REACTIONS OF 5-CYANO-1,4-DIPHENYLPYRIDAZINO[4,5-*a*]-INDOLIZINES WITH DIMETHYL ACETYLENEDICARBOXYLATE: REGIOSELECTIVE FORMATION OF 1:2 MICHAEL TYPE ADDUCTS

Kiyoshi Matsumoto*[a], Yukio Ikemi[b], Mitsuo Toda[a], Takane Uchida[c], and Akikazu Kakehi[d]

a Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-01, Japan

b College of Liberal Arts and Sciences, Kyoto University, Kyoto 606, Japan

c Faculty of Education, Fukui University, Fukui 910, Japan

d Faculty of Engineering, Shinshu University, Nagano 380, Japan

Abstract--Reactions of 5-cyano-1,4-diphenylpyridazino[4,5-*a*]indolizines with dimethyl acetylenedicarboxylate afforded regioselectively the 1:2 adducts in a Michael fashion rather than in a 1,3-dipolar manner. The structure was established by an X-ray crystallography.

Annulation of benzene ring at the 1,2-position proved to activate 3-cyanoindolizines as 1,3-dipolar species, probably because of aromatic stabilization in favor of the azomethine ylide structure (Scheme 1). Indeed, 6-cyanobenz[*a*]indolizines undergo smoothly 1,3-dipolar cycloaddition with activated alkynes such as dibenzoylacetylene[1] and dialkyl acetylenedicarboxylate.[2] Therefore, we expected that annulation of a heteroaromatic ring at the 1,2-position of 3-cyanoindolizine would also favor the azomethine ylide structure by means of aromatic stabilization. Since 1,2-pyridazine-fused 3-cyanoindolizines are readily available by 1,3-dipolar cycloaddition reactions of dicyanomethylides with dibenzoylacetylene, followed by treatment with hydrazine (Scheme 2),[1] we examined reactions of 1,4-diphenylpyridazino[4,5-*a*]indolizines with dimethyl acetylenedicarboxylate (DMAD).

Reaction of 1,4-diphenylpyridazino[4,5-*a*]indolizine (**1a**) with three equimolar amounts of DMAD in refluxing toluene for 14 h gave yellow crystals, mp 282-283°C. The mass spectral and microanalytical analysis established that the compound had a 1:2 adduct structure. Similarly, the 1:2 adducts were obtained in low to moderate yields from **1b-1f** with excess DMAD. The results are collected in Table 1. Initially, we assumed that the compounds had the structure (**2**), and could be formed by successive Michael type additions and subsequent cyclization (Scheme 3). There are precedents for this type of 1:2 structure being formed from nitrogen heterocycles such as azapentalenes[3] and azaazulenes.[4,5] However,

the ^{13}C value[6] of δ 116 does not seem to be high enough for an sp^3 secondary carbon. Furthermore, all attempts to convert the compounds to the corresponding [2.3.4]cyclazines failed. Fortunately, the 1:2 adduct obtained from the 1,4,8-triphenylpyridazino[4,5-*a*]indolizine (**1d**) formed suitable crystals for an X-ray analysis. An analysis of this adduct established that the compound had structure (**3d**) as shown in Figure 1.[7] No regioisomers (**4**) were unable to be isolated in our hands. Regiospecific formation of **3** could be explained by higher nucleophilicity of nitrogen at 2 position than that at 3 position due to the resonance hybrid (**5**), since the adducts probably arise from successive Michael additions shown in Scheme 4.

Table 1. 1:2 Adducts from 5-cyano-1,4-diphenylpyridazino[4,5-a]indolizines (**1**) and DMAD

1	R^1	R^2	R^3	Time (h)	Yield(%)	mp(°C)
a	H	H	H	14	43	282-283
b	H	Me	H	14	47	253-254
c	Me	H	Me	14	25	243-244
d	H	Ph	H	41	40	284-285
e	H	COPh	H	37	25	260-261
f	CH_2=CH-CH=CH_2		H	21	15	303-304

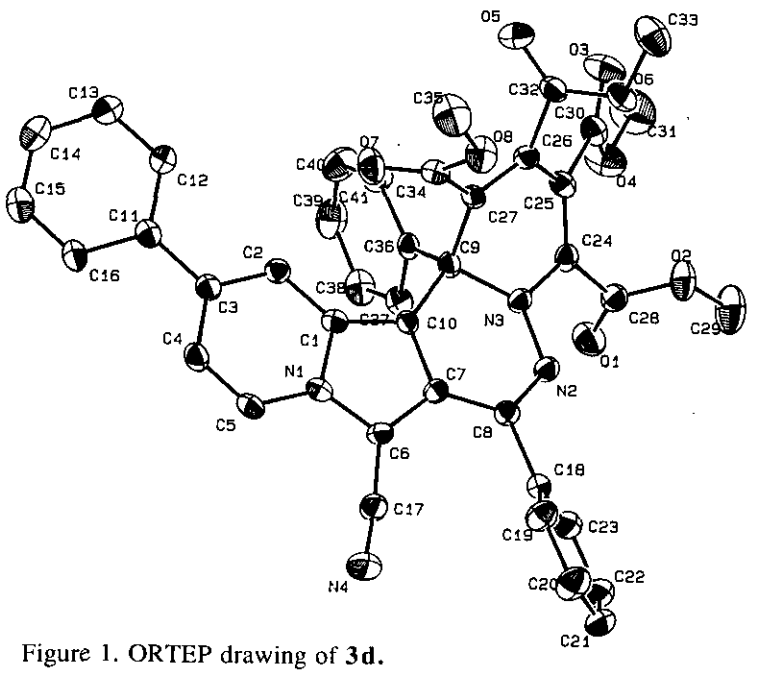
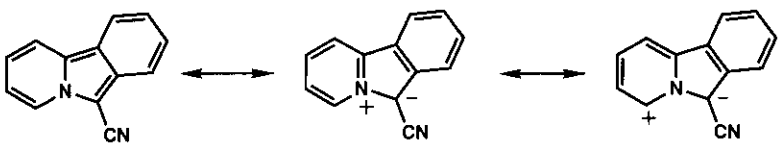
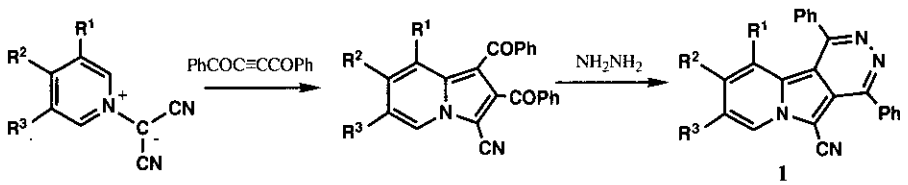


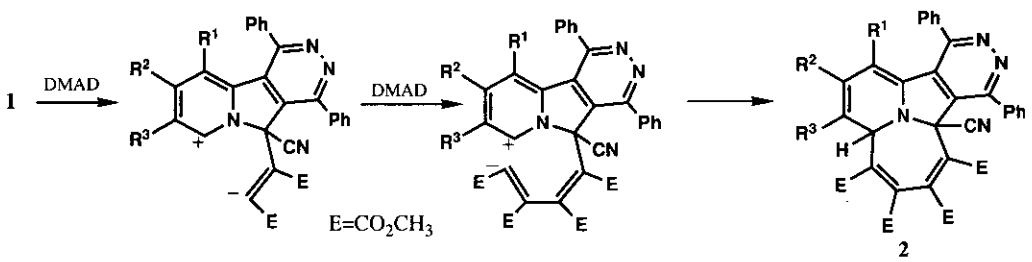
Figure 1. ORTEP drawing of **3d**.



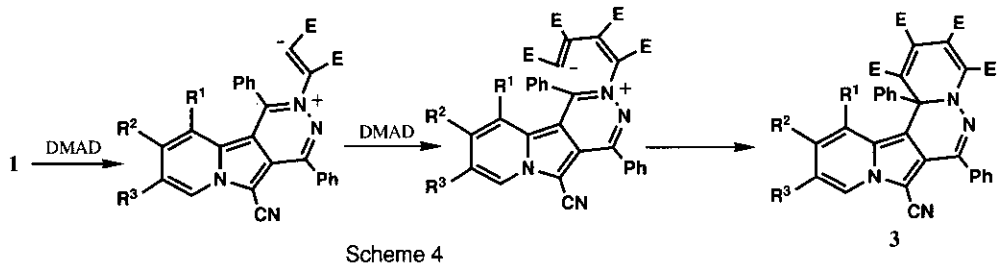
Scheme 1



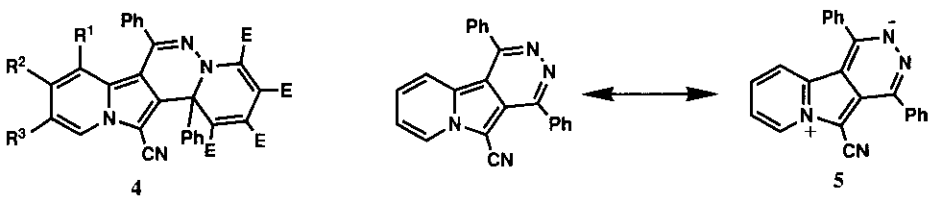
Scheme 2



Scheme 3



Scheme 4



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6. ^{13}C-nmr($CDCl_3$)δ 53.1, 53.2, 54.0, 54.1(each q), 65.2, 91.6, 103.5, 108.3, 109.5, 115.7, 118.0,132.6, 132.9, 134.4, 141.7, 144.5, 145.6(easch s), 116.1, 119.8, 124.8, 125.9(each d), 126.1, 128.5, 128.6, 128.7(each strong d), 129.5, 131.2(each d), 164.9, 165.0, 166.1, 169.5(each s,).
7. Crystal data of **3d**: $C_{42}H_{32}N_4O_8Cl_2$, M=791.64, monoclinic, space group $P2_1/c$ (#14), a=15.005(2), b=8.9852(9), c=29.129(4)Å, β=100.92(1)°, V=3856.2(9)Å^3, Z=4, Dc=1.363 gcm^{-3}, μ=20.14 cm^{-1}. The structure solution (direct methods) and refinement (full-matrix least-squares) was performed using the TEXSAN software and based on 3001 observed intensities [$F>3.0\sigma(F)$] from 5481 measured data (2θ<120°). Final R and R_w values were 0.053 and 0.071.

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