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Novel Photocyclization of Substituted α-Dehydronaphthylalanines via Electron Transfer

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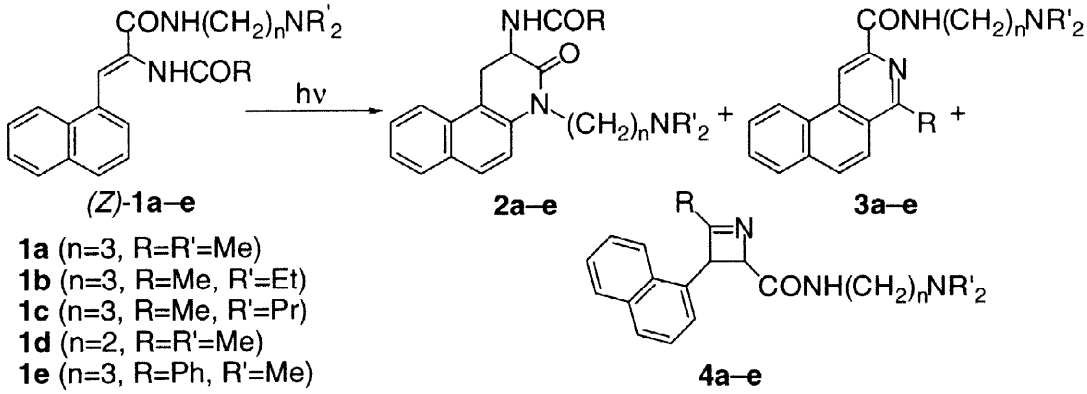
Abstract: Irradiation of substituted *N*-acyl α-dehydro(1-naphthyl)alanines (**1**) having the dialkylamino donor at the end of a side chain in methanol was found to give 1,2-dihydrobenzo[*f*]quinolinones (**2**) in good yields, which were formed via the electron-transfer reaction in the excited-state (*E*)-isomers, while intramolecular photoaddition reactions in the (*Z*)- and (*E*)-isomers afforded minor amounts of benzo[*f*]isoquinoline (**3**) and 1-azetine (**4**) derivatives, respectively. Analysis of substituent effects on the product distribution showed that the bulky diisopropylamino donor as well as the *N*-benzoyl group exerts their effects so as to enhance the relative yield of **3** to **2**.

In recent years much attention has been devoted to the synthetic application of excited-state processes initiated by one-electron transfer, owing to the fact that many photochemical electron-transfer (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 toward the characterization of the excited-state reactions of substituted α-dehydroamino acids[3] and dipeptide model compounds,[4] we discovered interesting photoaddition in dehydroamino acids as well as an efficient ET reaction in dipeptides with a 1-naphthyl acceptor and a dialkylamino donor. Thus, we designed *N*-acyl α-dehydro(1-naphthyl)alanines (**1**) for ET photochemistry of α-dehydroamino acids. In this communication we highlight the utility of ET reaction of **1** in the synthesis of heterocycles of a novel ring structure.



Scheme 1

The starting (*Z*)-isomers (**1a–e**) were prepared by the ring-opening reactions of 1-naphthyl-substituted oxazolones with dialkylaminoalkylamine in nearly quantitative yields.[5,6] After a nitrogen-purged methanol solution of **1a** (5.0×10^{-3} mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 400 W high-

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pressure Hg lamp for 120 min at room temperature, the crystalline product mixtures obtained were washed first with small amounts of dry ether and then with hexane, giving analytically pure 1,2-dihydrobenzo[*f*]quinolinone derivative (**2a**) in 60% yield, the structure of which was determined by its 2D NMR (^{1}H–^{1}H and ^{1}H–^{13}C COSY) spectra.[6] In addition, preparative thin-layer chromatography (silica gel) of the residual solid [that was obtained by evaporating the filtrate (ether–hexane) to dryness] enabled isolation of substituted benzo[*f*]isoquinoline (**3a**; <5%).[6] Careful ^{1}H NMR analysis of the product mixture suggested that there was very little formation of the *cis*-azetine isomer (**4a**) whose ring-proton signals with the $J_{3,4}$ value of 10.7 Hz were detected at 5.06 and 6.53 ppm,[3] though no attempt was made to isolate **4a** (Scheme 1).

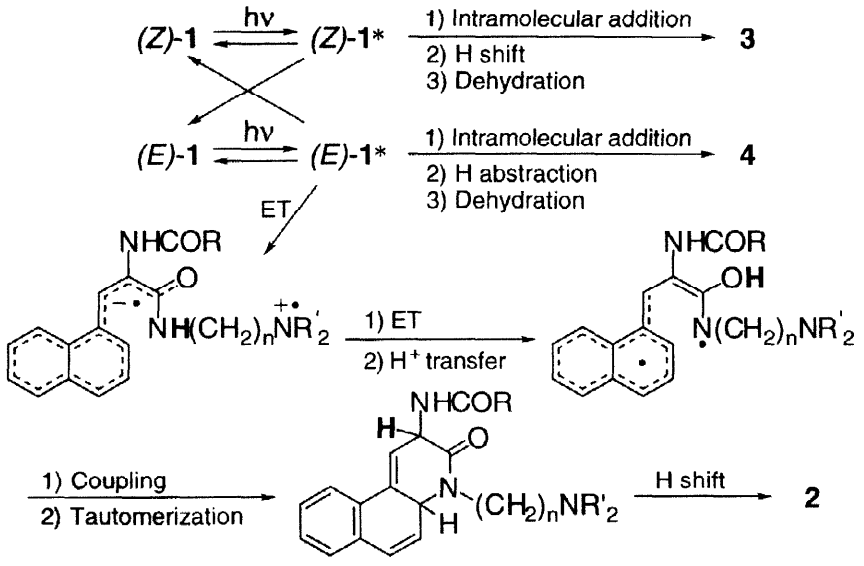
Table 1. Relation between irradiation time and composition (%) of each compound in methanol[a]

Compd	Irradiation time /min						
	0	15	30	45	60	90	120
(Z)-**1a**	100	39.0	27.4	18.7	11.8	3.2	0
(E)-**1a**	0	40.5	31.6	21.8	15.1	4.9	1.5
2a	0	14.8	31.6	46.2	58.9	74.9	78.5
3a	0	5.1	8.2	11.4	12.1	14.3	17.6
4a	0	0.5	1.2	1.7	2.1	2.7	2.4

[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 used allowed us to trace the reactions by means of ^{1}H NMR spectroscopy, as typically shown in Table 1. In a previous study[3] it was found that the rapid $Z \rightarrow E$ isomerization of *N*-acetyl α-dehydrophenylalanines occurs prior to the appearance of the photoproducts and, additionally, induces a relatively large downfield shift of the *N*-acetyl amide proton signal. Thus, taking into account the fact that the *N*-acetyl amide proton of (*Z*)-**1a** exhibits its singlet peak at 9.25 ppm, it is reasonable to assign the 9.70 ppm signal to the amide proton of (*E*)-**1a**.[7] The results in Table 1 demonstrate the rapid production of (*E*)-**1a** and the subsequent increase in yields for **2a**–**4a** with the decrease of these isomer yields, being consistent with the mechanism in which the excited-state (*E*)- and (*Z*)-isomers serve as precursors of these products. On the other hand, there was no indication of the formation of a benzoquinolinone derivative when an oxygen-free methanol solution of *N*-acetyl α-dehydro(1-naphthyl)alanine [(*Z*)-**5**] having the methyl group instead of the dimethylamino donor in **1a** was irradiated in the same manner as that described above (^{1}H NMR and UV analyses).[8] In addition to this finding, the occurrence of intramolecular fluorescence quenching in **1a** (emission-intensity ratio of **5** to **1a** at 376 nm= 1.4 in methanol) confirms that ET from the dimethylamino nitrogen to the excited-state naphthylmethylene moiety participates in the appearance of **2a** as the primary process. Chem 3D modeling of (*Z*)- and (*E*)-**1a** revealed that the (*E*)-isomer adopts a most suitable conformation for "through-space" ET. Accordingly, these considerations led us to propose Scheme 2 that explains the observed product distribution.

According to Scheme 2, we predict that the *N*-aminoalkyl amide hydrogen in the starting **1** should migrate to the 2-position of the benzoquinolinone ring upon forming **2**. After the H-D exchange reaction for the amide protons of **1a** in MeOD was completed (12 h incubation), deuterated **1a** was irradiated for 120 min in the same solvent under similar conditions. ^{1}H NMR spectra of the product in DMSO-d_6, obtained after usual work-up, clearly showed disappearance of the 4.58 ppm signal that had been ascribed to the proton attached to the 2-position in the ring. The above result is consistent with our prediction, thereby substantiating the mechanism proposed for the formation of **2**. In Table 2 are indicated substituent effects on the product distribution.



Scheme 2

Table 2. Substituent effects on the product distribution of the starting *(Z)*-**1a**, obtained in methanol

Compd	Irradiation time /min	Composition (%)				
		(Z)-**1**	*(E)*-**1**	**2**	**3**	**4**
1a	15 (120)	39.0 (0)	40.5 (1.5)	14.8 (78.5)	5.1 (17.6)	0.5 (2.4)
1b	15 (120)	46.8 (5.9)	36.0 (0.8)	14.6 (83.8)	2.0 (5.9)	0.7 (3.6)
1c	15 (120)	33.4 (0)	31.4 (0)	17.3 (49.8)	17.2 (48.8)	0.7 (1.4)
1d	15 (120)	41.3 (1.2)	39.6 (1.1)	12.5 (75.0)	5.8 (19.7)	0.8 (3.0)
1e	15 (120)	52.8 (1.1)	23.8 (1.1)	10.7 (45.5)	10.9 (46.1)	1.8 (6.2)

Interestingly, the introduction of a dipropylamino donor or *N*-benzoyl group into **1** greatly increases the relative yield of **3** to **2** as compared with that of **1a** with dimethylamino and *N*-acetyl substituents, while the diethylamino donor lowers the product ratio **3/2** to some extent (120 min irradiation). Since both electron-donating ability and steric bulkiness of the alkyl substituents on the amino nitrogen should be factors controlling the ET rate in the (*E*)-isomer,[4] a dramatic increase in the product ratio **3/2** for **1c** (0.98), compared with that for **1b** (0.07), may be explained in terms of the much larger steric bulkiness of the dipropylamino group that results in an acceleration of the reaction forming **3c** via (*Z*)-**1c***. Additionally, the difference in this product ratio between **1a** (0.22) and **1b** (0.07) should be due to the greater electron-donating ability of the diethylamino nitrogen than that of the dimethylamino. It is likely that dimethyl- and diethyl-amino groups in the (*E*)-isomer exert their steric effects on the ET rate to a similar extent.

The previous finding[3] that intramolecular addition in the excited-state (*Z*)-*N*-benzoyl α-dehydrophenylalanines is completely suppressed (owing to stereoelectronic effects of the bulky benzoyl group) to selectively give 1-azetines via the (*E*)-isomer provides an explanation for the increased yield of the azetine **4e** but cannot explain the formation of a substantial amount of the benzoisoquinoline **3e**. The higher electron-donating ability of the 1-naphthylmethylene moiety than the benzylidene in the excited state[9] as well as the stronger electron-accepting power of the benzoyl than the acetyl makes it possible to stabilize the excited-state (*Z*)-isomer through a charge transfer-type interaction and thereby to inhibit the isomerization to the (*E*)-isomer, resulting in an increase in the product ratio **3/2** as observed. The (*Z*)/(*E*) isomer ratio of >2 at the early stage of the reaction (15 min irradiation) for **1e** supports the above interpretation.

In conclusion, the photo-induced ET reaction of *N*-acyl α-dehydro(1-naphthyl)alanine derivatives constitutes a novel photochemical method for the construction of a benzoquinolinone ring structure.

References and Notes

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6. Data for (*Z*)-**1a**: mp 154.0–155.0℃. UV (MeOH): 224 (ε 48500), 310 nm (13300). IR (KBr): 3300, 3120, 2970, 2760, 1620 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.63 (tt, 2H, *J*= 7.0, 7.0 Hz), 1.85 (s, 3H), 2.14 (s, 6H), 2.27 (t, 2H, *J*= 7.0 Hz), 3.22 (dt, 2H, *J*= 5.5, 7.0 Hz), 7.48 (s, 1H), 7.51–7.59 (m, 4H), 7.95 (d, 1H, *J*= 3.1 Hz), 7.96 (dd, 2H, *J*= 4.9, 5.2 Hz), 8.18 (t, 1H, *J*= 5.5 Hz), 9.25 (s, 1H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 22.9, 26.7, 37.9, 45.1 (2C), 57.1, 123.0, 124.1, 125.4, 125.9, 126.1, 126.2, 128.3, 128.4, 131.0, 131.3, 132.6, 133.1, 164.5, 169.3. Anal. Calcd (Found) for $C_{20}H_{25}N_3O_2$: C, 70.77 (70.36); H, 7.42 (7.41); N, 12.38% (12.14%).
Data for **2a**: mp 148.0–149.5℃. UV (MeOH): 250 (ε 44100), 280 (5540), 292 (6740), 303 (6080), 320 (2280), 336 nm (1560). IR (KBr): 3300, 1630 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.63–1.75 (m, 2H), 1.96 (s, 3H), 2.11 (s, 6H), 2.18–2.30 (m, 2H), 3.00 (dd, 1H, *J*= 14.3, 15.5 Hz), 3.66 (dd, 1H, *J*= 6.4, 15.5 Hz), 3.99–4.12 (m, 2H), 4.58 (ddd, 1H, *J*= 6.4, 7.9, 14.3 Hz), 7.45 (dd, 1H, *J*= 7.0, 7.6 Hz), 7.54 (d, 1H, *J*= 8.9 Hz), 7.55 (dd, 1H, *J*= 7.0, 8.5 Hz), 7.91 (d, 1H, *J*= 7.6 Hz), 7.92 (d, 1H, *J*= 8.9 Hz), 7.99 (d, 1H, *J*= 8.5 Hz), 8.35 (d, 1H, *J*= 7.9 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 22.6, 25.3, 27.0, 40.8, 45.1 (2C), 48.0, 56.3, 116.1, 118.2, 123.0, 124.6, 127.0, 128.1, 128.3, 129.6, 130.8, 136.2, 168.1, 169.3. Anal. Calcd (Found) for $C_{20}H_{25}N_3O_2 \cdot H_2O$: C, 67.20 (67.06); H, 7.61 (7.52); N, 11.76% (11.56%).
Data for **3a**: oily liquid. UV (MeOH): 252 (ε 40300), 301 (12200), 312 (12500), 336 (3250), 352 nm (3000). IR (neat): 3370, 1700, 1650 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.74 (tt, 2H, *J*= 6.7, 7.0 Hz), 2.19 (s, 6H), 2.34 (dt, 2H, *J*= 6.1, 6.7 Hz), 3.04 (s, 3H), 3.44 (t, 2H, *J*= 7.0 Hz), 7.83 (d, 1H, *J*= 6.4 Hz), 7.84 (dd, 1H, *J*= 6.4, 7.0 Hz), 8.13 (m, 2H), 8.18 (d, 1H, *J*= 9.1 Hz), 8.93 (dd, 1H, *J*= 6.1, 7.0 Hz), 9.13 (s, 1H), 9.18 (t, 1H, *J*= 6.1 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 22.6, 26.9, 37.9, 45.2 (2C), 57.4, 112.9, 122.8, 123.8, 126.2, 127.9, 128.7, 129.0, 129.6, 132.8, 134.6, 144.4, 157.0, 164.0. Anal. Calcd (Found) for $C_{20}H_{23}N_3O \cdot 0.5H_2O$: C, 72.60 (72.70); H, 7.03 (7.32); N, 12.52% (12.72%). Spectroscopic data and physical properties of (*Z*)-**1b–e** and **2b–e** will be given elsewhere.
7. Any attempt to isolate (*E*)-**1a** from the mixture of (*Z*)- and (*E*)-isomers was not fruitful. However, in addition to the proton signals of (*Z*)-**1a** we were able to find the proton signals that are attributable to (*E*)-**1a** on the ^1H NMR spectrum of the isomer mixture.
8. The rapid isomerization of (*Z*)-**5** (5.0×10^{-3} mol dm^{-3}) to (*E*)-**5** took place to give the (*Z*)/(*E*) isomer ratio of 3.2 after 15 min irradiation. This isomer ratio was determined by the area ratio of the *N*-acetyl amide proton signals for (*Z*)-**5** (9.21 ppm) and (*E*)-**5** (9.71 ppm). On the other hand, irradiation of a methanol solution of (*Z*)-**5** (5.0×10^{-5} mol dm^{-3}) afforded no 250 nm absorption band which is characteristic of the benzoquinolinone skeleton.
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