SELECTIVE FORMATION OF 1-AZETINE DERIVATIVES *VIA* 1,3-PHOTOACYL MIGRATION OF SUBSTITUTED α-DEHYDRO-PHENYLALANINES

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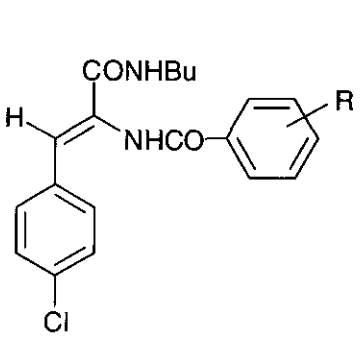
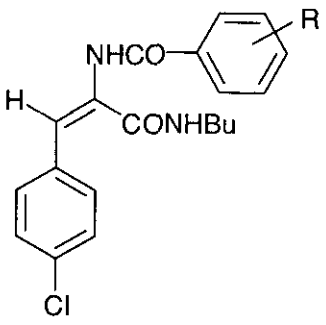
Abstract—Irradiation of (*Z*)-*N*-substituted benzoyl-α-dehydrophenylalanines in methanol with Pyrex-filtered light was found to selectively give 1-azetine derivatives, which may be derived from 1,3-acyl migration of the excited-state (*E*)-isomer, whereas no 1,5-acyl shift of the (*Z*)-isomer occurred owing to the stereoelectronic effects of the bulky aromatic acyl substituent.

Efficient synthetic routes to α-dehydroamino acids and dehydrooligopeptides have been discovered,[1] whereas there has been only limited preliminary investigation of the photochemistry of these dehydroamino acid derivatives.[2] Previously, we have reported that substituted α-dehydrophenylalanines [(*Z*)-2-acetylamino-*N*-butyl-3-(4-substituted phenyl)-2-propenamide] undergo a novel photoacetyl migration to give isoquinoline and 1-azetine derivatives in good yields.[3] As an extension of our systematic study on the photochemistry of α-dehydroamino acids, we prepared (*Z*)-2-substituted benzoylamino-*N*-butyl-3-(4-chlorophenyl)-2-propenamide (**1a–f**) by the ring-opening reactions of 2-substituted phenyl-4-(4-chlorobenzylidene)-5(4*H*)-oxazolone with butylamine,[4] and investigated the effects of aromatic acyl groups on the product distribution that had been obtained by the photoreaction of *N*-acetyl dehydrophenylalanines. In this paper we present a novel approach in which stereoelectronic effects of the aromatic acyl group force the starting **1** to choose the 1,3-photoacyl shift pathway that eventually affords only 1-azetine derivative.

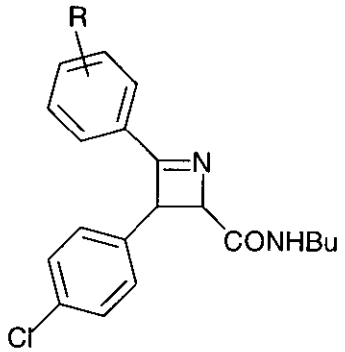
After a nitrogen-purged methanol solution of **1a** (4.0×10^{-3} mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 400 W high-pressure Hg lamp for 20 h at room temperature, the product mixture obtained was subjected to column chromatography over silica gel, which allowed us to isolate the starting **1a** [(*Z*)-**1a**, 49.0%], (*E*)-**1a** (9.1%) and *trans*-2-(4-tolyl)-3-(4-chlorophenyl)-4-butylaminocarbonyl-1-azetine (*trans*-**2a**, 19.4%).[5] The structure of *trans*-**2a** was confirmed by comparison of its spectroscopic properties with those of the previously isolated *trans*-2-methyl-3-(4-chlorophenyl)-4-butylaminocarbonyl-1-azetine.[3] Careful ^{1}H NMR analysis of the product mixture revealed that there was minor formation of the *cis*-azetine isomer (*cis*-**2a**), though its isolation was unsuccessful,[6] with a negligible amount of the expected isoquinoline. ^{1}H-^{1}H and ^{13}C-^{1}H COSY spectra also substantiated our structure determinations. The combined use of molecular mechanics (MM2) and the Karplus equation made it possible to assign the azetine with larger vicinal coupling constant ($J_{3,4}$) to the *cis*-isomer and that having the smaller $J_{3,4}$ value to



(*Z*)-**1a–f**



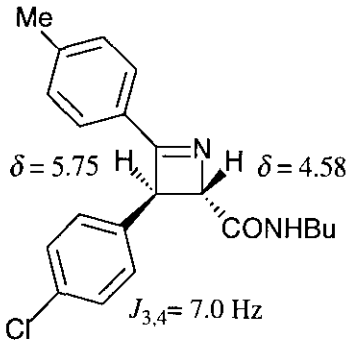
(*E*)-**1a–f**



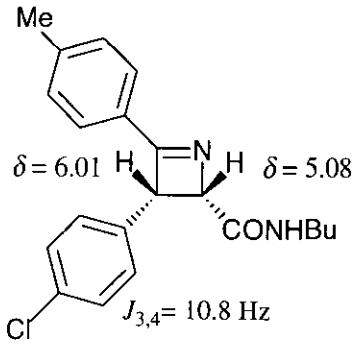
2a–f

a: R=*p*-Me, **b**: R=H, **c**: R=*p*-Cl, **d**: R=*m*-Cl, **e**: R=*o*-Cl, **f**: R=*p*-CF_3

the *trans*, as shown below.[3] In addition, PM3 calculations of the model azetine: 2,3-diphenyl-4-methylaminocarbonyl-1-azetine enabled determination of the heat of formation for *trans*-**2** (231 kJ mol^{-1}) and *cis*-**2** (243 kJ mol^{-1}), showing that the *trans*-isomer is thermodynamically more stable.[7] Thus, our calculations are consistent with the preferential formation of *trans*-**2a**. ^{1}H NMR spectra measured after 20 h



trans-**2a** (DMSO-d_6)



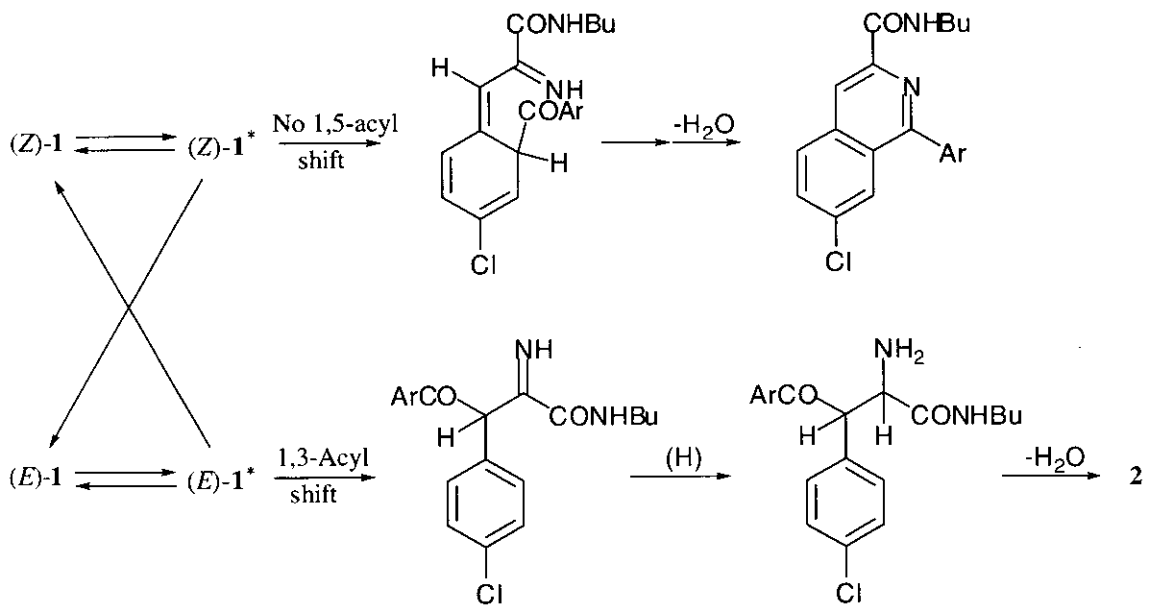
cis-**2a** (DMSO-d_6)

irradiation can be explained in terms of overlapping of the spectra of (*Z*)-**1**, (*E*)-**1**, *trans*-**2** and *cis*-**2**, and accordingly we are able to trace the reactions by means of ^{1}H NMR spectroscopy. As typically shown in Table 1, the fast isomerization of (*Z*)-**1** should occur (prior to the production of **2**) giving the (*E*)-**1** that is a likely precursor of **2**. In a previous study it was suggested that the isoquinoline is formed *via* 1,5-acetyl migration from the excited-state (*Z*)-isomer while 1,3-acetyl shift from the (*E*)-isomer is responsible for appearance of the 1-azetine.[3] If we adopt this mechanism for the simultaneous formation of these two products, the much larger steric bulkiness of the aromatic acyl groups as compared with that of the acetyl is considered to completely suppress the 1,5-acyl rearrangement resulting in an exclusive deactivation of the excited-state (*Z*)-**1** (Scheme 1).[8] The stronger electron-withdrawing ability of the aroyl groups than the acetyl may also play a role in causing the exclusive 1,3-acyl shift.

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

Product	Time/h					
	0	2	4	6	8	20
(*Z*)-**1a**	100	84.6	81.1	78.5	74.8	57.9
[(*Z*)-**1e**]	[100]	[75.4]	[71.3]	[67.5]	[65.1]	[50.6]
(*E*)-**1a**		13.0	13.5	13.7	14.0	12.6
[(*E*)-**1e**]		[21.5]	[23.2]	[25.0]	[24.7]	[26.9]
trans-**2a**		1.7	3.4	5.2	7.4	19.8
[*trans*-**2e**]		[2.4]	[4.2]	[5.9]	[7.9]	[16.3]
cis-**2a**		0.7	2.0	2.6	3.8	9.7
[*cis*-**2e**]		[0.7]	[1.3]	[1.6]	[2.3]	[6.2]

[a]At regular time intervals, an appropriate amount of the solution being irradiated was pipetted off and was 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.



Scheme 1 Possible mechanism for the selective formation of the azetine (**2**).

Significantly, the results shown in Figure 1 confirm that there is a good correlation between the relative rates at which (*E*)-**1** and **2** are generated. The increased rate for the isomerization has a propensity to accelerate the reaction that eventually gives the azetine (**2**), being consistent with the (*E*)-**1** which serves as the precursor of **2**. Because (*Z*)-**1a–f** exhibit the first absorption bands with almost the same maximum

wavelengths (λ_{max}= 282–283 nm) and intensities (ε_{max}= 2.2–2.3$\times 10^4$ dm^3 mol^{-1} cm^{-1}), it may be concluded that the isomerization of (*Z*)-**1** to (*E*)-**1** takes place in a higher efficiency on introducing a stronger electron-donating substituent and a more bulky one into the 4- and 2-positions on the benzene ring of aromatic acyl group, respectively. No attempt could not be made to compare the isomerization efficiency between **1b** and **1a,c–f** under the same reaction conditions, owing to the poor solubility of **1b**, the 20 h irradiation of which (4.0×10^{-4} mol dm^{-3}) afforded *trans*-**2b** (14.3%), *cis*-**2b** (8.7%) and (*E*)-**1b** (14.8%) along with (*Z*)-**1b** (62.2%) without forming any other products (^{1}H NMR analysis).

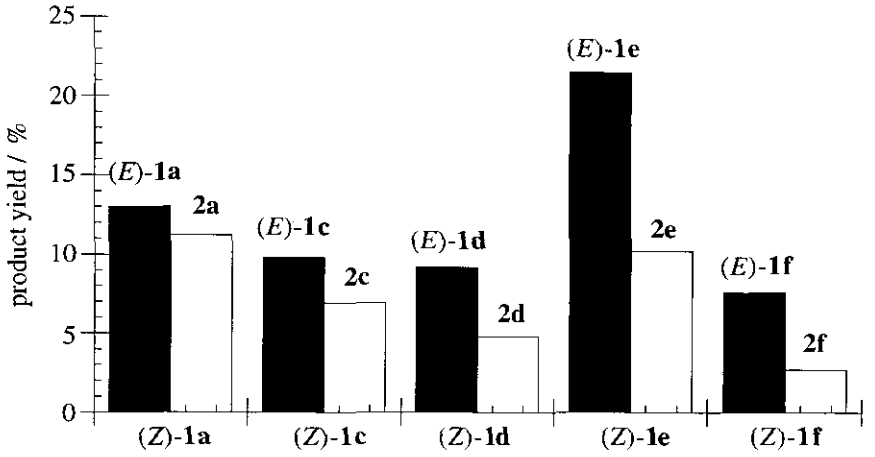


Figure 1 Correlation between chemical yields of (*E*)-**1** and **2** (*trans* + *cis*) obtained after 2 h [(*E*)-**1**] and 8 h (**2**) irradiations.

The photoreaction of *N*-aroyl α-dehydrophenylalanines described in this paper constitutes a new method for the preparation of substituted 1-azetines because convenient photochemical routes to these azetines are scarcely known.[9]

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5. Spectral data for (Z)-**1a**: mp 155.0–156.0°C; IR (KBr) ν/cm^{-1}= 3244, 1635, 1527; ^{1}H NMR (500 MHz; DMSO-d_6) δ= 0.88 (3H, t, *J*= 7.3 Hz), 1.30 (2H, tq, *J*= 7.2, 7.3 Hz), 1.44 (2H, tt, *J*= 7.2, 7.3 Hz), 2.38 (3H, s), 3.15 (2H, dt, *J*=5.8, 7.3 Hz), 7.13 (1H, s), 7.31 (2H, d, *J*= 8.2 Hz), 7.39 (2H, d,

J= 8.5 Hz), 7.55 (2H, d, *J*= 8.5 Hz), 7.89 (2H, d, *J*= 8.2 Hz), 8.15 (1H, t, *J*= 5.8 Hz), 9.85 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 13.7, 19.6, 21.0, 31.2, 38.9, 126.8, 127.9, 128.4, 128.8, 130.8, 130.9, 131.3, 132.7, 133.5, 141.6, 164.8, 165.6. Anal. Calcd for $C_{21}H_{23}N_2O_2Cl$: C, 68.01; H, 6.25; N, 7.55. Found: C, 68.19; H, 6.45; N, 7.52.

For (*E*)-**1a**: mp 144.0–145.0°C; IR (KBr) ν/cm^{-1}= 3298, 1641, 1539; ^{1}H NMR (500 MHz; DMSO-d_6) δ= 0.81 (3H, t, *J*= 7.3 Hz), 1.18 (2H, tq, *J*= 7.3, 7.3 Hz), 1.42 (2H, tt, *J*= 7.2, 7.3 Hz), 1.99 (3H, s), 3.04 (2H, dt, *J*= 5.8, 7.2 Hz), 6.69 (1H, s), 7.29 (2H, d, *J*= 8.2 Hz), 7.32 (2H, *d*, *J*= 8.5 Hz), 7.34 (2H, d, *J*= 8.5 Hz), 7.83 (2H, d, *J*= 8.2 Hz), 8.08 (1H, t, *J*= 5.8 Hz), 10.02 (1H, s); ^{13}C NMR (DMSO-d_6) δ= 13.6, 19.6, 21.0, 30.3, 48.6, 116.0, 127.8, 128.0, 128.9, 129.8, 131.0, 131.2, 134.2, 134.7, 141.8, 164.3, 164.7. Anal. Calcd for $C_{21}H_{23}N_2O_2Cl$: C, 68.01; H, 6.25; N, 7.55. Found: C, 67.78; H, 6.73; N, 7.10.

For *trans*-**2a**: oily liquid; IR (neat) ν/cm^{-1}= 3400, 3334, 1650, 1615, 1515; ^{1}H NMR (500 MHz; DMSO-d_6) δ= 0.88 (3H, t, *J*= 7.3 Hz), 1.28 (2H, tq, *J*= 7.3, 7.6 Hz), 1.43 (2H, tt, *J*= 7.2, 7.6 Hz), 2.39 (3H, s), 3.14 (2H, dt, *J*= 5.5, 7.2 Hz), 4.58 (1H, d, *J*= 7.0 Hz), 5.75 (1H, d, *J*= 7.0 Hz), 7.34 (2H, d, *J*= 8.2 Hz), 7.39 (2H, d, *J*= 8.5 Hz), 7.49 (2H, d, *J*= 8.5 Hz), 7.88 (2H, d, *J*= 8.2 Hz), 8.06 (1H, t, *J*= 5.5 Hz); ^{13}C NMR (DMSO-d_6) δ= 13.6, 19.5, 21.1, 31.1, 38.4, 76.8, 82.1, 123.9, 127.4, 128.2, 128.8, 129.2, 132.8, 139.3, 142.1, 163.3, 169.5. Anal. Calcd for $C_{21}H_{23}N_2OCl\cdot H_2O$: C, 67.64; H, 6.76; N, 7.51. Found: C, 67.89; H, 6.36; N, 7.15. Spectral data and physical properties of other new compounds will be given elesewhere.

6. When a DMSO-d_6 solution of *trans*-**2a** and *cis*-**2a** was allowed to stand for several days at room temperature, the negligible isomerization of the *cis* to the *trans* was observed but there was indication of the faster appearance of a *cis*-**2a**-derived azetidine derivative than that of the azetidine which is derived from *trans*-**2a** (^{1}H NMR). It is, thus, likely that the *cis*-isomer, which must be less stable, is subject to decomposition during work-up giving unidentified product(s). Fortunately, we succeeded in isolating a slight amount of *cis*-**2d** (oily liquid) whose ^{1}H and ^{13}C NMR spectra were consistent with the proposed structure, although the *cis*-isomer was contaminated with the azetine-derived decomposition product(s): ^{1}H NMR (500 MHz; DMSO-d_6) δ= 0.73 (3H, t, *J*= 7.0 Hz), 0.90–0.97 (4H, m), 2.70–2.79 (2H, m), 5.12 (1H, d, *J*= 10.7 Hz), 6.07 (1H, d, *J*= 10.7 Hz), 7.25 (2H, d, *J*= 8.2 Hz), 7.36 (2H, d, *J*= 8.5 Hz), 7.59 (1H, dd, *J*= 7.6, 8.2 Hz), 7.69–7.73 (2H, m), 7.94 (1H, d, *J*= 7.6 Hz), 8.01 (1H, br); ^{13}C NMR (DMSO-d_6) δ= 13.6, 19.4, 30.9, 37.9, 73.7, 82.4, 126.8, 127.7, 127.8, 128.5, 129.9, 130.8, 131.9, 132.6, 133.4, 135.3, 163.3, 167.0.
7. Computer calculations were accomplished by using the Mac SPARTAN *Plus* available from Wavefunction, Inc.
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