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Intermolecular Photoaddition Reaction of Aliphatic *tert*-Amines to *N*-Alkyl-2-pyridones

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N-Alkyl-2-pyridones reacted on irradiation with aliphatic *tert*-amines, such as triethylamine and N-methylpiperidine, by way of addition of an α-C–H bond of the amines to the pyridone nucleus, yielding 4-substituted 3,4-dihydropyridin-2(1H)-ones (4, 5 and 10) and 6-substituted 3,6-dihydropyridin-2(1H)-ones (3 and 9).

Keywords intermolecular photoaddition; N-alkyl-2-pyridone; aliphatic *tert*-amine; 3,4-dihydropyridin-2(1H)-one; 3,6-dihydropyridin-2(1H)-one

Studies on photochemical reactions of 2-pyridones have been focused on cycloaddition reactions, such as [4+4]-dimerization,[1] valence isomerization,[1b,2] [2+2]cycloaddition to olefins,[3] and sensitized oxygenation.[4] In the course of chemical investigations on lupin alkaloids, we have recently reported[5] that the cytisine-type lupin alkaloids can be photochemically transformed into the tsukushinamine-type lupin alkaloids which possess a new skeleton involving a cage structure. The photoreaction involves the intramolecular 1,4-addition of an α-C–H bond of the *tert*-amino moiety to the 2-pyridone nucleus. Although photoaddition reactions of aromatic hydrocarbons, such as benzene[6] and naphthalene,[7] with amines are well known, few reactions with aromatic nitrogen heterocycles have been reported[8] except for the photoreaction of pyridine with triethylamine,[9] which yields substitution products, formed presumably by oxidation of the addition intermediates, *viz*., the dihydropyridine derivatives. Thus, the application of tsukushinamine synthesis to intermolecular reactions between 2-pyridones and amines seems to be interesting from the view point of synthetic utility. In this paper, we wish to report the intermolecular photoaddition reaction of N-alkyl-2-pyridones with aliphatic *tert*-amines.

Results and Discussion

A degassed solution of N-methyl-2-pyridone (**1**, 214 mg, 1.96 mmol) and triethylamine (13.9 ml, 98.2 mmol) in CH_3CN (187 ml) was irradiated internally with a 400 W high-pressure mercury lamp for 8 h at ambient temperature. Thin layer chromatography (TLC) of the reaction mixture showed the consumption of the starting **1** and the formation of several compounds. The reaction mixture was repeatedly separated by silica gel column chromatography to give five products, **3a** (4 mg), **3b** (8 mg), **4** (25 mg), **6** (72 mg) and **8** (10 mg).

The chemical ionization mass spectra (CI-MS) of both **3a** and **3b** showed the $M^+ + 1$ ion peak at m/z 211, indicating that they were 1 : 1 adducts of **1** and triethylamine. The proton nuclear magnetic resonance (^{1}H-NMR) spectra of **3a** and **3b** revealed the presence of a $CH_3CH(CH<)N(CH_2CH_3)_2$ moiety in the molecules as shown in Table I.

The remaining signals in the ^{1}H-NMR spectrum of **3a** were in accordance with a 6-substituted 1-methyl-3,6-dihydropyridin-2(1H)-one structure. The two olefinic signals with similar chemical shifts (δ 5.82 and 5.89) were assigned to the non-conjugated olfinic protons at the 4- and 5-position. The signals at δ 2.93 (1H) and 3.02 (1H) which were coupled with each other with a large coupling constant (21.5 Hz) were assigned to the geminal methylene protons at the 3-position adjacent to two π-bonds.[10] The ^{1}H-NMR spectrum of **3b** exhibited similar signals to those of **3a**. Thus, adducts **3a** and **3b** were characterized as the diastereomers of 1-methyl-6-[1-(diethylamino)ethyl]-3,6-dihydropyridin-2(1H)-one.

Product **4** was shown to be a 1 : 1 mixture of two compounds by gas liquid chromatography (GLC). The two compounds exhibited the $M^+ + 1$ ion peak at m/z 211 in the GLC-CI-MS, indicating that they are also 1 : 1 adducts of **1** and triethylamine. The ^{1}H-NMR spectrum of **4** showed two sets of signals (**4a** and **4b** in Table I) which were similar to each other. The sets of signals also resembled those of **3a** and **3b** except that mutually coupled olefinic signals (δ 5.06 and 6.00, and δ 5.45 and 5.86) of both sets were apart from each other and one of each pair of coupled signals resonated at high field as compared with those of **3a** and **3b**, indicating that the double bond in **4a** and **4b** is adjacent to the lactam nitrogen. The coupling characteristics of the olefinic signals suggested that a methine group might be present on the other side of the double bond. Therefore, adduct **4** was concluded to be a 1 : 1 mixture of the diastereomers of 1-methyl-4-[1-(diethylamino)ethyl]-3,4-dihydropyridin-2(1H)-one.

Product **6** was determined to be the valence isomer (so-called photopyridone) of **1** from the agreement of the ^{1}H-

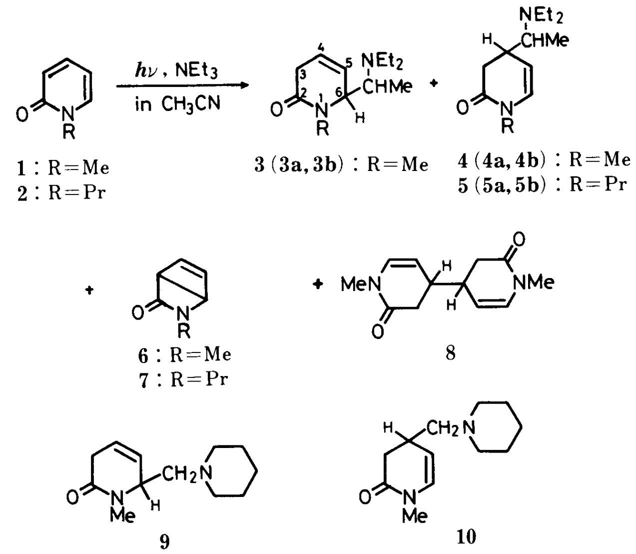

Chart 1

Table I. ^1H-NMR Spectral Data for Photoreaction Products (δ ppm in $CDCl_3$, J in Hz)

Comp. No.	3-H_2	4-H[a]	5-H[a]	6-H	1′-H and 1′-CH_3 or 1′-CH_2-		$N^2C\underline{H}_2CH_3$	$N^2CH_2C\underline{H}_3$	N^1-CH_3 or N^1-$C\underline{H}_2CH_2$-CH_3 and N^1-$CH_2CH_2C\underline{H}_3$	
3a	2.93, ddd (21.5, 4.6, 2.4) 3.02, dm (21.5)	5.82, ddd (10.0, 4.6, 2.0)	5.89, ddd (10.0, 4.6, 2.9)	3.65, m	3.00, dq (7.1, 3.9)	1.05, d (7.1)	2.55, dq (13.7, 7.1) 2.40, dq (13.7, 7.1)	0.92, t (7.1)	3.02, s	
3b	2.94, m	5.78, dm (10.2)	5.78, ddd (10.2, 3.3, 3.3)	3.90. m	3.04, m	0.88, d (6.8)	2.58, dq (13.7, 7.1) 2.49, dq (13.7, 7.1)	1.00, t (7.1)	3.02, s	
4a	2.76, dd (16.1, 7.1) 2.2—2.6, m	2.2—2.6, m	5.06, dd (7.8, 4.6)	6.00, dd (7.8, 1.2)	2.2—2.6, m	0.93, d (6.6)	2.2—2.6, m	0.99, t (7.1)	3.00, s	
4b	2.2—2.6, m	2.2—2.6, m	5.47, ddd (7.8, 2.7, 1.2)	5.86, dd, (7.8, 2.2)	2.2—2.6, m	0.91, d (6.6)	2.2—2.6, m	0.99, t (7.1)	3.00, s	
5a	2.76, dd (16.4, 7.1) 2.53, dd (16.4, 6.6)	2.35, m	5.05, dd (7.8, 4.6)	6.00, dd, (7.8, 1.2)	2.52, dq, (9.8, 6.6)	0.93, d (6.6)	2.48, dq (13.7, 7.1) 2.25, dq (13.7, 7.1)	0.98, t (7.1)	3.30, dt (14.4, 7.3) 3.52, dt (14.4, 7.3)	0.90, t (7.3)
5b	2.2—2.6, m	2.45, m	5.47, ddd (7.8, 2.7, 1.2)	5.96, dd (7.8, 2.2)	2.2—2.6, m	0.91. d (6.3)	2.2—2.6, m	0.99, t (7.1)	3.47, dt (14.7, 7.3) 3.35, dt (14.7, 7.3)	0.90, t (7.3)
9	2.95, m	5.78, ddd (9.8, 3.7, 1.2)	5.85, dm (9.8)	3.88, m	2.40, dd (12.8, 6.1)	2.49, dd (12.8, 4.9)			3.05, s	
10	2.57, dd (15.9, 6.7) 2.35, dd (15.9, 9.8)	2.70, m	5.12, dd (7.9, 3.7)	5.98, dd (7.9, 1.8)	2.20, dd (12.2, 7.9)	2.27, dd (12.2, 5.5)			3.04, s	

a) Assignments for 4-H and 5-H in each of **3a**, **3b** and **9** are interchangeable.

NMR spectrum with the reported data.[11)]

The electron impact (EI)-MS of product **8** showed the M^+ ion peak at m/z 220.1209 (Calcd for $C_{12}H_{16}N_2O_2$: 220.1213) and the base peak at m/z 110. The ^1H-NMR spectrum of **8** exhibited a two-proton doublet at δ 6.60 ($J=$ 7.8 Hz), a two-proton multiplet at δ 5.00, two methyl singlets at δ 3.016 and 3.021, and a multiplet at δ 2.62 to δ 2.39 (6H). From these results, product **8** was presumed to be the diastereomeric mixture of the dihydro dimer of **1**.

The photoreaction of *N*-propyl-2-pyridone (**2**) with triethylamine, and of **1** with *N*-methylpiperidine gave adducts **5a** and **5b**, and **9** and **10**, respectively, as isolated products. The adducts were assigned as the diastereomers (**5a** and **5b**) of 1-propyl-4-[1-(diethylamino)ethyl]-3,4-dihydropyridin-2(1*H*)-one, and 1-methyl-6-piperidinomethyl-3,6-dihydropyridin-2(1*H*)-one (**9**) and 1-methyl-4-piperidinomethyl-3,4-dihydropyridin-2(1*H*)-one (**10**), respectively, from the mass spectral results (see Experimental) and a comparison of the ^1H-NMR spectra with those of **3a**, **3b**, **4a** and **4b** (see Table I).

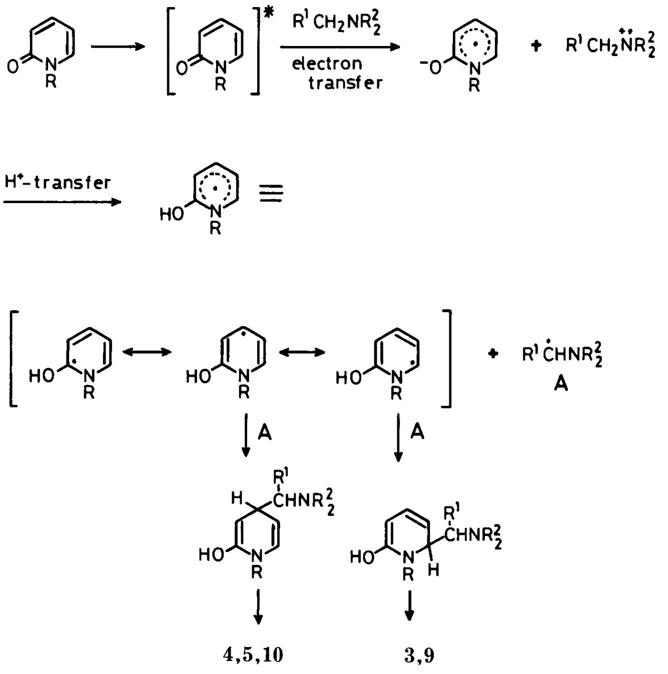

Chart 2

Thus, irradiation of *N*-alkyl-2-pyridones with aliphatic *tert*-amines resulted in the reductive addition of the α-C–H bond of the amines to *N*-alkyl-2-pyridones, yielding 4-substituted 1-alkyl-3,4-dihydropyridin-2(1*H*)-ones (**4**, **5** and **10**) and 6-substituted 1-alkyl-3,6-dihydropyridin-2(1*H*)-ones (**3** and **9**). It is known that because of their low oxidation potentials amines serve as efficient electron donors in electron transfer processes with excited states of ketones, olefins and aromatic hydrocarbons.[8a)] Electron transfer processes are proved to be responsible for the reductive addition of amines to benzene[6)] and naphthalene.[7)] The use of *N*,*N*-dimethylaminoacetonitrile, which has a higher oxidation potential ($E_{1/2}+1.40$ V *vs*. $Ag/AgNO_3$ (0.1 M)) than that of triethylamine ($E_{1/2}+0.66$ V) or *N*-

methylpiperidine ($E_{1/2}+0.80\,\text{V}$),[12] in the photoreaction with **1** did not give addition products. Therefore, the photoreaction of *N*-alkyl-2-pyridone–aliphatic *tert*-amine systems might be expected to proceed *via* an electron transfer process. A possible mechanism is shown in Chart 2. Further application of this reaction is under investigation.

Experimental

^{1}H-NMR spectra were recorded on a JEOL GX-400 spectrometer, and chemical shifts (δ) are given in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Coupling constants (J) are given in hertz (Hz); s, d, t, q and m indicate singlet, doublet, triplet, quartet and multiplet, respectively. EI-MS and CI-MS were measured with a JEOL D-300 instrument and isobutane was used as the chemical ionization reactant gas in CI-MS. GLC-CI-MS and GLC-EI-MS were measured with the same instrument as used for EI-MS and CI-MS, and GLC conditions were the same as in the analytical GLC except for the use of helium instead of N_2 as a carrier gas. Analytical GLC was carried out with Hitachi 263-30 gas chromatograph equipped with a column (0.3×200 cm) of 2% silicon OV-17 on Gas Chrom Q. Column chromatography was performed with Silica gel 60 (Merck, 70—230 mesh or 230—400 mesh) using CH_2Cl_2-MeOH solvent systems. A Riko 400W high-pressure mercury lamp was used as the irradiation source. Products were all obtained as colorless oils and their boiling points were not determined.

Materials **1**, *N*-methylpiperidine and triethylamine obtained from commercial sources were purified by distillation. *N*-Propyl-2-pyridone (bp_{12} 139 °C) was synthesized from 2-pyridinol and propylbromide, similarly to the reported method.[13] CH_3CN was purified by distillation on CaH_2 after being stirred with CaH_2 for 3 d at room temperature.

Irradiation of *N*-Methyl-2-pyridone (1) and Triethylamine A solution of **1** (214 mg, 1.96 mmol) and triethylamine (13.9 ml, 98.2 mmol) in dry CH_3CN (187 ml) was irradiated internally for 8 h under N_2 through a Pyrex filter after being flushed with N_2 for 30 min. The low-boiling materials were removed *in vacuo*. The residue was separated repeatedly by silica gel column chromatography to give **3a** (4 mg), **3b** (7 mg), **4** (25 mg), **6** (70 mg) and **8** (8 mg). **3a**: CI-MS *m/z*: 211 ($M^+ +1$). EI-MS (30 eV) *m/z*: 110 (15), 100 (100), 72 (30). **3b**: CI-MS *m/z*: 211 ($M^+ +1$). EI-MS (30 eV) *m/z*: 210.1729 (M^+, Calcd for $C_{12}H_{22}N_2O$: 210.1733, 0.2), 110 (2), 100 (100). **4** gave two peaks (**4a** and **4b**) on GLC. **4a**: GLC-EI-MS *m/z*: 100 (100). GLC-CI-MS *m/z*: 211 ($M^+ +1$). **4b**: GLC-EI-MS *m/z*: 100 (100). GLC-CI-MS *m/z*: 211 ($M^+ +1$). **6**: colorless oil. EI-MS (70 eV) *m/z*: 109 (M^+), 81, 52 (100). ^{1}H-NMR ($CDCl_3$) δ: 6.60 (2H, m), 4.32 (1H, t, $J=2$ Hz), 4.15 (1H, m), 2.81 (3H, s). These spectral data were consistent with reported values.[11] **8**: EI-MS (70 eV) *m/z*: 220.1209 (M^+, Calcd for $C_{12}H_{16}N_2O_2$: 220.1213, 0.2), 110 (100). CI-MS *m/z*: 221 ($M^+ +1$). ^{1}H-NMR ($CDCl_3$) δ: 6.06 (2H, d, $J=7.8$ Hz), 5.00 (2H, m), 3.016 (3H, s), 3.021 (3H, s), 2.62—2.39 (6H, m).

Irradiation of *N*-Propyl-2-pyridone (2) with Triethylamine A degassed solution of **2** (50 mg, 0.36 mmol) and triethylamine (2.5 ml, 18.2 mmol) in dry CH_3CN (12.5 ml) was irradiated externally for 8 h under N_2 through a Pyrex filter after being flushed with N_2 for 30 min. After removal of the low-boiling materials, the reaction mixture was separated by silica gel column chromatography to yield the starting **2** (30 mg), the photopyridone **7** (6 mg) and a diastereomeric mixture of **5** (6 mg), which was further separated by preparative TLC (Merck No. 13895) to give **5a** (1 mg) and **5b** (1 mg). **5a**: EI-MS (30 eV) *m/z*: 100 (100). CI-MS *m/z*: 239 ($M^+ +1$). **5b**: EI-MS (30 eV) *m/z*: 100 (100). CI-MS *m/z*: 239 ($M^+ +1$). **7**: EI-MS (70 eV) *m/z*: 137 (M^+, 5), 95 (10), 52 (100).

Irradiation of 1 with *N*-Methylpiperidine Irradiation of a solution of **1** (40 mg, 0.37 mmol) and *N*-methylpiperidine (1.8 g, 18.3 mmol) in dry CH_3CN (13 ml) for 8 h and separation of the products from the reaction mixture were conducted in the same manner as described for the photoreaction of **2** and triethylamine. Adducts **9** (1.5 mg), **10** (2 mg), the starting **1** (25 mg), the dihydro dimer **8** (1.5 mg) and the photopyridone **6** (3 mg) were isolated. **9**: EI-MS *m/z*: 208.1586 (M^+, Calcd for $C_{12}H_{20}N_2O$: 208.1577, 0.1), 98 (100). CI-MS *m/z*: 209 ($M^+ +1$). **10**: EI-MS (70 eV) *m/z*: 208.1564 (M^+, Calcd for $C_{12}H_{20}N_2O$: 208.1577), 98 (100). CI-MS *m/z*: 209 ($M^+ +1$).

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