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A novel photochemical cycloaddition of 2-alkoxy-3-cyanopyridines to 2-cyanofuran

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Abstract—Irradiation of a benzene solution of 2-alkoxy-3-cyanopyridines in the presence of 2-cyanofuran gave 4+4 photoadducts in good yields, and the structure was established by X-ray single crystal analysis.

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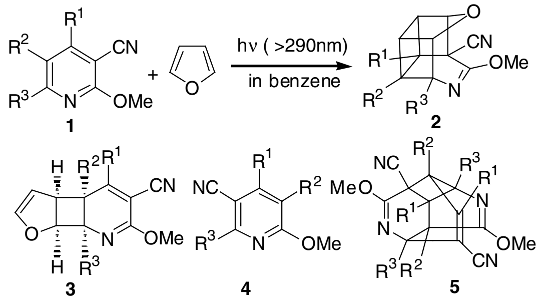
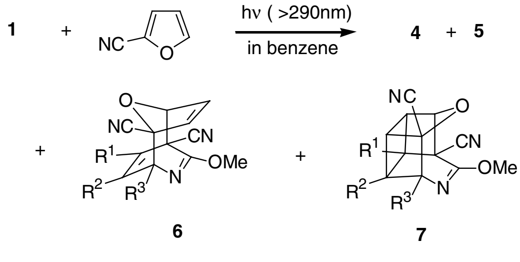
The photochemical cycloaddition reaction of aromatic compounds has received much attention from both mechanistic and synthetic perspectives, because it provides a useful method of synthesizing natural products or highly constrained compounds.[1] New development of ring transformation of heteroaromatics such as pyridines will result in useful synthetic methodology of heterocyclic compounds.[2,3] Previously, we found that introduction of both electron-donating and -withdrawing substituents to the pyridine ring shows high reactivity toward photodimerization and photocycloaddition reaction.[3] Furthermore, we reported the photocycloaddition of 2-alkoxy-3-cyanopyridine **1** with furan leading to cage-type adducts **2** and their rearranged products **3** accompanied by the positional isomer **4** and the dimer **5** as shown in Scheme 1.[4] We are interested in the photochemical reactivity of pyridine derivatives **1** with substituted furans.



Scheme 1.

When pyridine **1a** was irradiated in the presence of 2-methylfuran, the addition did not proceed and **1a** was recovered. In the case of the photolysis of **1a** with 2-methoxyfuran, unfortunately an intractable mixture was obtained. On the other hand, when an argon-purged benzene solution of **1a** (0.02 mol/L) and 2-cyanofuran (0.2 mol/L) in a Pyrex vessel was irradiated using a high-pressure mercury lamp, a 1:1 adduct, 1,5-dicyano-8-methoxy-11-oxa-7-azatricyclo[4.2.2.1^{5,5}]undeca-3,7,9-triene **6a** was obtained in 62% yield (Scheme 2, Table 1, entry 1). No other photoproducts, such as another type of adduct, transpositional isomer, or pyridine dimer, was isolated. Photolysis of other pyridines **1b–d** under the same conditions also gave the corresponding adducts **6b–d** in moderate yields (Table 1, entries 2–4). In the case of **1b**, pyridine dimer **5b** was also obtained in 20% yield (Table 1, entry 2). The photolysis of **1c** was accompanied by a minor amount of the transpositional



Scheme 2.

Keywords: Pyridine; Photocycloaddition; Diastereoselectivity; Furan.

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Table 1. Photoreaction of pyridine–cyanofuran system

Entry	Pyridine	R^1	R^2	R^3	Conv. (%)	Yield (%)[a]			
						6	**7**	**4**	**5**
1	**1a**	H	H	H	50	62	0	0	0
2	**1b**	H	H	Me	67	71	0	0	20
3	**1c**	Me	H	Me	45	68	0	21	0
4	**1d**	Me	Me	Me	50	54	20	0	0

[a] Reaction conversions and yields were determined by ^{1}H NMR spectroscopy with piperonal as a standard material.

isomer **4c** (entry 3). For the photolysis of **1d**, cage-type adduct **7d** was also obtained in 20% yield.

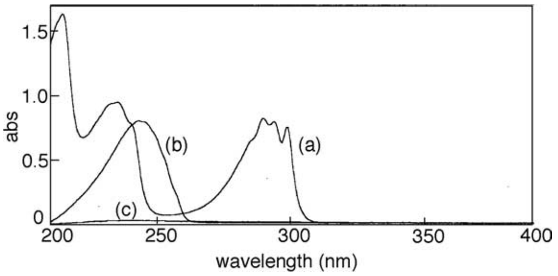


Figure 2. All UV spectra were measured at concentration of 1.0×10^{-4} mol/L in C_6H_{12}. (a) UV spectrum of **1a**. (b) UV spectrum of 2-cyanofuran. (c) UV spectrum of **6a**.

The chemical structure of **6a** was speculated based on spectral data. For example, mass spectroscopy (FAB) of **6a** showed a molecular ion peak at 228 (MH^+), which supported that the product was a 1:1 adduct of **1a** and 2-cyanofuran. Furthermore, the ^{1}H and ^{13}C NMR spectra strongly suggest the structure of the adduct **6a**.[5]

Whereas 4+4 adducts **6b–d** were not so stable, and gradually decomposed to perform the corresponding **1** and cyanofuran on recrystallization from hexane, stable crystals available to X-ray structural analysis were obtained from recrystallization of **6a**. This is due to decrease of steric repulsion in **6a**, which has $R^1 = H$. Finally, the 4+4 structure of **6a** was unequivocally established by X-ray structural analysis.[6] (Fig. 1). This is the first successful example of X-ray analysis of 4+4 adduct of pyridine derivatives. The sp^3 bridgehead carbons are not so distorted; however, the bond lengths C(6)–C(10) and C(7)–C(11) are 1.594(8) and 1.609(8) Å, respectively, which are longer than the usual carbon–carbon single bond (1.54 Å). The stretched and weakened bond resulted in prompt formation of **1a** and cyanofuran by heating at 80 °C in benzene for 1 h.

Figure 2 shows the UV spectra of the pyridine **1a**, 2-cyanofuran, and the adduct **6a** at concentration of each 1.0×10^{-4} mol/L in C_6H_{12}. 2-Cyanofuran has no absorption band above 260 nm. Since high pressure mercury lamp with a Pyrex filter was used as the irradiation source, light quantum of 313 nm line was absorbed by the pyridine **1a**. Furthermore, the absorbance of **6a** is small and most of the light is absorbed by **1a** under these conditions.

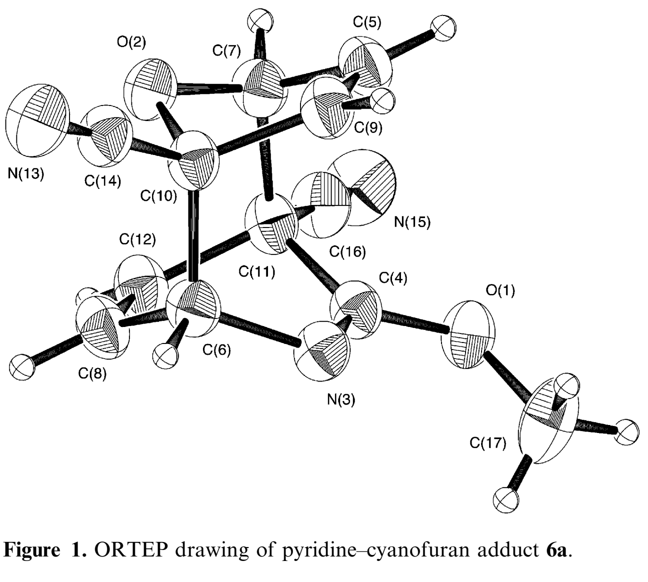
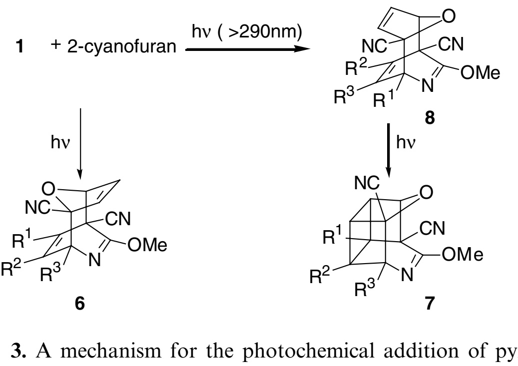


Figure 1. ORTEP drawing of pyridine–cyanofuran adduct **6a**.

The intermolecular photocycloaddition should be influenced by the concentration of the substrate. When a benzene solution of **1a** (0.02 mol/L) at a concentration under 0.2 mol/L of cyanofuran was used, the quantum yield of the cycloaddition (Φ) was 3.6×10^{-2}. The value decreased according to the concentration of cyanofuran, and was 1.8×10^{-2} and 0.7×10^{-2}, at 0.1 and 0.05 mol/L of concentration, respectively.

It is presumed that the formation of **6** involves direct bond formation between the C3- and C6-positions of the pyridine ring and the C5- and C2-positions of 2-cyanofuran. For the caged product **7d**, the mechanism should involve a diastereomeric 4+4 adduct **8** as shown in Scheme 3. The production of **6a** was not quenched by



Scheme 3. A mechanism for the photochemical addition of pyridine with 2-cyanofuran.

addition of 2,5-dimethylhexadiene (triplet quencher), and also the reaction was not sensitized by a triplet sensitizer such as 3-methoxyacetophenone. These results indicate that the photoaddition proceeds from the singlet-excited state of pyridine **6a** as in the case of the pyridine–furan system.[4]

The regioselectivity and stereoselectivity in many singlet photoadditions can be explained by orbital interactions.[7] Frontier-MO calculations by the AM1 method help to explain the selectivity for photocycloaddition.[8] The orbital surfaces of the H-SOMO and L-SOMO of **1a** and HOMO and LUMO of cyanofuran were obtained from the AM1 Hamiltonian contained within the MOPAC program as shown in Figure 3.[9] The ΔE value (2.93861 eV) between the H-SOMO of the excited state of the pyridine **1a** and the LUMO of 2-cyanofuran is smaller than the value (3.03703 eV) between the L-SOMO of the excited state of **1a** and the HOMO of cyanofuran. The coefficients at the 3- and 6-positions in the HSOMO of the singlet excited state of the pyridine ring and those of the 2- and 5-positions of the LUMO in the ground state of furan are larger than those at any other positions, and the phases are also consistent with each other. It is concluded that the bond formation between the C6–C3 positions of pyridine and the C2–C5 positions of cyanofuran occurs and leads to **6** and **8**.

There are two ways for 4+4 cycloadditions, and the formation of **6** is superior to lead to **8**. We cannot provide on obvious explanation of the diastereoselectivity now. However, it seems that two heteroaromatics, **1** and cyanofuran, make an approach with avoiding each electron-negative heteroatoms leading to 4+4 adduct **6**. Furthermore, final heat of formation of these two 4+4 adducts was calculated by the AM1 method contained within the MOPAC program. Each final heat of formation is 92.58636 or 93.61897 kcal mol^{-1} for **6** or **8**, respectively. The difference is small; however, the result also supports one reason for the control of the diastereoselectivity.

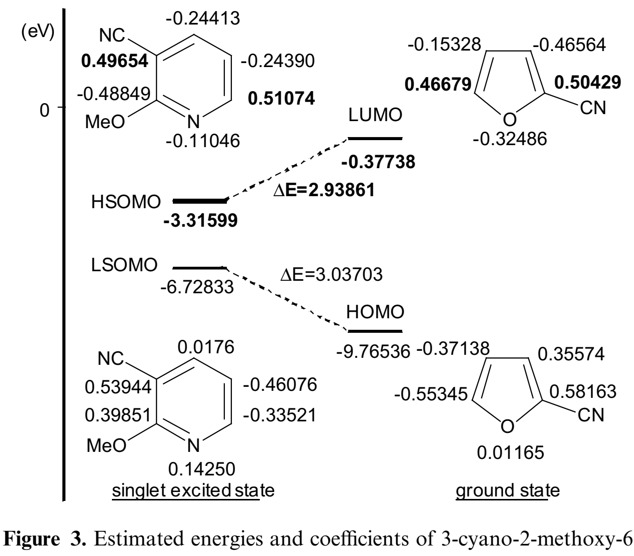


Figure 3. Estimated energies and coefficients of 3-cyano-2-methoxy-6-methylpyridine **1a** and 2-cyanofuran obtained from the AM1 Hamiltonian contained within the MOPAC program.

In conclusion, we have provided a fine example of a photochemical reaction of pyridine and 2-cyanofuran leading to 4+4 cycloadducts. This reaction proceeds in a highly controlled regioselective manner, and also provides a synthesis of new nitrogen-containing heterocycles.

Acknowledgements

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5. The ^{1}H NMR spectrum (CDCl$_3$) showed new peaks at δ 4.45 (d, $J = 1.7$ Hz, 1H), 4.64 (dd, $J = 1.5$ and 5.6 Hz, 1H), 6.35 (d, $J = 5.6$ Hz, 1H), 6.53 (dd, $J = 1.5$ and 7.7 Hz, 1H), 6.72 (dd, $J = 1.7$ and 5.6 Hz, 1H), 6.88 (dd, $J = 5.6$ and 7.7 Hz, 1H) in addition to the methyl and methoxy protons. The ^{13}C NMR showed peaks derived from sp^3 carbon atoms at δ 53.4, 64.4, 76.1, 81.1. Furthermore, five peaks owing to sp^2 carbons at 128.6, 134.2, 134.4, 135.2, and 171.3, were exhibited in addition to cyano groups at 115.4 and 115.8.
6. The colorless prismatic crystal was subjected to X-ray structural analysis and the triclinic space group P-1 with $a = 7.539(2)$ Å, $b = 8.430(1)$ Å, $c = 8.754(3)$ Å, $\alpha = 103.09(2)°$, $\beta = 92.81(2)°$, $\gamma = 91.34(2)°$, $V = 540.9(2)$ Å^3, $Z = 2$, $\rho = 1.389$ g/cm^3, and $\mu(\mathrm{Cu\,K\alpha}) = 0.82$ mm^{-1} was revealed. Final R and wR (on F^2) were 0.072 and 0.174

for 1704 reflections. The crystallographic data will be sent on quoting the CCDC number CCDC 228069 (e-mail: deposit@ccdc.cam.ac.uk).

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9. The predicted $\Delta\Delta E$ is proportional to $(ca_1cb_1)^2+(ca_2cb_2)^2$ where cX is the orbital coefficient in the interaction site of the a_1–a_2 and the b_1–b_2 bonds using the Salem–Klopman equation (see, for example: Fleming, I. *Frontier Orbital and Organic Chemical Reactions*; Wiley–Interscience: New York, 1976).