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Simultaneous Formation of Isoquinoline and 1-Azetine Derivatives via Photoacetyl Migration of Substituted α-Dehydrophenylalanine

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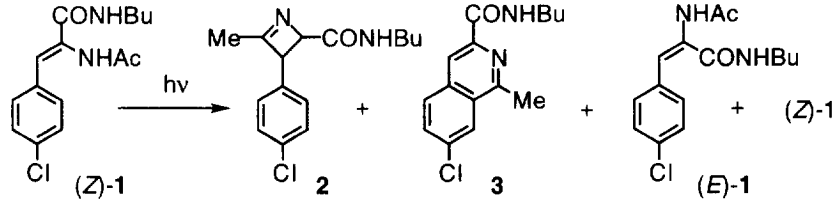
Abstract: Irradiation of substituted α-dehydrophenylalanine in methanol or acetonitrile with Pyrex-filtered light was found to give isoquinoline and 1-azetine derivatives in relatively good yields, which may be formed via 1,5-acetyl shift from the (*Z*)-isomer and 1,3-acetyl migration from the (*E*)-isomer, respectively. The photoreaction in methanol afforded the azetine in preference to the isoquinoline, while the reverse result was obtained in acetonitrile. Copyright © 1996 Elsevier Science Ltd

Synthetic organic photochemistry has continued to contribute to the developement of efficient and selective transformations for the preparation of natural products as well as complicated molecules which could not have been synthesized by conventional methods.[1] Efficient synthetic routes to α-dehydroamino acids and dehydrooligopeptides have been discovered,[2] whereas there has been only limited preliminary investigation of the photochemistry of these dehydroamino acid derivatives.[3] Thus, systematic study is required to characterize the photochemical processes of α-dehydroamino acids. This paper reports the novel photoreaction of substituted α-dehydrophenylalanine **1** [*N*-butyl-2-acetylamino-3-(4-chlorophenyl)acrylamide; (*Z*)-isomer] derived from the ring-opening reaction of 2-methyl-4-(4-chlorobenzylidene)-5(4*H*)-oxazolone with butylamine.[4]

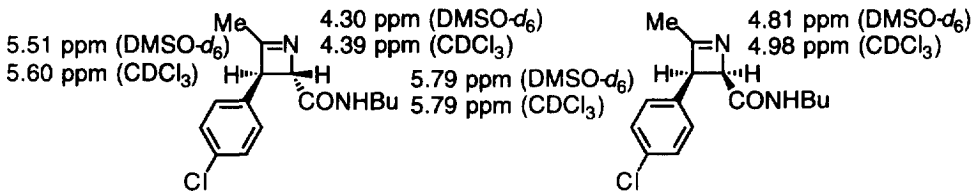
Irradiation of a nitrogen-purged methanol solution of **1** (0.010 mol dm^{-3}) with Pyrex-filtered light (>280 nm) from a 400 W high-pressure Hg lamp for 24 h at room temperature gave product mixtures with Rf values of 0.26, 0.40, 0.70 and 0.86 on a silica gel TLC plate (EtOAc). Column chromatography of the reaction mixtures over silica gel allowed us to isolate (*E*)-isomer of **1** [(*E*)-**1**; Rf= 0.26], the starting **1** [(*Z*)-**1**; Rf= 0.40], *trans*-2-



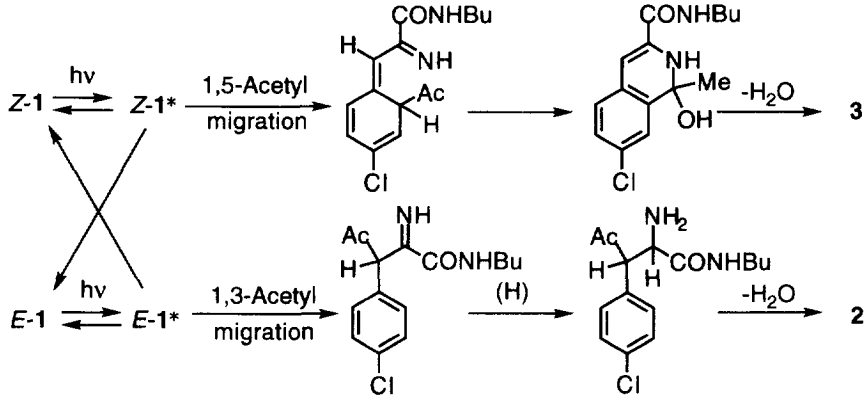
Scheme 1

methyl-3-(4-chlorophenyl)-4-butylaminocarbonyl-1-azetine monohydrate (**2**; Rf= 0.70) and 1-methyl-3-butylaminocarbonyl-7-chloroisoquinoline (**3**; Rf= 0.86) in 0.4, 6.8, 21 and 29% yields, respectively (Scheme 1). The structures of isolated products were determined based on their spectroscopic and physical properties.[5]

The much lower yield of (*E*)-**1** than that expected from a ^{1}H NMR analysis of the mixtures must be due to conversion into the thermodynamically more stable (*Z*)-**1** during work-up. The NMR analysis also reveals that there is formation of the *cis*-azetine isomer, isolation of which was unsuccessful, with $J_{3,4}$ on the azetine ring= 9.4 (DMSO-d_6) and 10.9 Hz ($CDCl_3$) (Karplus $J_{3,4}$= 8.2 Hz)[6] along with the isolated *trans*-azetine [$J_{3,4}$= 7.2 (DMSO-d_6) and 7.6 Hz ($CDCl_3$); Karplus $J_{3,4}$= 4.4 Hz]. The structure of **2** was verified also by ^{1}H–^{1}H and ^{13}C–^{1}H COSY spectra.



The finding that ^{1}H NMR spectrum obtained after 24 h irradiation can be explained in terms of overlapping of the spectra of **1** (*Z* and *E*), **2** (*trans* and *cis*) and **3** made it possible to trace the reaction by means of ^{1}H NMR spectroscopy. As seen from Table 1, after 0.5 h irradiation (*E*)-**1** was detected in 15% yield without leading to either **2** or **3**. Additionally, its yield went up to 25% and then gradually decreased as the reaction proceeded, indicating that the isomerization of (*Z*)-**1** to (*E*)-**1** must take place prior to the formation of **2** and **3**. Thus, we were led to propose Scheme 2 to explain the observed product distribution.



Scheme 2

Interestingly, irradiation of **1** in CH_3OD and CD_3OD under similar conditions resulted in an incorporation of deuterium into the 4-position on the azetine ring but did not into the isoquinoline ring, thus rationalizing the proposed Scheme 2. Taking into account that the photo-Fries rearrangements[7] as well as photoacyloxy migrations[8] proceed through a caged singlet radical pair intermediate, the acetyl migration reaction by way of a singlet radical pair is considered to be most likely candidate although there remains the possibility of concerted 1,3-sigmatropic rearrangement to eventually afford **2**. No 1,3-acyl shift in the excited-state (*Z*)-**1** occurred, presumably due to steric effects of the benzene ring. While **2** was formed in preference to **3** in methanol, the

Table 1. Relation between irradiation times and product yields (%) in methanol and acetonitrile[a]

Product	Solvent	Time/h							
		0	0.5	1	3	6	12	18	24
(Z)-**1**	MeOH	100	84	78	71	56	44	31	20
	(MeCN)	(100)	(89)	(87)	(83)	(75)	(61)	(47)	(33)
(E)-**1**	MeOH		15	19	20	25	22	18	14
	(MeCN)		(11)	(11)	(13)	(14)	(16)	(17)	(16)
trans-**2**	MeOH			1.1	3.9	10	16	27	34
	(MeCN)			(0.1)	(0.5)	(1.6)	(4.8)	(7.8)	(12)
cis-**2**	MeOH			0.3	1.2	2.7	5.0	7.0	8.0
	(MeCN)				(0.3)	(0.8)	(2.7)	(4.9)	(6.9)
3	MeOH			1.3	3.5	6.8	12	18	24
	(MeCN)			(1.2)	(4.0)	(8.0)	(16)	(24)	(32)

[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 yields were estimated from the area ratio of a given signal for each product.

reverse was found for the reaction in acetonitrile (Table 1). The fact that no incorporation of deuterium into the azetine ring is detected in the reaction in CD_3CN suggests the participation of contaminants such as water in the hydrogen abstraction step of the imine, the precursor of **2**. Accordingly, further studies are necessary in order to determine factors controlling the product ratio **2**/**3**.

Although there are extensive synthetic routes to isoquinoline[9] and 1-azetine[10] derivatives, convenient photochemical routes to these derivatives are scarcely known.[11] The procedure for preparing the starting **1** is very simple and is easily applicable to its related compounds.[12] The photoreaction of substituted α-dehydrophenylalanine described in this paper should, therefore, find application in the simultaneous synthesis of various kinds of isoquinoline and 1-azetine derivatives.

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5. Data for (*Z*)-**1**: mp 153.5–154.5°C. UV(CH_3OH): 281 nm (ε 21400). IR (KBr): 3448, 1650, 1616 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.88 (t, 3H, *J*= 7.3 Hz), 1.29 (tq, 2H, *J*= 7.3, 7.3 Hz), 1.43 (tt, 2H, *J*= 7.3, 6.5 Hz), 1.98 (s, 3H), 3.13 (dt, 2H, *J*= 6.5, 6.5 Hz), 6.95 (s, 1H), 7.43 (d, 2H, *J*= 8.5 Hz), 7.53 (d, 2H, *J*= 8.5 Hz), 7.99 (t, 1H, *J*= 6.5 Hz), 9.36 (s, 1H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.5, 22.8, 31.2, 38.8, 125.6, 128.4, 130.8, 131.0, 132.6, 133.2, 164.6 (C=O), 169.2 (C=O). Anal. Calcd (Found) for $C_{15}H_{19}N_2O_2Cl$: C, 61.12 (60.90); H, 6.50 (6.40); N, 9.50% (9.40%). Data for (*E*)-**1**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.80 (t, 3H, *J*= 7.3 Hz), 1.10 (tq, 2H, J= 7.3, 7.3 Hz), 1.29 (tt, 2H, *J*= 7.3, 7.3 Hz), 1.95 (s, 3H), 3.01 (dt, 2H, *J*= 7.3, 6.0 Hz), 6.82 (s, 1H), 7.22 (d,

2H, J= 8.4 Hz), 7.31 (d, 2H, J= 8.4 Hz), 8.10 (t, 1H, J= 6.0 Hz), 9.62 (s, 1H). This isomer was contaminated with a small amount of (*Z*)-**1**.

Data for **2**: mp 42.0–43.0°C. UV(CH_3OH): 223(ε 7410), 253(250), 259(260), 266(260), 275 nm(190). IR (KBr): 3310, 1677, 1617 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.87 (t, 3H, J= 7.4 Hz), 1.26 (tq, 2H, J= 7.4, 7.4 Hz), 1.40 (tt, 2H, J= 7.4, 7.0 Hz), 2.06 (d, 3H, J= 1.4 Hz), 3.10 (dt, 2H, J= 7.0, 6.0 Hz), 4.30 (dd, 1H, J= 7.2, 1.4 Hz), 5.51 (d, 1H, J= 7.2 Hz), 7.34 (d, 2H, J= 8.3 Hz), 7.47 (d, 2H, J= 8.3 Hz), 7.90 (t, 1H, J= 6.0 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.5, 13.6, 19.5, 31.1, 38.3, 76.8, 81.9, 127.4, 128.7, 132.7, 139.4, 164.9 (C=O), 169.7 (C=N). EI-MS: *m/z* (%) 296 (M^+, 0.36), 298 (M^++2, 0.10). Anal. Calcd (Found) for $C_{15}H_{19}N_2OCl{\cdot}H_2O$: C, 60.70 (60.70); H, 7.13 (7.13); N, 9.44% (9.43%). When *trans*-isomer was allowed to stand for several weeks at room temperature, there was indication of the appearance of an azetidine derivative obtained from the addition reaction of this isomer with water (^1H NMR). Thus, it is likely that *cis*-isomer, which should be less stable, is mainly converted into the water adduct of the azetine though no attempt was made to isolate the azetidine derivatives.

Data for **3**: mp 91.0–92.0°C. UV(CH_3OH): 235(ε 34500), 284(12400), 317(2780), 331 nm(2910). IR (KBr): 3400, 1668 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.92 (t, 3H, J= 7.3 Hz), 1.34 (tq, 2H, J= 7.3, 7.3 Hz), 1.56 (tt, 2H, J= 7.3, 6.7 Hz), 2.96 (s, 3H), 3.35 (dt, 2H, J= 6.7, 6.7 Hz), 7.87 (dd, 1H, J= 8.7, 2.0 Hz), 8.22 (d, 1H, J= 8.7 Hz), 8.35 (d, 1H, J= 2.0 Hz), 8.41 (s, 1H), 8.76 (t, 1H, J= 6.7 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 13.7, 19.6, 22.2, 31.4, 38.5, 117.8, 125.0, 127.3, 128.5, 130.9, 131.4, 133.2, 134.1, 143.0, 163.7 (C=O). Anal. Calcd (Found) for $C_{15}H_{17}N_2OCl$: C, 65.10 (65.47); H, 6.19 (6.16); N, 10.12% (10.03%).

6. Vicinal coupling constants ($J_{3,4}$) between protons on the azetine ring were roughly estimated using the Karplus equation (Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; 2nd Edn.; Pergamon Press: London, 1969, pp. 280—283). MM2 calculation of 2-methyl-3-phenyl-1-azetine allowed us to determine dihedral angles of 134.8° for the *trans*-isomer and of 0.8° for the *cis*. It is, thus, reasonable to assign the azetine with larger $J_{3,4}$ value to the *cis*-isomer and that having the smaller value to the *trans*.
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12. We prepared α-dehydrophenylalanine derivatives having substituents (R) at the 4-position on the benzene ring and determined ^1H NMR yields of each product obtained after 24 h irradiation of oxygen-free methanol solutions of these derivatives under identical conditions as follows. (*Z*)-**1**: 26(R= OCH_3); 12(CH_3); 20(H); 55%(CF_3). (*E*)-**1**: 12(R= OCH_3); 12(CH_3); 10(H); 15%(CF_3). *trans*-**2**: 11(R= OCH_3); 17(CH_3); 22(H); 7.0%(CF_3). *cis*-**2**: 8.0(R= OCH_3); 10(CH_3); 7.0(H); 1.0%(CF_3). **3**: 43(R= OCH_3); 49(CH_3); 41(H); 22%(CF_3). Spectroscopic data and physical properties of these compounds will be given elsewhere.

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