36 g, 36 %, needles from hexane, mp 58°C).[5]

The structure of 1a inclusive of the position where the piperidino group was introduced was synthetically confirmed. Namely, the product which was obtained (ca. 5 % yield) by the aminolysis ($C_5H_{10}NLi$/THF) of 3-chloroindolizine (6)[6] was identical with 1a. Other 3-dialkylaminoindolizines (1b-e) were obtained in a similar way and 3-chloro-6-methylpyridazine (2d) was also transformed into 1f as shown in the Table.

Table. Preparetion of dialkylaminoindolizines

Halide	Amine	Conditions °C	hr	Product	Yield(%)	Remark
2a 2-Br-pyridine	$(CH_2)_5NH$	80	16	1a	36	mp 58°C
		80	16	1b	12	mp 85°C
	Et_2NH	70	3[a]	1c	11	bp_3 50°C[b]
2b 2-Cl-quinoline	Et_2NH	70	16	1d	17	bp_2 140°C
2c 1-Cl-isoquinoline	Et_2NH	70	16	1e	18	bp_3 210°C
2d 3-Cl-6-Me-pyridazine	Et_2NH	70	16	1f	49	bp_1 100°C

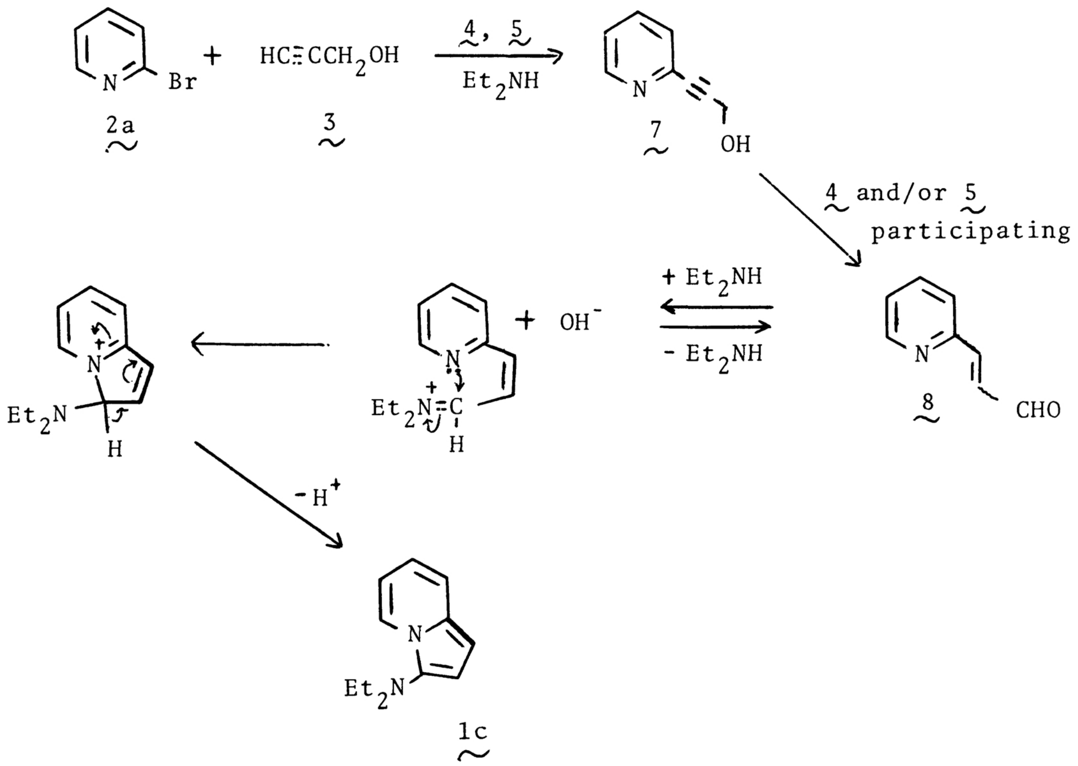
a) Prolonged reaction time (16 h) lowered the yield.
b) All boiling points present bath temperature.

The mechanism of the formation of 1c could be explained by the scheme in the Chart (next page). It has been known that the α-halo-azaaromatics undergo alkynylation with monosubstituted acetylenes in the presence of amines and $Pd(PPh_3)_2Cl_2$-CuI,[7] and actually, the reaction of 2a with 3, Et_2NH, 4, and 5 under a mild condition (30°C for 16 h) afforded the 2-alkynylated pyridine, i.e., 3-(2-pyridyl)-2-propyn-1-ol (7, 89 %),[8] although 7 was not obtained in the absence of either 4 or 5.

When 7 was heated (80°C, 16 h) in Et_2NH with 4 and 5, the expected indolizine (1c) was obtained in 15 % yield. Heating of 7 in Et_2NH did not give 1c and the starting material was recovered.

These observations support the idea that 7 is formed initially and subsequent ring closure of 7 to 1c requires the catalysts although their roles in the postulated course are as yet unclear.

Moreover, the fact that the alternatively available 2-(2-pyridyl)acrylaldehyde (8)[9] gave 1c (56 %) on treatment with Et_2NH at room temperature suggests that 8 might be the intermediate in the cyclization of 7 to 1c. Further investigation on the mechanism is in progress.



References and Notes

1) For example, A. Gamba and G. Favini, Gazz. Chim. Ital., **98**, 167 (1968) and references therein.

2) T. Uchida and K. Matsumoto, Synthesis, 209 (1976) and references therein.

3) E. Wenkert, Chem. and Ind., 1088 (1953).

4) The use of primary amines did not afford the expected products.

5) UV spectrum of **1a** (EtOH); 241 nm (ε=3.8 x 10^4), IR ($CHCl_3$); 2800-3000 (ν_{C-H}) and 1628 cm^{-1} ($\nu_{C=C}$), ^{1}H-NMR ($CDCl_3$); δ 1.4-2.0 (6H, br. m), 2.7-3.1 (4H, br. m), 6.2-6.7 (4H, m), 7.1-7.4 (1H, m), and 7.7-8.0 (1H, m).

6) K. B. Nielsen, Acta Chem. Scand., **B31**, 224 (1977); 3-chloroindolizine was obtained from the reaction of 2-vinylpyridine and dichlorocarbene in very low yield.

7) a) K. Sonogashira, Y. Tohda, and N. Hagihara, Tetrahedron Letters, 4467 (1975),
b) K. Edo, H. Yamanaka, and T. Sakamoto, Heterocycles, **9**, 271 (1978),
c) Y. Abe, A. Ohsawa, H. Arai, and H. Igeta, Heterocycles, **9**, 1397 (1978).

8) Formation of **1c** was negligible.

9) I. Hagedorn and W. Hohler, Angew. Chem., **87**, 486 (1975); the preparation of **8** from commercially available materials requires three steps and the overall yield of **8** is far lower than those shown in the Table.

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