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Synthesis of Tricyclic Lactones Containing 2-Azabicyclo[3.3.1]nonane Skeleton via Tandem Intramolecular Photocyclization of 2-(1-Naphthyl)ethyl ω-Anilinoalkanoate

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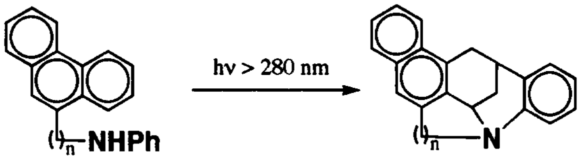
Abstract: **Irradiations of 2-(1-naphthyl)ethyl 3-anilinoalkanoates (3a-c) in degassed benzene afforded tricyclic lactones (4a-c) containing 2-azabicyclo[3.3.1]nonane skeleton as major products via photo-induced electron transfer.** © 1997 Elsevier Science Ltd.

There have been many studies on the mechanistic and synthetic aspects of additions of amines to excited alkenes or arenes.[1] These photoreactions have extensively applied to the synthesis of nitrogen heterocycles.[2] In the course of our investigation, we have found that a series of tricyclic compounds (**2a-f**; n = 6-10, 12) containing 2-azabicyclo[3.3.1]nonane skeleton have been produced by the successive intramolecular photocyclization of 9-(6-anilinohexyl)phenanthrene (**1a**; n = 6) and its related compounds (**1b-f**; n = 7-10, 12).[3,4] However, the yields of **2** were not high. We now report the synthesis of tricyclic lactones to construct the functionalized 2-azabicyclo[3.3.1]nonanes using the tandem intramolecular photocyclization of 2-(1-naphthyl)ethyl ω-anilinoalkanoates.[5]



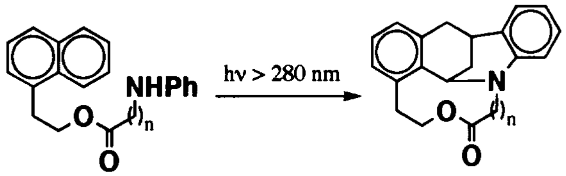
1a-f

a : n = 6, **b** : n = 7, **c** : n = 8
d : n = 9, **e** : n = 10, **f** : n = 12

2a-f

a : n = 6, **b** : n = 7, **c** : n = 8
d : n = 9, **e** : n = 10, **f** : n = 12

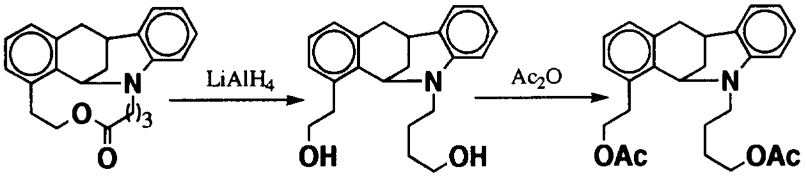
Irradiation of a benzene solution containing 2-(1-naphthyl)ethyl ω-anilinobutanoate (**3b**) (0.008 mol/L) using a high-pressure mercury lamp (300W) through Pyrex filter (>280 nm light) under argon atmosphere gave a tricyclic lactone (**4b**) in a 39% isolated yield accompanying 20% recovery of **3b** and a few minor products.[6] Similar irradiations of **3a** and **3c** afforded the corresponding lactones **4a** and **4c** in 16 and 13% yields, respectively. These products were isolated by column chromatography on silica gel. The structures of **4a-c** were identified by their analytical and spectral data.[7] The IR spectra did show the disappearance of NH group and



3a-c **a** : n = 2
b : n = 3
c : n = 4

4a-c **a** : n = 2
b : n = 3
c : n = 4

n	Yield (Recovery)/%
2	16 (0)
3	39 (20)
4	13 (42)



4b **5** **6**

the existence of the carbonyl group remaining. The mass spectra clearly showed the respective parent peaks. The ^{1}H NMR showed the disappearance of five aromatic protons and the appearance of two unequivalent methylene and two methine protons. Finally, the structures of **4b** and **4c** were confirmed by the X-ray crystallographic analyses.[8] Moreover, **4b** was converted to **5** and **6** by the reduction using LiAlH$_4$ followed by the acetylation.[7] The yield of **4b** slightly depended on the concentration of **3b** (Table 1). Although the better result was obtained at the lower concentration of **3b**, the higher concentration of **3b** also resulted in the satisfactory yield of **4b** to the preparative purpose.

Table 1. Concentration Effects on the Yields of **4b**[a)]

Conc (mmol/L)	Yield/%[b)]	Recovery/%
0.8	45	0
8	36	28
12	29	31
16	25	28

a) 4 h irradiation in degassed benzene.
b) Isolated yields based on **3b** used.

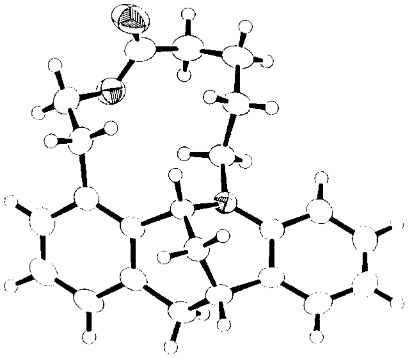
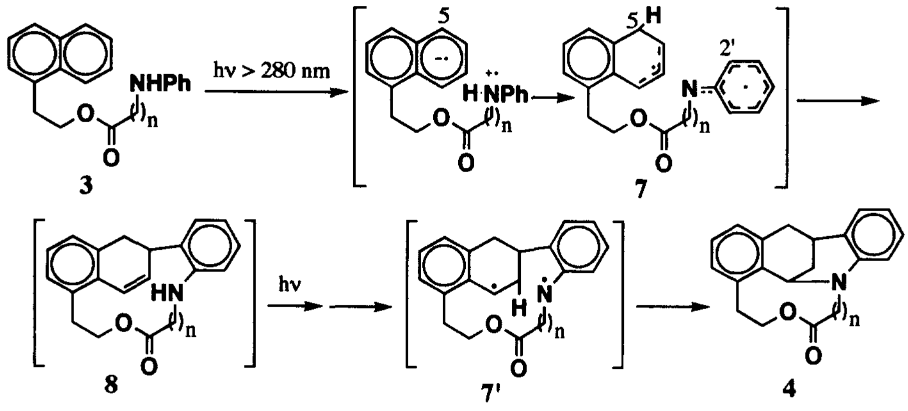


Fig. 1 ORTEP drawing of **4c**

These photoreactions presumably proceed via the tandem photoinduced electron-transfer mechanism as shown in Scheme 1, which we have proposed previously.[3] The primary single electron-transfer from anilino group to naphthyl group followed by the proton transfer produces the radical pair (**7**), which couples to give the bicyclic lactones (**8**). We have failed to isolate **8**.[9] Probably, the rate for the formation of **4** via the radical pair **7'**, generated by the secondary electron-transfer from anilino group to 1,2-dihydronaphthyl group, is much faster than that for the formation of **8**. Molecular model of **8** showed the quite favorable conformation for the addition of NH group to the alkene.



Scheme 1

In conclusion, the introduction of an ester group into the polymethylene chain between anilino group and naphthyl group resulted in the formation of the tricyclic lactones containing 2-azabicyclo[3.3.1]nonane skeleton. The chemical yields of 2-azabicyclo[3.3.1]nonane derivatives depended on the chain length and the functionality of the chain. The $-(CH_2)_2-OCO-(CH_2)_3-$ group (seven-atoms chain) matched for the formation of this ring system. In the case of the polymethylene chain $[-(CH_2)_n-]$, the best result was obtained when $n = 6$ was used,[3] suggesting that the $-(CH_2)_2-OCO-(CH_2)_3-$ group is more flexible than the methylene chain. The compound connected by the ethereal bond $[-CH_2-O-(CH_2)_5-]$ (seven-atoms chain) caused the C-O bond cleavage and gave the many unexpected products.[10,11] Finally, it is notable here that the construction of 2-azabicyclo[3.3.1]nonane skeleton, which is included in some alkaloids such as strychnine, would be developed to be pharmaceutical active compounds.

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5 The starting materials **3a-c** were prepared by the reaction of 2-(1-naphthyl)ethyl ω-haloalkanoate with aniline. **3a** : mp 55-56°C, **3b** : mp 64-65°C, **3c** : mp 39-40°C. All compounds exhibited satisfactory spectroscopic data (^{1}H NMR, IR, and UV) and elemental analyses.

6 Some minor products were the structural isomers and their identification was in progress.

7 Spectroscopic and analytical data for the photo products: **4b** (n = 3): mp 150-151°C, ; UV (methanol) λmax 253 (log ε 4.02), 282 sh (3.70), and 306 (3.49) nm; IR (KBr): ν 1731 (C=O) and 1146 (C-O-C) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 1.23-1.40 (1H, m, CH), 1.91-1.97 (1H, m, CH), 2.11-2.23 (3H, m, CH), 2.36-2.40 (1H, m, CH), 2.65-3.72 (7H, m, CH), 4.40-4.50 (1H, m, CH), 4.75 (1H, s, CH), 5.10-5.16 (1H, m, CH), 6.55-6.66 (2H, m, ArH), 6.95-6.97 (1H, m, ArH), and 7.03-7.26 (4H, m, ArH); Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C; 79.37; H, 6.90; N, 4.21. m/z=333; Crystal data of **4b**. $C_{22}H_{23}NO_2$; orthorhombic; space group $P2_12_12_1$ (No. 19); a = 10.748(6), b = 16.23(1), c = 9.765 (6) Å; U = 1704(1)Å^3; Z = 4; D_c = 1.300 g cm^{-3}; μ = 0.77 cm^{-1}. R (Rw) = 0.053 (0.052), S = 1.70. Crystal data of **4c**. $C_{23}H_{25}NO_2$; monoclinic; space group $P2_1$/a (No. 14); a = 16.470(2), b = 6.326(2), c = 17.267(2) Å, β = 94.171(10)°; U = 1794.3(5)Å^3; Z = 4; D_c = 1.286 g cm^{-3}; μ = 0.81 cm^{-1}. R (Rw) = 0.038 (0.041), S = 1.60. **5**: viscous oil (not solidify); IR (neat): ν 3345 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20 (1H, t, CH), 1.54-1.65 (2H, m, CH), 1.80-1.94 (2H, m, CH), 2.20-2.26 (1H, m, CH), 2.93-3.59 (7H, m, CH), 3.66-3.82 (3H, m, CH), 3.95-4.01 (1H, m, CH), 4.60 (1H, s, CH), 6.76-6.88 (3H, m, ArH), and 7.01-7.14 (4H, m, ArH). Diacetate **6**: mp. 54-56°C (from methanol); UV (methanol) λmax 255 (log ε 4.04) and 308 (3.53) nm; IR (neat): ν 1735 (C=O) and 1241 (C-O-C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.61-1.74 (4H, m, CH), 1.95-2.11 (8H, m, CH), 2.98-3.02 (2H, m, CH), 3.19-3.40 (4H, m, CH), 3.64-3.69 (1H, m, CH), 4.06-4.11 (2H, m, CH), 4.24-4.29 (2H, m, CH), 4.62 (1H, s, CH), 6.64-6.69 (2H, m, ArH), 6.88-6.91 (1H, m, ArH), and 6.98-7.11 (4H, m, ArH). Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C; 73.95; H, 7.51; N, 3.36.

8 X-Ray diffraction data were collected by using a Rigaku AFC5R diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å) and 18 kW rotating anode generator. Cell dimensions were obtained by least-squares fitting from 20 high angle reflections. All computations for the structure determination were carried out on VAX station 3100 or INDY R5000 using a crystallographic program package TEXSAN or teXsan [Crystal Structure Analysis Package, Molecular Structure Corporation (1985 and 1992)].

9 In the case of phenanthrene derivatives, **8** type intermediate was isolated and identified: See ref. 3.

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