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Photocyclization of 2-(*N*-Benzoyl-*N*-benzylamino)ethyl Benzoylacetate via Remote Hydrogen Abstraction. Enhancing Effect on Biradical Cyclization by the *N*-Benzoyl Group

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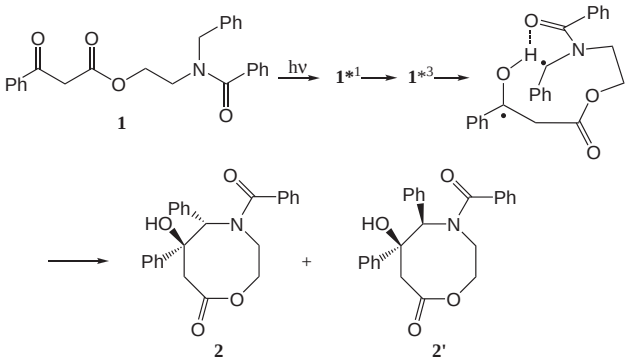
Upon irradiation 2-(*N*-benzoyl-*N*-benzylamino)ethyl benzoylacetate underwent photocyclization to give 8-membered azalactones in high yields. Intramolecular hydrogen bonding between the hydroxy and benzoyl carbonyl group in the 1,8-biradical intermediate produced from the benzoylacetate enhanced the photocyclization.

Photocyclization of carbonyl compounds through intramolecular hydrogen abstraction by excited carbonyl oxygen is a useful method for the preparation of cyclic alcohols.[1,2] Cyclobutanol formation, known as the Norrish–Yang reaction,[1] has been applied to organic synthesis[3] and is now well established.[4] Cyclization occurs through 1,4-biradical intermediates and is usually accompanied by cleavage as a predominant process.[4] Selectivity in organic reactions is still an important problem in synthetic and industrial chemistry, and recently, any technique by which the course of reaction may be greatly enhanced has received special attention from the aspect of green chemistry.[5] *N*-Acyl, aroyl, and tosyl groups have been reported to enhance 1,4-biradical cyclization of amino ketones.[6] For example, 2-(*N*-benzoyl-*N*-methylamino)acetophenone mainly undergoes cyclization upon irradiation,[6a] while 2-(dimethylamino)acetophenone undergoes only Type II cleavage.[6b,7] The lack of a charge-transfer interaction,[6a] the presence of dipole–dipole interactions between the amide and ketone carbonyl oxygen[6c–e] in the starting *N*-acylamino ketones, and intramolecular hydrogen bonding in 1,4-biradical intermediates have been proposed as tentative reasons for the enhancement. We have reported that 2-(dialkylamino)ethyl benzoylacetates undergo photocyclization to 8-membered azalactones via remote hydrogen transfer.[8] Enhanced photocyclization may occur in the corresponding *N*-benzoyl derivative even via remote hydrogen transfer, and clear evidence for the enhancement effect in the cyclization may be obtained from the analysis of the structure of the products. Conformational flexibility of 8-membered rings should be larger than that of cyclobutanol rings, meaning that the conformation of the 8-membered azalactones must reflect that of the intermediary biradical. We report here the photocyclization of 2-(*N*-benzoyl-*N*-benzylamino)ethyl benzoylacetate (**1**) via remote hydrogen abstraction and clear evidence for the origin of the enhancement effect by the *N*-benzoyl group on the cyclization.



Scheme 1.

Irradiation of a benzene solution of **1** under nitrogen with a 450-W high-pressure mercury lamp through a Pyrex filter gave the 8-membered azalactone isomers **2** and **2′** in 66 and 30% yields, respectively (Scheme 1). The formation of **2** and **2′** was efficiently quenched with 2,5-dimethyl-2,4-hexadiene, indicating that the cyclization proceeds from the triplet excited state of **1**. The structures of **2** and **2′** were determined on the basis of their spectral data and elemental analyses. The IR spectra of **2** and **2′** had characteristic absorptions for hydroxy (**2**: 3270 and **2′**: 3150 cm^{-1}) and lactone carbonyl groups (**2**: 1725 and **2′**: 1720 cm^{-1}). The wavenumbers of the lactone carbonyl absorptions in **2** and **2′** are higher than those in the corresponding azalactones (1710 and 1690 cm^{-1}, respectively) from 2-(dibenzylamino)ethyl benzoylacetate.[8c] The transannular effect between the lactone carbonyl and nitrogen is weaker in **2** and **2′** than in the corresponding azalactones from the dibenzylamino derivative. This is attributed to the electron-withdrawing effect of the *N*-benzoyl group, which decreases the electron density on nitrogen.

The amide carbonyl absorptions in **2** and **2′** appeared at rather lower wavenumber (1615 and 1610 cm^{-1}, respectively) than in *N*-benzoylazacyclooctane (1635 cm^{-1}).[9] These results strongly indicate the presence of the intramolecular hydrogen bonding between the amide carbonyl and hydroxy group in **2** and **2′**. X-ray crystallographic structure analysis of **2** was performed to verify this feature, however, the analysis of **2′** was not possible because it was difficult to prepare a single crystal suitable for analysis. The results are given in Fig. 1. The distance between the OH hydrogen (H1) and amide carbonyl oxygen (O4) (dotted line) was 1.96(5) Å, and the O3–O4 distance was 2.706(4) Å, which are well within the hydrogen-bonding range.[10] It is also worth noting that the dihedral angle (C14–C3–C4–C20) between the phenyl groups (from C14 to C19 and from C20 to C25) on the azalactone ring was 36.2(5)°, though the groups were in a *cis* geometry. This twisted configuration with such a dihedral angle might be characteristic in medium-sized rings.[8c]

The long-chain 1,8-biradical just before cyclization should have nearly the same configuration as that of the azalactones

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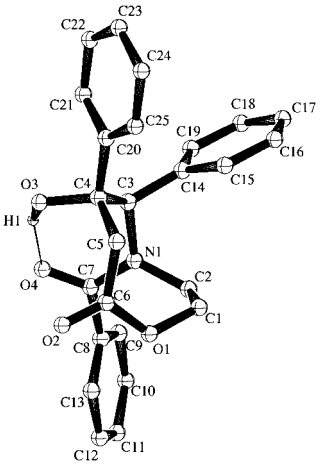
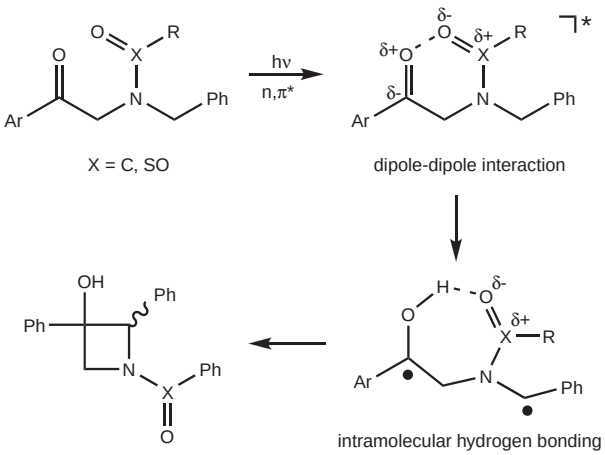


Fig. 1. ORTEP drawing of **2** (21% probability).



Scheme 2.

2 and **2′**. Therefore, hydrogen bonds must be present in the 1,8-biradical and facilitate the biradical cyclization process. Indeed, the yields of the azalactones **2** and **2′** were much higher than those of the corresponding azalactones (21 and 31%)[8] from the dibenzylamino derivative. The formation of intermolecular hydrogen bonds between the hydroxy group of the biradical intermediate and a solvent molecule would predominate over that of the intramolecular hydrogen bonding in a polar solvent. In that case, efficiency of the cyclization should decrease in the solvent. Indeed, irradiation of **1** in benzene containing 10% *t*-butanol gave **2** and **2′** in 42 and 20% yields, respectively. This result strongly supports the presence of intramolecular hydrogen bonds in the biradical intermediate from **1**. The yield of **2** is higher than that of **2′** as in the case of irradiation in benzene. This probably indicates that intramolecular hydrogen bonding is still present in a part of the starting benzoylacetate molecules even in the mixed solvent.

Fuhrmann et al. have reported that *N*-benzyl-*N*-phenacylamides undergo diastereoselective photocyclization to give *trans*- and/or *cis*-*N*-acylazetidin-3-ols.[6c–e] They have proposed that the *N*-acyl group favors diastereoselective photocyclization because of the intramolecular dipole–dipole interaction between the amide and the ketone carbonyl oxygen in the excited state of the starting amides and the hydrogen bonding between the amide carbonyl oxygen and hydroxy hydrogen in 1,4-biradicals (Scheme 2). The hydroxy group in the 1,8-biradical should be nearly *cis* to the amide carbonyl in order to form an intramolecular hydrogen bond. Diastereoselectivity in the photocyclization of **1** was lower. This configuration should prefer the *cis*-configuration of the two phenyl groups in the biradical. Diastereoselectivity in the photocyclization of **1** is lower than that reported by Fuhrmann et al., though the IR spectra of the azalactones **2** and **2′** showed the presence of strong hydrogen bonds. This is possibly due to the comparable flexibility of the medium-sized rings.[8c] The ring size of the circularly arranged biradical, which is due to intramolecular hydrogen bonding, must be an important factor determining yields of cyclization products. The ring size of the biradical produced from *N*-benzyl-*N*-phenacylamides is seven, and the yields of *N*-acylazetidin-3-ols were 10 to 66%.[6c,e] However, the ring size of the biradical from **1** is eleven, and cyclization occurred almost quantitatively. The 8-membered ring may be unsuitable for the cyclic arrangement of the biradical, because *N*-alkyl-*N*-2-benzoylphenylalkanamide gave no cyclization products.[11] The ability to form the circularly arranged biradical by the intramolecular hydrogen bonding is most likely determined by transannular, Pitzer, and large angle strain effects.[12] This seems to be a useful rule for efficient photocyclization of acylamino ketones in organic synthesis, which meets the demand of green chemistry.

The presence of the hydrogen bonding between the amide and hydroxy groups in **2** and **2′** was shown to clear evidence for the presence of the bonding in biradical intermediates. This intramolecular hydrogen bonding must be the cause for the enhanced biradical cyclization in photochemistry of acylamino ketones, and this enhancement is quite effective even in the photocyclization of long-chain biradicals produced via remote hydrogen abstraction by excited carbonyl oxygen.

Experimental

IR spectra were recorded with a JASCO IR Report-100 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-FX90Q spectrometer and a Bruker AVANCE 300 spectrometer using tetramethylsilane as an internal standard. An Ushio 450-W high-pressure mercury lamp was used as the irradiation source. X-ray crystallographic data was acquired a Bruker AXS SMART APEX.

Preparation of 2-(*N*-Benzoyl-*N*-benzylamino)ethyl Benzoylacetate (1). Ethyl benzoylacetate (5.1 g), 2-(*N*-benzoyl-*N*-benzylamino)ethanol (3.8 g), and a lump of iodine were dissolved in 60 cm^3 of benzene. To the solution was added activated zinc (2.6 g, 39.8 mmol).[13] The mixture was stirred and refluxed for 20 h under nitrogen. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica-gel column. Elusion with a mixture of hexane–ethyl acetate (1:1 v/v) gave 1.6 g (26%) of **1**. The starting ester (3.4 g) was also recovered. **1**: mp 73–75 °C, IR (KBr) 1745, 1685, and 1630 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.70 (2H, m, CH_2N), 4.08 (2H, s, CH_2Ph), 4.60 (2H, m, OCH_2), 4.78 (1.4H, s, $COCH_2CO$), 5.76 (0.3H, s, olefin), 7.1–7.4 (15H, m, ArH), and 12.73 (0.3H, s, OH). Found: C, 74.62; H, 5.91; N, 3.80%. Calcld for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49%.

Procedure for Irradiation of 1. A solution of **1** (115 mg) in benzene (15 cm^3) was irradiated for 20 h under nitrogen with a 450-W high-pressure mercury lamp. After removal of the solvent

under reduced pressure, the residue was chromatographed on a silica-gel column. Elusion with a mixture of dichloromethane–ethyl acetate (10:1 v/v) gave 76 mg (66%) of **2** and 35 mg (30%) of **2′**. **2**: mp 177–177 °C, IR (KBr) 3270, 1725, and 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (1H, d, $J = 12.2$ Hz, COH_2), 3.1–3.4 (1H, m, NCH_2), 3.3–3.6 (1H, m, NCH_2), 3.77 (1H, d, $J = 12.2$ Hz, COH_2), 3.8–4.1 (1H, m, NCHPh), 4.6–4.8 (1H, m, OCH_2), 5.91 (1H, s, OH), 6.2–6.5 (1H, m, OCH_2), and 7.0–7.7 (15H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.1, 48.3, 66.0, 69.5, 84.0, 125.8 (2C), 127.3 (2C), 127.8 (2C), 128.5 (2C), 128.7 (2C), 128.8 (2C), 129.7, 131.8 (2C), 133.7, 136.4, 144.6, 173.4, and 177.3. Found: C, 74.78; H, 5.67; N, 3.41%. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49%. **2′**: mp 215–216 °C, IR (KBr) 3150, 1720, and 1610 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.54 (1H, s, OH/H_2O), 2.80 (1H, d, $J = 13.0$ Hz, COH_2), 3.06 (1H, d, $J = 13.0$ Hz, COH_2), 3.6–3.8 (1H, m, NCH_2), 3.9–4.1 (1H, m, NCH_2), 4.3–4.7 (2H, m, OCH_2), 5.07 (1H, s, NCHPh), and 6.9–8.1 (15H, m, ArH). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 48.4, 54.9, 64.9, 72.1, 79.7, 125.5 (2C), 126.6 (2C), 127.6, 128.1, 128.2 (2C), 128.6 (2C), 129.1 (2C), 130.0 (2C), 130.6, 135.8, 136.7, 145.0, 171.3, and 175.5. Found: C, 74.78; H, 5.74; N, 3.42%. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49%.

Crystal Structure Determination of 2. Crystal data for a clear block crystal of $C_{25}H_{23}NO_4$: $0.46 \times 0.34 \times 0.22$ mm^3, orthorhombic, *Pbca* (#61), $a = 10.950(1)$ Å, $b = 16.786(2)$ Å, $c = 22.213(3)$ Å, $V = 4082(8)$ $Å^3$, $\lambda = 0.71073$ Å, $Z = 8$, FW 401.46, $D_{calcd} = 1.582$ g cm^{-1}, μ (Mo Kα) = 8.378 cm^{-1}, Bruker Apex CCD-area 15 s. exposures, $2\theta_{max} = 56.6°$, $T = 296(1)$ K.; 25903 reflections collected, 2486 unique ($R_{int} = 0.025$) included in the refinement; no decay corrections were needed; min/max transmission = 0.89; Direct and difference Fourier methods solutions (teXsan package, Molecular Science Corporation), full-matrix least-squares based on F; final $R_1 = 0.067$, $R_w = 0.0607$ for all data; for 1610 reflections ($I > 2.5\sigma(I)$, $2\theta = 4.5$–$51.8°$) with 274 variable parameters. All non-hydrogen atoms were modeled anisotropically and one hydrogen atom's coordinates were refined. All other hydrogen atoms were added with calculated geometries and distances but not refined. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-631278 for compound No. **2**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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