SYNTHESIS AND PROPERTIES OF PORPHYRIN-LINKED INDOLIZINE

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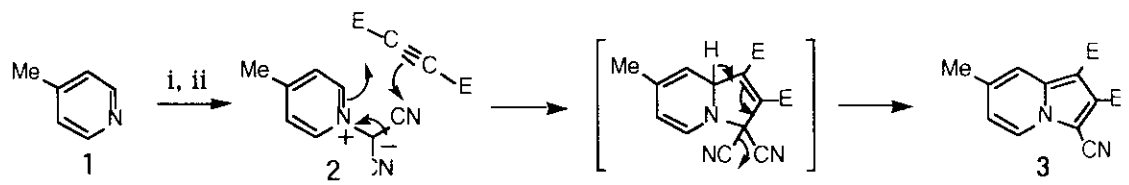
Abstract-The synthesis of porphyrin-linked indolizine has been achieved for the first time in a simple process from the reaction between a 5-formylindolizine (**8**) and dipyrrolomethane (**10**) giving the desired 1,7-bisindolidinoporphyrin (**12**). The electronic effect of the heterocyclic nuclei (**12**) is prominently observed in the Soret band of the UV−VIS spectrum. Temperature-dependence ^{1}H NMR analysis of **12** suggests the existence of an association of **12** causing restricted rotation around the bond between indolizine and porphyrin.

Keen interest has recently been paid to the chemistry of indolizine[1] and porphyrin[2] which are representative nuclei of heterocyclic compounds. Indolizine is isoelectronic with indole and undergoes an electrophilic attack, thus acting as an electrodonating group.[1] A new diversified function in the heterocycles would be generated and developed according to linkage of the both compounds in their peripheral region. Such new functions are expected to reveal the correlation of the effects of the steric environment of molecule and those of electronic properties. However, no trial of pinch bond formation between indolizine and porphyrin have been performed despite its importance. Thus, we have embarked on synthetic studies of a novel type of bisindolizines which have a porphyrin nucleus as a spacer to observe the effects due to the electronically changed heterocyclic structure. This paper describes the first synthesis of porphyrin-linked indolizine.

For a direct construction of pinch bonds between indolizine and porphyrin rings, we have employed a formylindolizine derivative and pyrrole, as the starting substrates. Our strategy is to build up the pinch

Scheme 1. A Facile Synthesis of Precursor, 1-Cyano-5-methylindolizine derivative (**3**).[a]



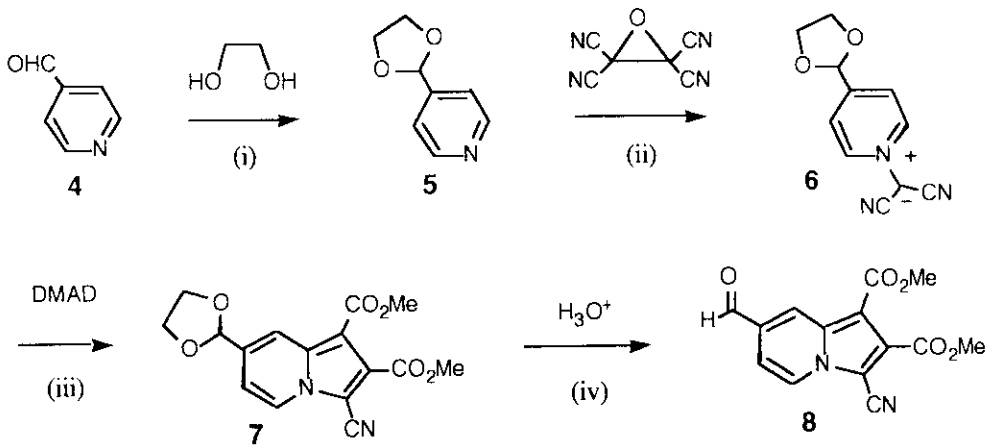
[a] Reagents and conditions: (i) TCNEO, THF, O °C, 5 h, 86%. (ii) DMAD, toluene, reflux, 17 h, 79%.

bondings between both the molecules by condensing a formylindolizine and heterocycles in a simple process.

In order to introduce the formyl function to an indolizine, we initially attempted to prepare the desired indolizine starting with 4-methylpyridine (**1**) (Scheme 1). Addition of **1** to tetracyanoethylene oxide[3] (TCNEO) gave 4-methylpyridinium dicyanomethyllide (**2**) whose 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) led to an exclusive formation of the desired precursor, 1-cyano-5-methylindolizine derivative (**3**) in good yield. However, neither the oxidation[4] of the methyl group of **3** with ceric(IV) ammonium nitrate (CAN) nor the reduction[5] of the cyano group with $LiAlH(OEt)_3$ to the desired formyl group were successful, leading to a complex mixture.

Scheme 2 illustrates the successful synthetic route to the desired starting material, 5-formylindolizine (**8**). Starting from 4-formylpyridine (**4**), the formyl group of the compound (**4**) was protected with ethylene glycol to form 4-(1,3-dioxolan-2-yl)pyridine (**5**) (93%) which reacted with TCNEO to afford the corresponding dicyanomethylide (**6**) (53%). 1,3-Dipolar cycloaddition of **6** with DMAD readily afforded the indolizine (**7**). The protecting group of 7 was released under acidic conditions in methanol to give the desired 5-formylindolizine (**8**) in 80% yield.

Scheme 2. Synthetic Route to 5-Formylindolizine (**6**)[a]



[a] Reagents and conditions: (i) ethylene glycol, *p*-TsOH, toluene, 110 °C, 21 h, 93%. (ii) TCNEO, THF, O °C, 2 h and rt 1 h, 53%. (iii) DMAD, CH_2Cl_2, rt, 3 d, 24%. (iv) MeOH/H_2O, *p*-TsOH, reflux, 3 h, 80 %.

Initially, we used a well-known method by Lindsay[6] to achieve the combination of both indolizine and porphyrin rings, and thus the reaction of **8** with pyrrole was performed. According to the traditional procedure, however, extensive attempts at the direct construction of a tetraindolizinylporphyrin were unsuccessful, only complex mixtures being obtained.

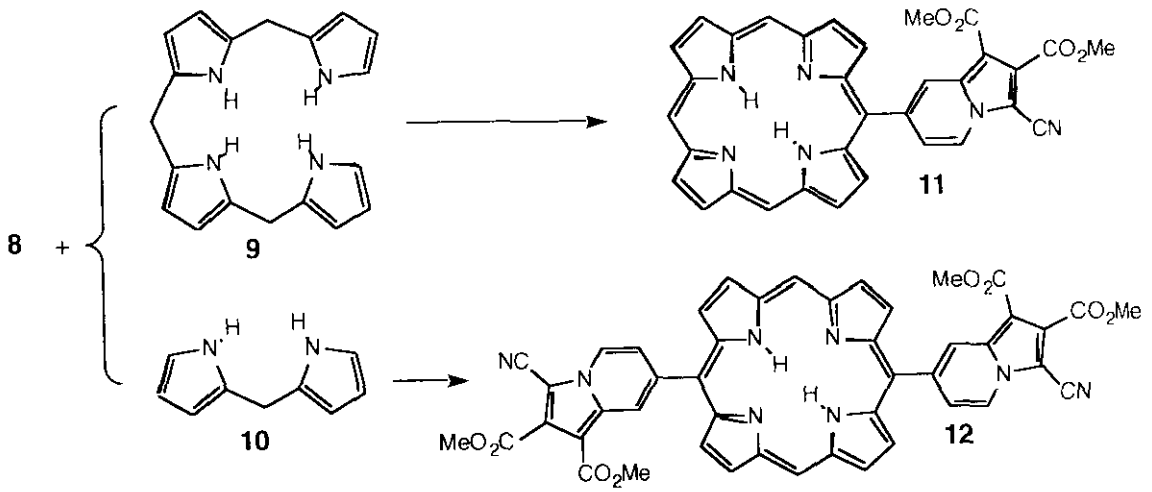
Instead of the conventional method using pyrrole itself, we have employed tetrapyrrolotrismethane (**9**) and dipyrrolomethane (**10**)[7] to improve the reactivity of the reactant as shown in Scheme 3. Table 1 summarizes the results along with the experimental conditions. The reaction between **8** and **9** in refluxing propionic acid (10^{-1} M) afforded a 1:1 adduct minus the elements H_2O in low yield (<1%). The compound obtained is identified to be **11** according to the MS (M+ m/z 566) and NMR data. On the other hand, the reaction

of **10** with **8** in refluxing CH_2Cl_2 led to the formation of the desired porphyrin (**12**)

Table 1. Reaction between *1*-Cyano-5-formylindlizine (**8**) and Dipyrrolomethanes (**9** and **10**).

entry	concentration (mol/L)	solvent	temperature (°C)	time	catalyst	yield (%)
1	10^{-1}	methanol	60	1 day	*p*-TsOH	complex mixture
2	10^{-1}	methanol	rt	1 day	*p*-TsOH	complex mixture
3	10^{-1}	acetic acid	reflux	1 day	----------	complex mixture
4	10^{-1}	propionic acid	reflux	2 h	----------	**11** (1%)
5	10^{-2}	CH_2Cl_2	rt	3 h	TFA	**12** (14%)

Scheme 3. Formation of Porphyrin-Linked Indolizines.[a]



[a] For experimental conditions, see entries 4 and 5 in Table 1.

in moderate yield (14 %) under dilute conditions (10^{-2} M). The MS (M$^+$ *m/z* 822) and NMR (^{1}H and ^{13}C) spectral dada show that the compound (**12**) is a 2:2 adduct minus the elements $(H_2O)_2$. ^{1}H NMR spectral data of **11** and **12** demonstrate that both the compounds link with indolizine(s) at 3- and 3,9-position in porphyrin, respectively.

The UV–VIS spectrum of the disubstituted porphyrin (**12**) exhibits the Soret band at 416 nm and the absorption shifts 13 nm to the red compared with that (403 nm) of the mono-substituted porphyrin (**11**). This shift is attributed to the electronic effect by the additional introduction of indolizine ring to the porphyrin. Variable-temperature ^{1}H NMR spectroscopy of **11** does not reveal any change in the chemical shifts of the methyl signals in the ester groups within the temperature rage 25–100 °C. In contrast, we have explicitly observed a prominent change in the ^{1}H NMR spectra of **12** depending on temperatures. At 25 °C, the spectrum of **12** indicates eight sharp-singlet signals due to the ester methyl groups, while they

do only two sharp singlets at an elevated temperature of 100 °C. At this temperature, complex signals due to porphyrin-ring protons coalesce and give a simple pattern. Dilution (10^{-4} M) of the sample also brings the signals to be sharp at 25 °C. These NMR spectroscopic behavior of **12** suggests strongly an association of the molecule which might cause the hindered rotations of the two pinch bonds between the indolizine and the porphyrin.

In summary, we have succeeded in synthesizing the porphyrin-linked indolizine (**12**) in a simple way. The diversified properties have been observed in the electronic and ^{1}H NMR spectroscopies.

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8. Selected spectroscopic data for the reported compounds. **11**: mp >300°C; ^{1}H NMR($CDCl_3$) δ 3.59 (s, 2 H), 3.83 (s, 3 H), 4.14 (s, 3 H), 8.07 (d, 1 H, J = 6.7 Hz), 8.70 (d, 1 H, J = 6.7 Hz), 9.0–9.12 (m, 3 H), 9.47–9.52 (m, 6 H), 10.33 (s, 1 H), 10.38 (s, 2 H); UV-VIS (CH_2Cl_2) λmax 403, 497, 530, 569, 641 nm. **12**: mp >300 °C; ^{1}H NMR($CDCl_3$, sealed tube, 100 °C) δ 3.20 (s, 2 H), 3.81 (s, 6 H), 4.12 (s, 6 H), 8.20–8.22 (m, 2 H), 8.94–8.98 (m, 4 H), 9.23 (d, 4 H, J = 4.6 Hz), 9.65 (d, 4 H, J = 4.6 Hz), 10.6 (s, 2 H); UV-VIS (CH_2Cl_2) λmax 416, 506, 543, 578, 634 nm.

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