Facile Dehydrogenative Dimerization of Indolizine Derivatives

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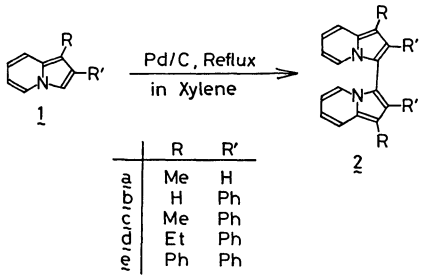
Synopsis. Treatment of 3-unsubstituted indolizines with a dehydrogenating agent such as palladium on carbon in refluxing xylene gave the corresponding 3,3′-biindolizine derivatives in 19—74% yields.

It is well known that indolizines react smoothly at the 3-position with various electrophiles, as observed, for example, in the cycloaddition and the Michael addition with electron-poor olefins[1-3] and substitution with diazonium salts[4] or an acylating agent.[5] In order to study nitrogen-bridged heterocycles, a method for direct functionalization of indolizine derivatives was required. Attempts to obtain the corresponding adducts by the reactions of an indolizine with electron-poor olefins such as diethyl fumarate and ethyl cinnamate under various conditions were unsuccessful. However, in the reaction in the presence of a dehydrogenating agent, an unexpected product, *i.e.* a dimer of the indolizine was obtained. In this note we wish to report a facile dehydrogenative dimerization of some 3-unsubstituted indolizine derivatives and the structural assignment of the resulting biindolizines.

When the reaction of 1-methylindolizine (**1a**) with diethyl fumarate or ethyl cinnamate was carried out in refluxing xylene in the presence of palladium on carbon (Pd/C), a product (**2a**, pale yellow needles), mp 144—145 °C, was separated as the only isolable compound. Elementary analysis (Table 1), and the mass spectrum (M^+ 260) of the product show that **2a** is a bimolecular dehydrogenative coupling product from **1a**. The same product (**2a**) was also formed by the reaction of **1a** with Pd/C in the absence of the olefin in 38% yield. In order to confirm the generality of this reaction, we carried out the reactions of some indolizines with Pd/C. As expected, the corresponding pale yellow products (**2b—e**) were formed from 2-phenyl- (**1b**), 1-methyl-2-phenyl- (**1c**), 1-ethyl-2-phenyl- (**1d**), and 1,2-diphenyl-indolizine (**1e**), respectively. Elementary analyses and mass spectra (Table 1) of **2b—e** were also in accord with the expected structures. The site of the coupling in these biindolizines (**2a—e**) was determined mainly by means of their NMR spectral data (Table 2): For example, the NMR spectrum of **2a** exhibited signals at δ 6.40 (2H, dt, J=7.0, 7.0, and 1.5 Hz, 6-H and 6′-H), 6.71 (2H, br t, J=9.0 and 7.0 Hz, 7-H and 7′-H), 7.46 (2H, br d, J=9.0 Hz, 8-H and 8′-H), and 7.72 (2H, br d, J=7.0 Hz, 5-H and 5′-H) due to the protons on the pyridine rings, and at δ 2.43 (6H, s, 1-Me and 1′-Me) and 6.86 (2H, s, 2-H and 2′-H) due to the methyl groups and the protons on the pyrrole rings. As compared with the original 1-methylindolizine (**1a**),[6] in particular, the disappearance of the 3- and 3′-protons and the absence of the coupling of the 2- and 2′-protons (δ 6.86, singlet) in **2a** are ultimate evidences that **2a** is 3,3′-biindolizine derivative. Furthermore, distinct symmetrical structures of **2a—e** were also suggested by their IR spectra in which only a few weakened absorption bands appear in contrast with those of **1a—e**. From these results we conclude the structures of **2a—e** to be 3,3′-biindolizines.



Scheme 1.

Similar reactions of aromatic substrates by the action of palladium(II) compounds[7,8] are well established, but that with Pd(O) as described above is unprecedent. The dehydrogenative dimerization with Pd/C is of interest and high synthetic value because of its simplicity and low cost, though the yields were not satisfactory.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalysis was carried out in a Perkin-Elmer 240 Elemental Analyzer. NMR spectra were determined with a Varian EM360A NMR spectrometer in deuteriochloroform with tetramethylsilan as an internal standard, chemical shifts being expressed in terms of δ, mass spectra with a JEOL LMS-01SG-2 mass spectrometer with a JEC-6 spectrocom-

Table 1. Data of 3,3′-biindolizine derivatives

Compd No.	Yield %	Mp/°C	ν/cm^{-1}(KBr)			M^+	Formula	Calcd (%)			Found (%)		
								C	H	N	C	H	N
2a	38	144—145	1436	1420	732	260	$C_{18}H_{16}N_2$	83.04	6.20	10.76	82.91	6.30	10.70
2b	19	169—171	1600	1449	1336	384	$C_{28}H_{20}N_2$	87.47	5.24	7.29	87.29	5.31	7.26
2c	35	244—246	1595	1435	1336	412	$C_{30}H_{24}N_2$	87.34	5.87	6.79	87.39	5.98	6.63
2d	38	194—196	1596	1437	1339	440	$C_{32}H_{28}N_2$	87.23	6.41	6.36	86.94	6.53	6.26
2e	74	230—231	1598	1520	1340	536	$C_{40}H_{28}N_2$	89.52	5.26	5.22	89.33	5.52	5.14

Table 2. Proton NMR spectra of 3,3′-biindolizine derivatives

2a	2.43(6H, s, 1-Me and 1′-Me), 6.40(2H. dt, J=7.0, 7.0, and 1.5 Hz, 6-H and 6′-H), 6.71(2H, br t, J= 9.0 and 7.0 Hz, 7-H and 7′-H), 6.86(2H, s, 2-H and 2′-H), 7.46(2H, br d, J=9.0 Hz, 8-H and 8′-H), and 7.72(2H, br d, J=7.0 Hz, 5-H and 5′-H).
2b	6.34(2H, dt, J=7.0, 7.0, and 1.5 Hz, 6-H and 6′-H), 6.80(2H, br t, J=9.0 and 7.0 Hz, 7-H and 7′-H), 7.03(2H, s, 1-H and 1′-H), and 7.1—7.7(14H, m, 2-Ph, 2′-Ph, 5-H, 5′-H, 8-H, and 8′-H).
2c	2.44(6H, s, 1-Me and 1′-Me), 6.40(2H, dt, J=7.0, 7.0, and 1.5 Hz, 6-H and 6′-H), and 6.6—7.7(16H, m, 2-Ph, 2′-Ph, 5-H, 5′-H, 7-H, 7′-H, 8-H, and 8′-H).
2d	1.19(6H, t, J=7.0 Hz, 2 $CH_2C\underline{H}_3$), 2.88(4H, q, J=7.0 Hz, 2 $C\underline{H}_2CH_3$), 6.40(2H, dt, J=7.0, 7.0, and 1.5 Hz, 6-H and 6′-H), and 6.6—7.7(16H, m, 2-Ph, 2′-Ph, 5-H, 5′-H, 7-H, 7′-H, 8-H, and 8′-H).
2e	6.3—8.1(28H, m).

puter attached, and IR spectra with a Hitachi 260—10 Infrared spectrophotometer.

Materials. Indolizines (**1b—2e**) were synthesized by the Tschitschibabin reaction of the corresponding 1-phenacylpyridinium bromides.[9-11] 1-Methylindolizine (**1a**)[12] was prepared in overall 45% yield by the reaction of 1-(ethoxycarbonylmethyl)-2-ethylpyridinium bromide with ethyl (ethoxymethylene)cyanoacetate in ethanol in the presence of potassium carbonate at 40—50 °C followed by acidic hydrolysis of the resulting ethyl 1-methylindolizine-3-carboxylate.

*Preparation of 3,3′-Biindolizines (**2a—e**).* General Method. A mixture of indolizine (2 mmol), palladium on carbon (5%, 0.8—1.0 g), and dry xylene (50 ml) was heated under reflux in a 100 ml round flask equipped with a condenser for 20—25 h and then cooled. Insoluble substances were removed from the reaction solution by filtration and the filtrate was concentrated at reduced pressure. The residue was separated carefully by column chromatography (alumina) using hexane and then ether as eluents. Recrystallization several times from ether–hexane gave the corresponding 3,3′-biindolizine derivatives as pale yellow needles (**2a**) or prisms (**2b—e**).

Similar treatment of the parent indolizine with Pd/C did not afford the expected 3,3′-biindolizine because of its instability.

These results and some properties of **2a—e** are given in Tables 1 and 2.

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