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REACTION OF DICYANOMETHYLIDES WITH 3-(3',3'-DIMETHYLTRIAZENE-1-YL)-PYRIDINE-4-CARBOXYLIC ACID. UNEXPECTED PREFERENTIAL FORMATION OF PYRIDO[4,3-a]INDOLIZINES

Kiyoshi Matsumoto,*[a] Takane Uchida,[b] Mituo Toda,[a] Kinuyo Aoyama,[b] Akikazu Kakehi,[c] Atsushi Shigihara,[d] and J. William Lown*[e]

[a]*Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-01, Japan.* [b]*Faculty of Education, Fukui University, Fukui 910, Japan.* [c]*Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Nagano 380, Japan.* [d]*Hoshi College of Pharmacy, Tokyo 142, Japan.* [e]*Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2*

Abstract: Contrary to theoretical predictions on the basis of a discrete hetaryne intermediate (frontier orbitals, total atomic charges on C-3 and C-4, and activation energies for the concerted process) from the MO calculations, reactions of dicyanomethylides with 3-(3',3'-dimethyltriazene-1-yl)pyridine-4-carboxylic acid, a formal precursor of 3,4-didehydropyridine, afforded exclusively the pyrido[4,3-a]indolizines. The results are better in accord with a mechanism involving a zwitterionic hetaryne precursor.

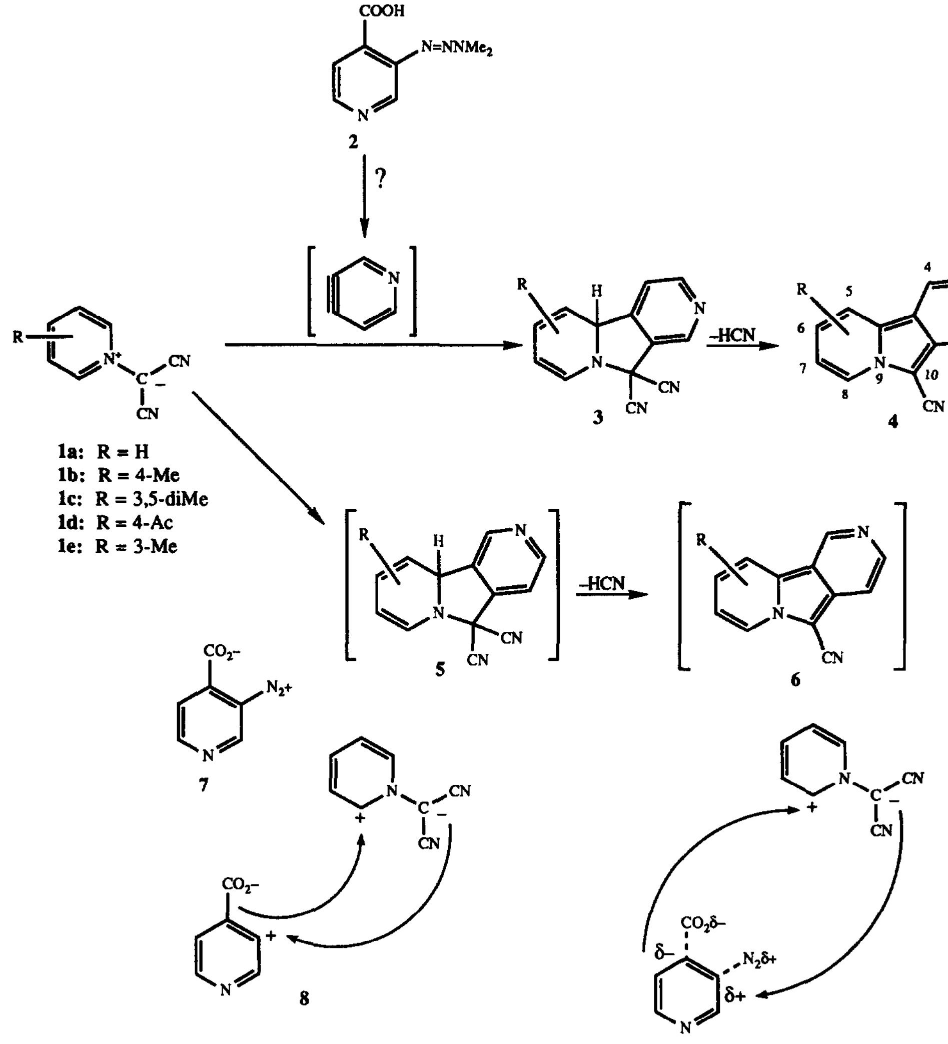
In contrast to numerous examples of cycloaddition reactions of didehydrobenzene (benzyne), relatively few reports have been made for the comparable reactions of didehydroheteroarenes (hetarynes).[1,2] Previously, we have reported on the reactions of dicyanomethylide with benzyne which afforded 6-cyanobenz[a]indolizines together with the novel 1,2,3,4-dibenzo[2.2.3]cyclazines.[3] As an extension of these studies, we have investigated the reactions of 3,4-didehydropyridine (3,4-pyridyne) with dicyanomethylides since a convenient precursor to this hetaryne is now readily available.[2g] In addition since no work directed toward regioselective aspects of 1,3-dipolar reactions[4] of hetarynes has been reported, we describe herein regiospecific formation of the pyrido[4,3-a]indolizines from such reactive intermediates.

Reaction of the dicyanomethylide **1a** with 3-(3',3'-dimethyltriazene-1-yl)pyridine-4-carboxylic acid **2**[2g] (3 fold excess) in refluxing toluene gave, after usual work up and flash chromatography, a single isomer of the dehydrocyanated product in 27% yield. Mass, ^{1}H-NMR and ^{13}C-NMR spectra are in agreement with the pyridoindolizine structure,[5] but did not permit an assignment of the regiochemistry of the adduct. Analogous reactions of the dicyanomethylides **1b–e** with **2** afforded the corresponding pyrindoindolizines albeit in low yields (**Table 1**).

The adduct from **1c** and **2** formed single crystals suitable for an X-ray analysis from which it was evident that the product was not **6c** but **4c** (**Fig. 1**).[6] All attempts either to isolate (by high pressure chromatography) or detect (by NMR) the regioisomer **6** were unsuccessful. Therefore, compounds of type **4** are the only identifiable products even if we have mixtures of regioisomers. In contrast to the reactions with benzyne,[3b] none

Table 1. Reactions of dicyanomethylides 1 with 2

4	Yield (%)	m.p. (°C)
a	27	132–134
b	17	207–208
c	16	246–249
d	14	185–200
e	6	100–110



of the 1,2,3,4-dipyrido[2.2.3]cyclazines were obtained in these cases. This supports the previously suggested view that 3,4-pyridyne has less predictable dienophilic (and dipolarophilic) character than benzyne.[1,2g]

Theoretical treatments have been performed to explain this regioselectivity. The MO calculations were carried out using MOPAC Version 5.0 and Gaussian 86 programs.[7,8] All the geometrical parameters were optimized. Only a single closed-shell electron configuration was taken into account since recent *ab initio* calculations using CASSCF[9] and GVB/3-21G[9] revealed that 3,4-pyridyne has a singlet ground state. The MO characters of **1a** and 3,4-pyridyne do not depend on the calculation methods within PM3, MNDO, and STO-3G. As expected, the least energy interaction is found between the HOMO of **1a** and the LUMO of 3,4-pyridyne. Since the electron density of the LUMO has almost the same distribution on C-3 and C-4 (**Table 2**),[10,11] the two possible orientations are almost equally likely for cycloaddition.[12]

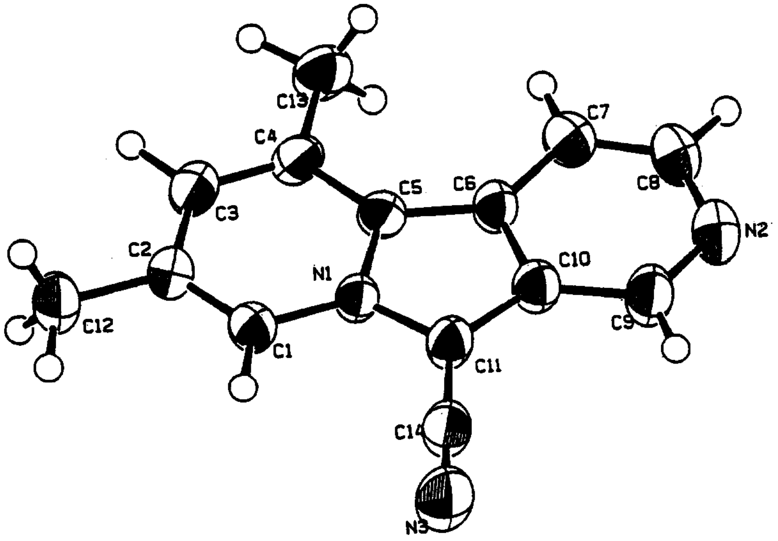


Fig. 1. The X-ray crystal structure of 5,7-dimethyl-10-cyanopyrido[4,3-a]indolizine 3c.

In agreement with the higher level of calculation,[13] the total negative charge on C-3 is always larger than that on C-4 (**Table 3**).[14,15] This predicts preferential formation of **6** which is contrary to the observed isolation of **4**. Only in the case of PM3 level calculations, where the negative charges on C-2 of **1a** are predicted to be slightly larger than that on the opposite end of the dipole, is significant formation of **3** anticipated. Therefore, it was inappropriate that Sasaki *et al.* had tentatively assigned the regiochemistry of the adducts in certain of the 1,3-dipolar reactions based only upon the total electron densities at C-3 and C-4.[2c]

Table 2. Electron densities of LUMO on C-3 and C-4

Method	C-3	C-4
PM3	0.801	0.797
MNDO	0.837	0.843
STO-3G	1.168	1.190

Table 3. Total atomic charges of 3,4-pyridyne on C-3 and C-4

Method	C-3	C-4	Ref.
EHT	-0.35	0.03	10
SCF	0.035	0.087	11
CVB/3-21G	-0.09	0.07	9
PM3	-0.168	-0.091	this work
MNDO	-0.167	-0.068	this work
STO-3G	-0.054	-0.027	this work

The transition state structures for the concerted process were optimized using PM3 and MNDO methods. The estimated activation energies (PM3, 3.9 and 3.5 kcal/mol; MNDO, 13.3 and 12.9 kcal/mol for the primary 1:1 adducts corresponding to **4a** and **6a**) predict that, on a thermodynamic basis, the two reactions should take place to an equal extent. A stepwise mechanism involving nucleophilic attack on the pyridyne was next considered,[1] but, far from being exclusively at C-3, such a process would predict predominant reaction at C-4. The pyridyne precursor **2** may be regarded as a masked version of pyridine-3-diazonium-4-carboxylate **7**.[2g] Therefore, if we assume that the reaction proceeds formally either *via* **8** (analogous to a Sandmeyer reaction) or *via* **9**, the regiochemical consequence can be explained. The structures in the scheme symbolize these alternatives.

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5. IR (KBr) ν_{max}/cm^{-1}: 2180; ^{1}H-NMR (90 MHz, $CDCl_3$): δ (8.87 (1H, s, 1-H), 8.37, 8.48 (1H, m, 8-H), 7.,75, 8.23 (2H, ABq, *J* 5.5 Hz, 3,4-H), 7.93–8.120 (1H, m, 7H), and 7.11–7.33 (2H, m, 5,6-H); ^{13}C-NMR (22.49 MHz, $CDCl_3$): δ 18.6, 19.6 (q, Me), 85.3 (s, C-10), 113.8 (s, *C*N), 115.1 (d, C-4), 121.6 (d, C-6), 126.0 (d, C-8), 127.0 (s, C-1a), 132.3 (s, 5-C), 138.3 (d, C-3), 141.9 (d, C-1), HRMS calc. for $C_{12}H_7N_3$: 193.0640. Found: *m/z* 193.0635.
6. Crystal data for $C_{14}H_{11}N_3$: M = 226.26, monoclinic, $P2_1/n$, a = 7.299(4), b = 9.331(2), c = 16.442(2) Å, $\beta = 95.71(2)^\circ$, U = 1114.2(6) Å^3, Z = 4, Dc = 1.319 gcm^{-1}, λ (Cu-Kα) = 1.54178 Å, μ = 6.04 cm^{-1}, F (000) = 464, T = 296°. Diffraction data were collected with a Rigaku AFC5R diffractometer. The structure solution (direct methods) and refinement (full-matrix least-squares) was performed using the TEXSAN software and based on 1161 observed intensities [(F > 3.0 σ(F)] from 1944 measured data (2θ < 120°). Final R and R_w values were 0.067 and 0.112. An X-ray analysis of the *N*-methyl derivative prepared from **3b** and methyl iodide has also established the same regiochemistry.
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10. However, it is said that C-4 has a slightly larger coefficient in the LUMO of 3,4-pyridyne than C-3 which may lead to a predominant formation of **4**; see Ref. 11.
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