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ELECTRON TRANSFER-INITIATED PHOTOCYCLIZATION OF SUBSTITUTED α-DEHYDRO(1-NAPHTHYL)ALANINES

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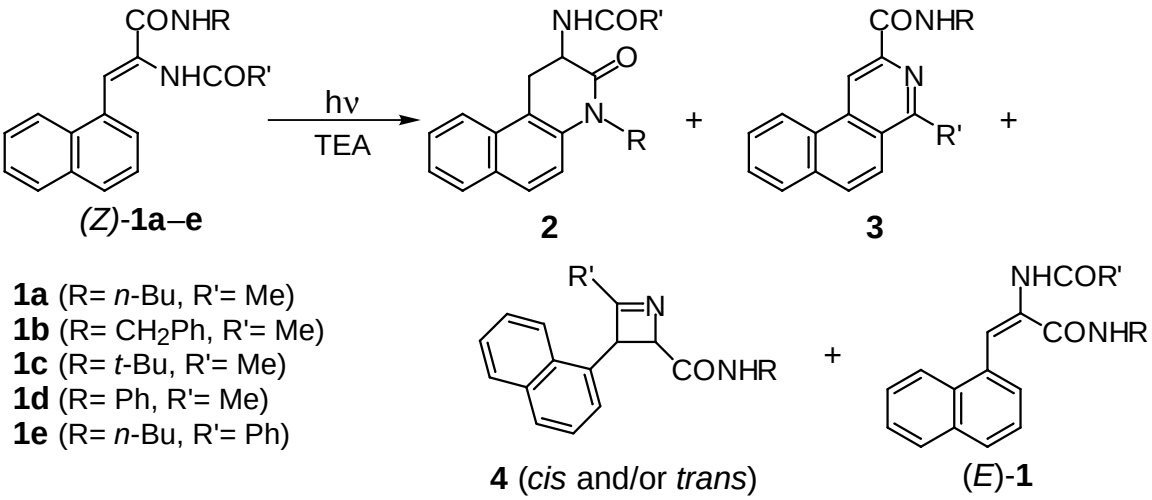
Abstract–On irradiation in the presence of triethylamine, the title compounds (**1**) having *n*-butyl and benzyl groups gave preferentially dihydrobenzoquinolinones (**2**) *via* electron transfer, whereas the introduction of the bulky *tert*-butyl and phenyl substituents into **1** resulted in the formation of benzoisoquinoline (**3**) and 1-azetine (**4**) derivatives without affording **2**.

In recent years much attention has been devoted to the synthetic application of excited-state processes initiated by electron transfer (ET), owing to the fact that many photoinduced ET reactions proceed in high chemical and quantum yields enabling the construction of heteroatom-containing polycyclic compounds.[1,2] In the course of our systematic study towards the characterization of the excited-state reactions of substituted α-dehydrophenylalanines, we have discovered interesting photocyclization reactions giving isoquinoline and 1-azetine derivatives.[3] If we introduce a naphthyl group (instead of a phenyl) into α-dehydroamino acids, it is expected that we might be able to explore ET-initiated photoreactions of naphthyl-substituted α-dehydroamino acid derivatives in the presence of an aliphatic amine.[1,4] In this communication we demonstrate that the photoreaction of *N*-acyl α-dehydro(1-naphthyl)alanines (**1**) bearing *n*-butyl and benzyl groups on its carboxamide side chain in MeOH containing triethylamine (TEA) proceeds by an ET mechanism to give 1,2-dihydro[*f*]benzoquinolinone derivative (**2**) as the major product, whereas the introduction of bulky *tert*-butyl and phenyl substituents into **1** completely suppresses the appearance of **2** resulting in the formation of benzo[*f*]isoquinoline (**3**) and 1-azetine (**4**) derivatives (Scheme 1).

The starting (*Z*)-isomers (**1a**–**e**) were prepared in nearly quantitative yields by the ring-opening reactions of 1-naphthyl-substituted oxazolones with primary amines.[5] After a nitrogen-purged MeOH solution of **1a** (5.0×10^{-3} mol dm^{-3}) containing TEA (0.10 mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 450 W high-pressure Hg lamp for 1.5 h at room temperature, the product mixture obtained was subjected to preparative thin-layer chromatography over silica gel, which allowed us to isolate (*Z*)-**1a** (22%: isolated yield), (*E*)-**1a** (20%), **2a** (12%), and **3a** (5%).[6] A careful ^{1}H NMR analysis of the product mixture suggested the detectable formation of the *cis*-azetine isomer (**4a**) whose ring-proton signals with the $J_{3,4}$ value of 10.7 Hz were detected at 5.04 and 6.50 ppm,[3] though no attempt was made to isolate **4a** owing

to its poor yield (Scheme 1).



Scheme 1 Product distribution derived from the photoreaction of (*Z*)-**1a**–**e** in MeOH containing TEA.

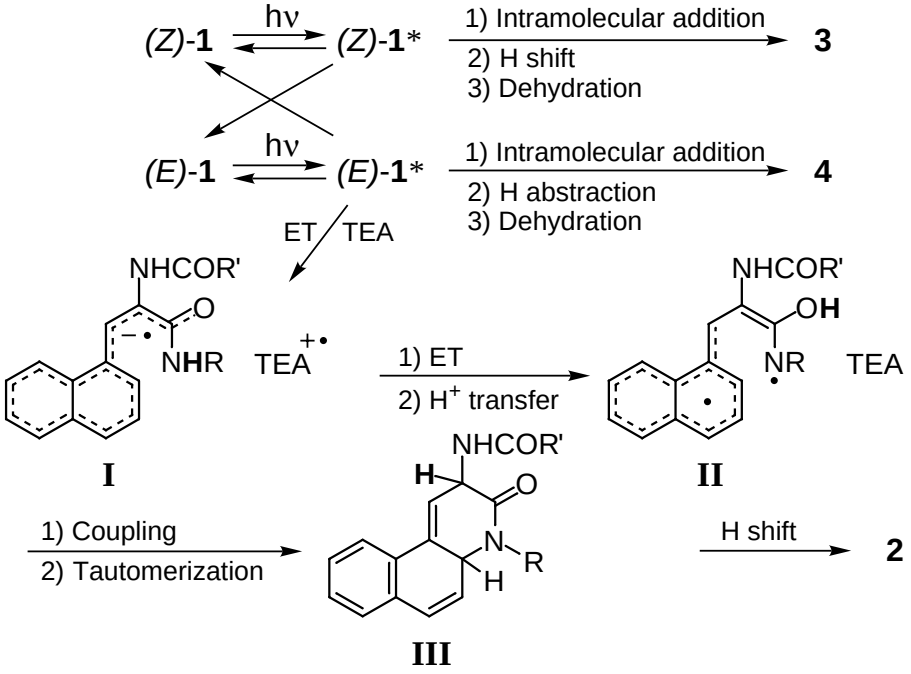
Table 1. Relation between irradiation time and composition (%) of each compound in methanol[a]

Compound	Irradiation time /h						
	0	0.5	1.0	1.5	2.0	3.0	5.0
(Z)-**1a**	100	66.0	45.9	37.4	27.7	16.3	3.2
(E)-**1a**	0	28.8	38.2	36.7	32.8	20.3	4.5
2a	0	3.9	10.3	18.3	28.6	47.9	71.7
3a	0	1.0	5.1	6.9	9.9	13.9	18.4
4a	0	0.2	0.4	0.7	1.0	1.6	2.1

[a] At regular time intervals, an appropriate amount of the solution being irradiated was pipetted off and concentrated to dryness in vacuo, giving the residue which was subjected to ^{1}H NMR analysis in DMSO-d_6. ^{1}H NMR compositions were estimated from the area ratio of a given signal for each compound.

The finding that the photoproducts (**2**–**4**) are stable enough such that they undergo only negligible decomposition under the irradiation conditions made it possible to monitor the reactions by means of ^{1}H NMR spectroscopy, as typically shown in Table 1. The result obtained for (*Z*)-**1a** demonstrates the rapid production of (*E*)-**1a** and the subsequent increase in compositions for **2a**–**4a** with the decrease of (*E*)- and (*Z*)-isomer compositions, being consistent with the mechanism in which these excited-state isomers serve as precursors of these products. On the other hand, there was no formation of the benzoquinolinone derivative (**2a**) when an oxygen-free MeOH solution of (*Z*)-**1a** (5.0×10^{-3} mol dm^{-3}) containing no TEA was irradiated with Pyrex-filtered light (UV and ^{1}H NMR analyses), suggesting that ET from TEA to the excited-state naphthylmethylene moiety in **1a** participates in the appearance of **2a** as the primary process.

The same results were obtained also for **1b** and **1e**. The suggestion described above is substantiated by the following findings: (1) the fluorescence of **1a** (5.0×10^{-5} mol dm^{-3}) in MeOH is quenched by TEA according to the Stern-Volmer equation, $I_0/I = 1 + 4.5\pm0.5$[TEA], where I and I_0 refer to the fluorescence intensities of **1a** with and without TEA and (2) the 250 nm absorption (which is characteristic of the benzoquinolinone skeleton) increases with an increase in TEA concentration (absorbance at 250 nm= 1.00 and 2.20 at [TEA]= 0 and 0.10 mol dm^{-3}, respectively) when a MeOH solution of **1a** (5.0×10^{-5} mol dm^{-3}) is irradiated for 12 min in the same manner. Chem 3D modeling of (*Z*)- and (*E*)-**1a** showed that the (*E*)-isomer adopts a most suitable conformation for the cyclization affording **2a**. Accordingly, these considerations (in addition to the previous result)[3a] led us to propose Scheme 2 that explains the observed product distribution.



Scheme 2 Proposed mechanism for the formation of **2**.

According to Scheme 2, we predict that the *N*-alkyl amide hydrogen in the starting **1** should migrate to the 2-position of the benzoquinolinone ring upon forming **2**, and that the TEA concentration should remain constant during the reaction. After the H-D exchange reaction for the amide protons of **1a** (5.0×10^{-3} mol dm^{-3}) in MeOD was completed (12 h incubation), deuterated **1a** was irradiated for 5.0 h in the same solvent under the same conditions. ^{1}H NMR spectra of the product in DMSO-d_6, obtained after usual work-up, clearly showed disappearance of the 4.56 ppm signal which was ascribed to the proton attached to the 2-position in the ring. Furthermore, a ^{1}H NMR analysis of the reaction mixture obtained by the irradiation of a CD_3OD solution of **1a** (0.025 mol dm^{-3}) containing TEA (0.10 mol dm^{-3}) and 1,4-dioxane (internal standard; 0.10 mol dm^{-3}) for a given period of time showed no sign of a change in this amine concentration during the reaction. These results are consistent with our prediction, thereby substantiating the mechanism proposed for the formation of **2**.

In Table 2 are shown substituent and solvent effects on the product distribution and composition. Interestingly, the introduction of bulky *tert*-butyl (**1c**) and phenyl (**1d**) groups into **1** completely inhibits the appearance of the corresponding benzoquinolinone derivative (**2**), while the phenyl substituent in **1d** substantially lowers the excited-state reactivity of this naphthylalanine derivative. Because the fluorescence of **1c** was also quenched by TEA ($I_0/I = 1 + 3.0 \pm 0.4$[TEA]), ET from TEA to the excited-state (*E*)-**1c** must take place giving the **1c** anion and TEA cation radical pair (**I**) (Scheme 2). Taking into account that the enol-type biradical (**II**) [generated by ET and the subsequent proton transfer within its precursor (**I**)] may adopt a nearly planar structure, it is reasonable to conclude that the bulky *tert*-butyl and phenyl substituents exert their great steric effects on the coupling process of **II** so as to completely inhibit this process, providing also a piece of evidence for the mechanism shown in Scheme 2. There were negligible products other than (*E*)-**1**, **3**, and **4** in the reaction mixtures obtained by the irradition of **1c** and **1d** in the presence (and even in the absence) of TEA (^{1}H NMR analysis). This observation suggests that on prevention of the cyclization of **II** affording **2** *via* **III**, the intermediate (**II**) eventually reverts to the (*E*)-isomer.

Table 2. Substituent and solvent effects on the composition of each compound obtained by 1.0 and 5.0 h irradiations of the starting *(Z)*-**1a**–**e** (5.0×10^{-3} mol dm^{-3}) in a given solvent

Compound	Irradiation time /h	Composition (%)				
		(Z)-**1**	*(E)*-**1**	**2**	**3**	**4**
1a[a]	1.0 (5.0)	45.9 (3.2)	38.2 (4.5)	10.3 (71.7)	5.1 (18.4)	0.4 (2.1)
1b[a]	1.0 (5.0)	49.8 (4.7)	37.9 (6.6)	8.0 (68.6)	3.8 (17.5)	0.4 (2.7)
1c[a]	1.0 (5.0)	52.1 (27.6)	40.0 (37.6)	0 (0)	6.4 (25.8)	1.4 (9.0)
1d[a]	1.0 (5.0)	82.2 (51.9)	17.1 (38.6)	0 (0)	0.7 (4.6)	0 (4.9)
1e[a]	1.0 (5.0)	65.4 (11.8)	27.3 (11.7)	6.0 (64.1)	0 (1.7)	1.3 (10.8)
1a[b]	1.0 (5.0)	70.0 (38.0)	24.3 (26.3)	3.6 (25.3)	2.0 (10.5)	0 (0)

[a] In MeOH. [b] In MeCN.

The previous finding[3b] that intramolecular cyclization in the excited-state (*Z*)-*N*-benzoyl-α-dehydrophenylalanines leading to isoquinoline derivatives is almost completely suppressed (owing to stereoelectronic effects of the bulky benzoyl group) to selectively give 1-azetines *via* the (*E*)-isomer provides a good explanation for the increased composition of the azetine (**4e**) (10.8%) as compared to that of **4a** (2.1%, 5.0 h irradiation).

An analysis of solvent effects on the reactivity of **1a** shows that the excited-state reactivities of both isomers are much higher in the protic polar solvent, MeOH, than in the aprotic polar solvent, MeCN, which lowers not only the relative rate for the $Z \rightarrow E$ isomerization (1.0 h irradiation, Table 2) but also the product-composition ratio **2a**/(**2a**+**3a**+**4a**) (77.8→70.7% at 5.0 h irradiation). The fact that a tertiary amine undergoes hydrogen-bonding solvation to decrease its electron-donating ability,[4] therefore, confirms that this solvation of the excited singlet-state (**1a**) by MeOH accelerates the $Z \rightarrow E$ isomerization and then greatly

enhances the electron-accepting ability of the naphthylmethylene moiety.

Although there are several synthetic routes to lactams fused to an aromatic ring,[7] no convenient photochemical route to substituted dihydroquinolinones is known. The procedure for preparing the starting **1** is very simple and is easily applicable to its related compounds carrying less bulky alkyl substituents on the carboxamide side chain. Taking into consideration the fact that the benzoquinolinone derivatives (**2**) obtained are photochemically very stable, we are led to conclude that the photoreaction of substituted α-dehydro(1-naphthyl)alanines (**1a**–**e**) in the presence of TEA presents a new method for constructing the quinolinone skeleton and also offers significant information regarding the mechanism for the novel photocyclization reactions of **1** *via* ET.

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6. Selected data for (*Z*)-**1a**: mp 187.0–188.5 °C (EtOH-hexane); IR (KBr) ν/cm^{-1} = 3306, 1660, 1625, 1550; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 0.90 (3H, t, *J*= 7.3 Hz), 1.33 (2H, tq, *J*= 7.3, 7.6 Hz),1.48 (2H, tt, *J*= 6.7, 7.6 Hz), 1.83 (3H, s), 3.17 (2H, dt, *J*= 6.4, 6.7 Hz), 7.46 (1H, s), 7.50–7.57 (4H, m), 7.89 (1H, d, *J*= 7.9 Hz), 7.93–7.96 (2H, m), 8.06 (1H, t, *J*= 6.4 Hz), 9.20 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 13.7, 19.5, 22.6, 31.2, 38.8, 123.7, 124.1, 125.4, 125.9, 126.2(2C), 128.2, 128.3, 131.0, 131.3, 132.7, 133.1, 164.6, 169.3. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03%. Found: C, 73.54; H, 7.02; N, 9.13%.
   For (*E*)-**1a**: mp 148.0–149.0 °C (EtOAc-hexane); IR (KBr) ν/cm^{-1} = 3250, 1650, 1629, 1539; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 0.66 (3H, t, *J*= 7.3 Hz), 0.88 (2H, tq, *J*= 7.3, 7.6 Hz), 1.06 (2H, tt, *J*= 7.0, 7.3 Hz), 2.00 (3H, s), 2.87 (2H, dt, *J*= 6.1, 7.0 Hz), 7.36–7.40 (2H, m), 7.43 (1H, s), 7.52 (2H, m), 7.75 (1H, t, *J*= 6.1 Hz), 7.77–7.79 (1H, m), 7.89 (1H, d, *J*= 7.3 Hz), 7.98 (1H, d, *J*= 7.6 Hz), 9.69 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 13.6, 19.4, 23.5, 30.3, 38.3, 112.6, 124.6, 125.3, 125.6, 125.8, 126.0, 127.1, 128.2, 131.3, 132.6, 133.1, 135.1, 164.4, 168.6. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03%. Found: C, 73.29; H, 7.19; N, 9.14%.
   For **2a**: mp 157.0–158.0 °C (EtOH); IR (KBr) ν/cm^{-1} = 3308, 1668, 1642; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 0.89 (3H, t, *J*= 7.3 Hz), 1.53 (2H, m), 1.95 (3H, s), 2.96 (1H, dd, *J*= 14.3, 15.6 Hz), 3.64 (1H, dd, *J*= 6.1, 15.6 Hz), 3.95–4.14 (2H, m), 4.56 (1H, ddd, *J*= 6.1, 7.9, 14.3 Hz), 7.45 (1H, dd, *J*= 7.6, 7.9 Hz), 7.51 (1H, d, *J*= 8.2 Hz), 7.55 (1H, dd, *J*= 7.6, 8.2 Hz), 7.91 (1H, d, *J*= 8.5 Hz),

7.92 (1H, d, *J*= 8.5 Hz), 8.00 (1H, d, *J*= 8.2 Hz), 8.34 (1H, d, *J*= 7.9 Hz); ^{13}C NMR (DMSO-d_6)δ= 13.7, 19.4, 22.6, 27.0, 29.4, 41.7, 48.1, 116.2, 118.2, 123.1, 124.6, 127.1, 128.1, 128.3, 129.6, 130.8, 136.0, 168.2, 169.4. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03%. Found: C, 73.24; H, 7.13; N, 9.11%.

For **3a**: mp 61.5–62.5 °C (EtOAc-hexane); IR (KBr) ν/cm^{-1}= 3382, 1668, 1530; ^{1}H NMR (500 MHz, DMSO-d_6) δ= 0.94 (3H, t, *J*= 7.3 Hz), 1.37 (2H, tq, *J*= 7.3, 7.6 Hz), 1.60 (2H, tt, *J*= 7.0, 7.6 Hz), 3.04 (3H, s), 3.41 (2H, dt, *J*= 6.1, 7.0 Hz), 7.81–7.85 (2H, m), 8.12 (1H, d, *J*= 9.2 Hz), 8.13 (1H, m), 8.17 (1H, d, *J*= 9.2 Hz), 8.83 (1H, t, *J*= 6.1 Hz), 8.92 (1H, m), 9.12 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 13.7, 19.6, 22.6, 31.5, 38.6, 113.0, 122.8, 123.8, 126.2, 127.9, 128.65, 128.71, 129.1, 129.5, 132.9, 134.6, 144.4, 157.0, 164.1. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58%. Found: C, 77.85; H, 7.09; N, 9.74%.

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