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PHOTOCHEMICAL CYANATION OF QUINOLINES AND ISOQUINOLINES
PARTICIPATION OF ENHANCED BASICITY IN EXCITED SINGLET STATES

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When 7-methoxyquinoline and excess NaCN in aqueous MeCN was irradiated with a 100 W high pressure mercury lamp under bubbling O_2 for 3.5 hr to give 8-cyano-7-methoxyquinoline in 39% yield, whereas quinoline was recovered unchanged under similar conditions. 6-Methoxyquinoline was more reactive and gave 5-cyano-6-methoxyquinoline in 48% yield after irradiation for 1.5 hr. Isoquinoline gave 3-cyanoisoquinoline only in 11% yield, while 6- and 7-methoxyisoquinolines gave 5-cyano-6-methoxyisoquinoline (12%) and 8-cyano-7-methoxyisoquinoline (38%), respectively. The mechanism involving the participation of excited singlet state pKa was elucidated on the basis of quantum yield measurements for disappearance of 6- and 7-methoxyquinolines and for formation of the products and their pH dependence.

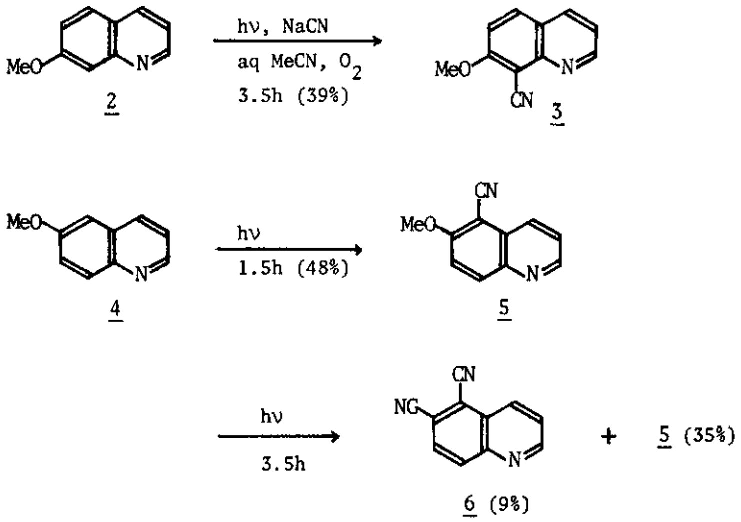
Common nucleophilic substitutions of quinoline and isoquinoline occur only at C-2 and C-1, respectively, unless these positions are occupied.[1] The benzene rings in these heteroaromatics are usually less reactive and introduction of electron-donating substituents such as methoxy groups results in the complete loss of the reactivity of the benzene rings toward nucleophiles. The Reissert reaction though not the direct substitution with cyanide anion is also the case.[2] On the other hand, methoxybenzenes and methoxynaphthalenes in their excited states react readily to nucleophiles, though not necessarily in high yield, with the orientation opposite to that in their ground states.[3] We have now examined a photochemical cyanation, which is important because of a direct introduction of carbon units to aromatic rings, of quinoline, isoquinoline, and their methoxy derivatives from synthetic and mechanistic points of view, disclosing a role of excited state pKa.

Synthetic Studies

Quinoline (1) is rather inactive to the photocyanation, *e.g.*, 84% of 1 was recovered without any isolable product when an aqueous MeCN solution (pH 9.4) of 1, excess NaCN, and I_2 was irradiated with a 100 W high pressure mercury lamp for 8 hr.[4]

On the other hand, irradiation of 7-methoxyquinoline (2) and a 5-fold excess of NaCN in aqueous MeCN (pH 10.4) under bubbling O_2 for 3.5 hr gave readily 8-cyano-7-methoxyquinoline (3) in 39.1% yield (46.7%),[5] mp 139-140° (from EtOAc),[6] and the recovered 2 (16.3%). The spectral data are consistent with the structural assignment of 3 and especially the nmr spectrum clarifies the position substituted by a cyano group. Under similar conditions using N_2 instead of O_2, the yield of 3 decreased to only 9.7% and ca. 1/3 of the starting 2 was recovered.

The isomeric compound, 6-methoxyquinoline (4) was more reactive than 2 to this photocyanation. Thus, when 4 was irradiated under bubbling O_2 only for 1.5 hr, 5-cyano-6-methoxyquinoline (5) was isolated in 48.4% yield (53%),[5] mp 175-177° (EtOAc),[7] in addition to 11.9% of the recovered 4. Prolonged irradiation (3.5 hr) of 4 brought about further photocyanation (photosubstitution of a methoxy group)[8] to give 5,6-dicyanoquinoline (6, 9%),[9] mp 209-

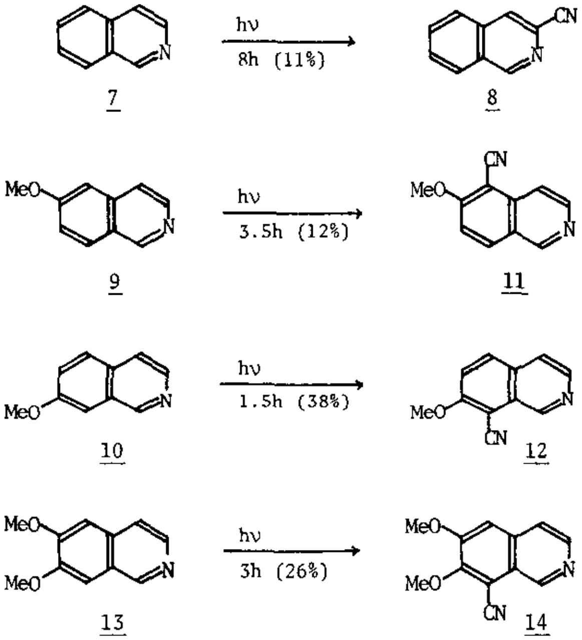


210° (dec) (EtOAc), as well as 5 (35%).

When isoquinoline (7) was irradiated similarly for 8 hr, 3-cyanoisoquinoline (8),[10] mp 121-123° (ether-pet.ether),[11] was isolated though in a poor yield (11%)[5] in addition to the recovered 7 (49%).

Two methoxy derivatives, 6- and 7-methoxyisoquinolines (9 and 10) were next subjected to the reaction and the latter was found to be more reactive. Thus, irradiation of 9 for 3.5 hr gave 5-cyano-6-methoxyquinoline (11) in 12% yield (20.4%),[5] mp 183-185° (EtOAc),[12] and recovered 9 (41.1%), while irradiation of 10 for 1.5 hr gave 38% (40%)[5] of 8-cyano-7-methoxyisoquinoline (12), mp 164-166° (EtOAc),[13] and only 5% of the recovered 10.

Finally, 6,7-dimethoxyisoquinoline (13) gave 8-cyano-6,7-dimethoxyisoquinoline (14) in 26.5% yield, mp 173° (dec).[14]



Mechanistic Studies

In order to establish the mechanism of these photocyanations clarifing some effects of methoxy substituents and excited state pKa, quantum yields (Φ) for disappearance of two methoxyquinolines (2, 4) and for formation of the products (3, 5) and their pH dependence were examined as shown in Fig. 1.

It is well known that aromatic compounds in their excited states have quite different electron densities on the ring carbons, compared with those in the ground state molecules, and hence the completely reverse orientation in both electrophilic and nucleophilic substitutions was usually observed. Acid-base properties are also known to vary considerably as a result of electronic excitation. The basicity of acridine, for example, increases about five oders of magnitude [$pK(S_0) = 5.5$, $pK(S_1) = 10.6$].[15] If quinoline and isoquinoline have the same property, the enhanced basicity in their singlet excited state is expected to change the reactivity toward nucleophiles.

Valence bond representations with zwitter ionic limiting structures in the π-π* excitation of 2 and 4 can be described as 2a and 4a, respectively, which explain the reactivity difference between 2 and 4 as well as the most reactive position in each quinoline for nucleophilic substitutions. Structure 4a is clearly more stable than 2a, and this stability difference is probably reflected in the difference in reactivity between 2 and 4. In analogy with in usual substitution reactions of naphthalenes, the most reactive site in 2a and 4a under these photocyanations are C-8 and C-5, not C-6 and C-7, respectively.

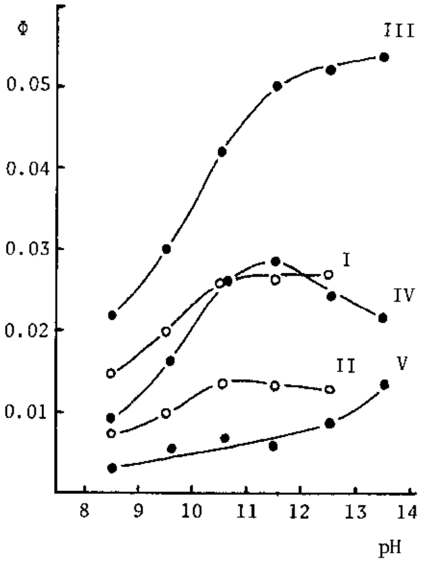
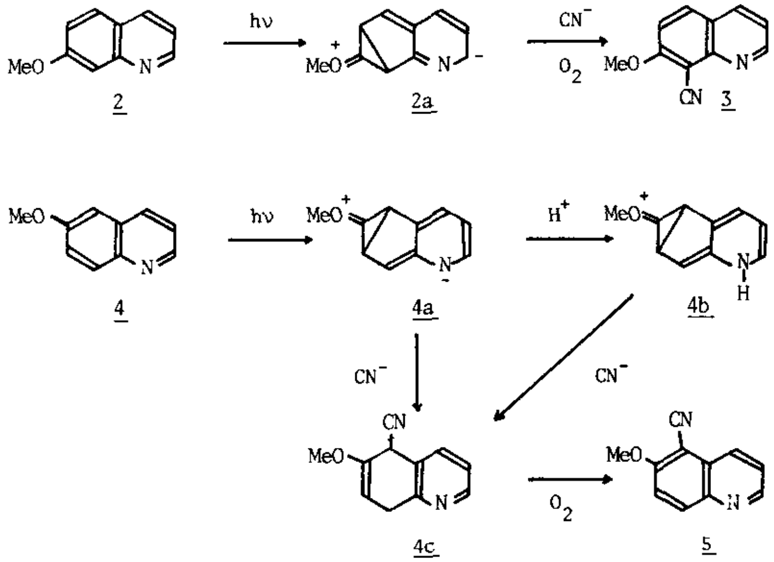


Figure 1. PH dependence on quantum yields (Φ) of photocyanations of 2 and 4.
I: Disappearance of 2 in the presence of NaCN.
II: Formation of 3.
III: Disappearance of 4 in the presence of NaCN.
IV: Formation of 5.
V: Disappearance of 4 in the absence of NaCN.
[Quantum yields (Φ) on irradiation with 322 ± 7.5 nm from a spectro-irradiator were determined relative to the potassium ferrioxalate actinometer]

There are two important features revealing the mechanism in Figure 1.

1) The actual cyanating species is cyanide anion rather than hydrocyanic acid because the quantum yields (Φ in curve I-IV) increase rather sharply on going from pH 8.5 up to pH 10.5 (pKa of HCN is 9.21).[16]

2) An optimum pH around 11.5 is observed only in the formation of 5 and probably corresponding to the excited singlet state pKa of 4. As already mentioned, the excited pKa of quinoline is estimated to be 10-11 and its basicity is enhanced by a methoxy substituent.[17] Since a protonated species (4b) must be more reactive than 4a in nucleophilic reactions, the photocyanation of 4 proceeds mainly via a series of 4a, 4b, and 4c to yield 5.[18] This is probably the first report estimating the excited singlet state pKa based on mechanistic studies of photoreactions.



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1) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry", W. A. Benjamin, Inc., New York, 1968, p 289: R. C. Elderfield, ed., "Heterocyclic Compounds", Vol. 4, John Wiley & Sons, London, 1952, p 231, 424; G. Illuminati, " Adv. in Heterocyclic Chemistry", Vol. 3, Academic Press, New York, 1964, pp 285-371.

2) A. Reissert, Chem. Ber., 38, 1603 (1905); W. E. McEwen and R. L. Cobb, Chem. Rev., 55, 511 (1955); F. D. Popp, "Adv. in Heterocyclic Chemistry", Vol. 9, Academic Press, New York, 1968, p 1.

3) J. Cornelisse and E. Havinga, Chem. Rev., 75, 353 (1975).

4) The use of bubbling O_2 instead of I_2 did not improved the reaction.

5) The yield in parentheses is based on the consumed starting material. Although the yield is less satisfactory, this direct cyanation is probably useful synthetically because the product is easily isolable almost in a pure state from the reaction mixture after only one recrystallization of the fraction soluble in usual organic solvents.

6) NMR δ ($CDCl_3$) 4.11 (3H, s, OCH_3), 7.35 (1H, d, J = 9 Hz, C-6), 7.38 (1H, dd, J = 4.5, 8 Hz, C-3), 8.03 (1H, d, J = 9 Hz, C-5), 8.15 (1H, dd, J = 1.8, 8 Hz, C-4), 8.99 (1H, dd, J = 1.8, 4.5 Hz, C-2).

7) NMR δ ($CDCl_3$) 4.12 (3H, s, OCH_3), 7.50 (1H, d, J = 9.5 Hz, C-7), 7.54 (1H, dd, J = 4.5, 8.5 Hz, C-3), 8.28 (1H, d, J = 9.5 Hz, C-8), 8.38 (1H, dd, J = 1.5, 8.5 Hz, C-4), 8.85 (1H, dd, J = 1.5, 4.5 Hz, C-2).

A. Lablache-Combier quoted in his review as an unpublished result by R. L. Letsinger that 4 was converted to 5 in 92% yield (Φ = 0.35), but these values , especially Φ seem to be too high in such a intermolecular photoreaction; A. Lablache-Combier, "Elements de Photochemie Avancee", P.Courtot, ed., Hermann, Paris, 1972, p 343.

8) Many exmples have been reported, see ref. 3.

9) NMR δ ($CDCl_3$) 7.78 (1H, dd, J = 4, 8.5 Hz, C-3), 7.99 (1H, d, J = 9 Hz, C-7), 8.45 (1H, d, J = 9 Hz, C-8), 8.58 (1H, dd, J = 1.5, 8.5 Hz, C-4), 9.15 (1H, dd, J = 1.5, 4 Hz, C-2).

10) H. Watanabe, Y. Kikugawa, and S. Yamada, Chem. Pharm. Bull., 21, 465 (1973); G. A. Swan , J. Chem. Soc., 2038 (1958).

11) NMR δ ($CDCl_3$) 7.78-8.17 (5H, m), 9.29 (1H, s).

12) NMR δ ($CDCl_3$) 4.13 (3H, s, OCH_3), 7.39 (1H, d, J = 9 Hz, C-7), 7.85 (1H, d, J = 6 Hz, C-4), 8.15 (1H, dd, J = 0.9, 9 Hz, C-8), 8.62 (1H, d, J = 6Hz, C-3), 9.20 (1H, broad s, C-1).

13) NMR δ ($CDCl_3$) 4.12 (3H, s, OCH_3), 7.51 (1H, d, J = 9 Hz, C-6), 7.64 (1H, dd, J = 0.7, 6 Hz, C-4), 8.06 (1H, dd, J = 1, 9 Hz, C-5), 8.56 (1H, d, J = 6 Hz, C-3), 9.45 (1H, broad s, C-1).

14) NMR δ ($CDCl_3$) 4.05 (3H, s, OCH_3), 4.22 (3H, s, OCH_3), 7.22 (1H, s, C-5), 7.55 (1H, d, J = 5.6 Hz, C-4), 8.55 (1H, d, J = 5.6 Hz, C-3), 9.39 (1H, broad s, C-1).

15) E. V. Donckt, "Progress of Reaction Kinetics", Vol. 5, G. Porter, ed., Pergamon, Oxford, 1970, p 291.

16) This feature, of course, is common in usual cyanation reactions.

17) Compound 2 may also have an optimum pH, although the results are obscure because of too low Φ.

18) Although position of a double bond in the dihydrobenzene ring is still obscure, a dihydro compound 4c can be detected GLC-Mass spectrometrically as a main product of the photocyanation without bubbling O_2. The isolated 4c is fairly stable in an argon atmosphere, but is rapidly converted to 5 when treated with bubbling O_2.

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