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THE PHOTOCHEMICAL REACTIONS OF N,N-DIALKYL α,β-UNSATURATED AMIDES

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Abstract—Upon benzene-sensitized irradiation N,N-dibenzyl α,β-unsaturated amides **1a–1c** cyclized to the corresponding 2-azetidinones **2a–2c** in good yields via intramolecular hydrogen abstraction by the β-C atom. Under the same conditions N,N-diisopropyl amides **1e** and **1f** were found to undergo a novel photoreaction to give N-isopropyl saturated amides via the abstraction. Irradiation of N,N-diethyl and dimethyl amides gave neither 2-azetidinones nor N-monosubstituted amides.

The similarity of photoinduced intramolecular hydrogen abstraction by a double bond of an olefin to that by a CO group has been pointed out, and the similarity is attributed to the resemblance between the electronic configuration in the carbonyl n,π^* state and that in the olefin π,π^* state.[1] Recently the first example of hydrocarbon analog to the Type II elimination was reported.[2] Although photocyclization via intramolecular hydrogen abstraction by the β-C atom in cyclopentenones[3,4] and 1-acylcyclopentenes[5,6] has been reported, much less is known about the cyclization in acyclic α,β-unsaturated carbonyl compounds.[8] We wish to report here photocyclization of N,N-dialkyl α,β-unsaturated amides to 2-azetidinones† via unprecedented intramolecular hydrogen abstraction by the β-C atom in the simple α,β-unsaturated carbonyl system, and novel photodealkylation of the amides accompanied with reduction of a double bond.

Benzene-sensitized irradiation of N,N-dibenzylacrylamide (**1a**) with a low-pressure mercury lamp under nitrogen gave *trans* - 1 - benzyl - 3 - methyl - 4 - phenyl - 2 - azetidinone (**2a**) in a 70% yield. The structure of **2a** was determined by the direct comparison with an authentic sample.[10,11] A trace of *cis* isomer was also detected.

Benzene-sensitized irradiation of the amides **1b** and **1c** under the same conditions gave the corresponding 2-azetidinones **2b** (30%) and **2c** (84%) respectively, while no reaction took place in irradiation of **1d**. The configuration of the C(3)-Et group *trans* to the C(4)-Ph group in **2b** was estimated by using the NMR spectrum. The NMR spectrum of photoproduct **2b** showed the characteristic peak at δ 4.05 (d, J = 2.1 Hz) attributable to the C(4)-hydrogen, while that of unequivocally synthesized **2b**, *cis-trans* mixture, appeared the C(4)-hydrogen peaks at δ 4.05 (d, J = 2.1 Hz) and 4.56 (d, J = 5.5 Hz). Since the chemical shifts and the coupling constants correspond to those of reported *trans* and *cis* isomers of **2a**,[11] the signal at δ 4.05 can be assigned to the C(4)-hydrogen *cis* to the C(3)-Et group. Therefore, the photoproduct **2b** has the C(3)-Et group *trans* to the C(4)-Ph one.

In the case of photolysis of **1c** a trace of N-benzylisobutyramide (**3c**) was also obtained, while N-benzylpropionamide or butyramide was not detected in photolyses of **1a** or **1b**, respectively.

Irradiation of **1a** in benzene with a high-pressure mercury lamp also gave **2a** with low efficiency, and the formation of **2a** was effectively sensitized by *p*-methoxyacetophenone (E_T = 71.8 kcal)[12] and not by *p*-aminoacetophenone (E_T = 65 kcal),[12] Michler's ketone (E_T = 62 kcal),[12] nor acetonaphthone (E_T = 59.4 kcal).[12] On the other hand, direct irradiation of **1a** in n-hexane with a low-pressure mercury lamp gave **2a** in a low yield with some by-products. These results indicate that the 2-azetidinone **2a** was produced from the triplet excited state of the amide **1a**.

The formation of the 2-azetidinones **2a–2c** can be explained in terms of photocyclization via hydrogen abstraction by the β-C atom through the 6-membered transition state as shown below (path A). An alternative path B, which involves hydrogen abstraction by CO oxygen through the 5-membered transition state followed by 1,4-hydrogen migration and rotation of the C–N bond, seems to be improbable because (i) no 2-pyrrolidinones **4** were detected in all cases, (ii) there have been only a few reports on intramolecular hydrogen abstraction by amide CO oxygen,[13] and (iii) abstraction by excited CO oxygen through the 5-membered transition state is the rarely observed process.[14]

Moreover, evidence in support of hydrogen abstraction by the β-C atom in formation of the 2-azetidinones was obtained by the experiment using the deuterium labeled amide **1c–d₄**. Sensitized-irradiation of **1c–d₄** gave the corresponding 2-azetidinone **2c–d₄**. One of the deuteriums on the benzylic position in the starting amide **1c–d₄** completely incorporated into the C(3)-Me group in the 2-azetidinone **2c–d₄**. On the other hand, the deuterium incorporation was not observed in the product 2-azetidinone **2c** when the amide **1c** was irradiated in benzene containing D_2O. These results support the above mechanism (path A).

†Although Chapman and Adams reported Photocyclization of acrylamides to 2-azetidinones,[9] our results are fundamentally different from their ones in the process of cyclization.

In the case of irradiation of **1c–d_4** a small amount of N-dealkylated saturated amide **3c–d_3** was obtained as in the case of **1c**. Deuterium incorporation into a Me group of **3c–d_3** indicates that the amide **3c–d_3** was also produced via intramolecular hydrogen abstraction by the β-C atom. However, detailed mechanism of the formation of the amide is not clear at present.

Irradiation of N,N-diisopropylacrylamide (**1e**) and methacrylamide (**1f**) under the same conditions gave saturated amides, N-isopropylpropionamide (**3e**, 30%) and isobutyramide (**3f**, 53%), respectively. On the other hand, irradiation of a crotonamide **1g** and a cinnamamide **1h** gave no saturated amides. In these cases no 2-azetidinones could be detected.

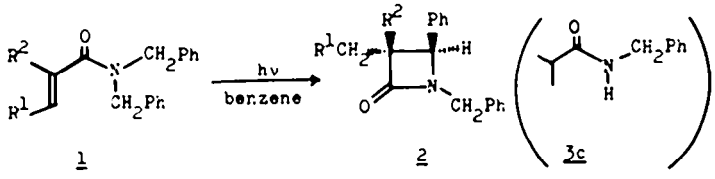
The formation of **3e** and **3f** can be rationalized with the following mechanism which involves hydrogen abstraction by the β-C atom followed by isomerization of the resulting biradical to an enamide **9** and subsequent hydrolysis of the enamide. Recently similar photochemical dealkylation of N,N-dialkyl amides via enamides has been reported by Wilson and Commons.[14]

Irradiation of N,N-diethyl and dimethyl α,β-unsaturated amides **1i–1n** gave neither 2-azetidinones nor saturated amides. The process of hydrogen abstraction by the β-C atom is a surprisingly rare event in organic photochemistry. The abstraction in N,N-dialkyl α,β-unsaturated amides seems to be remarkably affected by substituents on nitrogen. An alkyl group on the N atom producing a extensively stable radical facilitates the abstraction.

A substituent on the β-C atom seems to also affect the abstraction. Irradiation of the crotonamide **1c** gave **2c** in a low yield, and that of the cinnamamides **1d** and **1h**, and the crotonamide **1g** gave neither 2-azetidinones nor saturated amides. A substituent on the β-C atom inhibits the abstraction.

Finally we describe the effect of ground-state conformation in the starting amides on hydrogen abstraction by the β-C atom. Lewis *et al.* reported that the product composition in photoreaction of ketones apparently depended upon ground-state molecular conformation and γ-hydrogen abstraction by excited CO reflected O–H, distance.[16]

Hydrogen abstraction by the β-C atom requires the geometrical isomer, the s-*trans* α,β-unsaturated amide. Two conformers **1** and **1'** populates in the s-*trans* amide when different alkyl substituents are on the N atom (Fig. 6). The conformer **1** is favorable to the abstraction because only benzylic hydrogen is abstractable. Population of **1** and **1'** is different in the N-benzyl-N-methyl amide **1o** and the N-benzyl-N-t-butyl amide **1p**; The conformer **1** populates predominantly in the amide **1p** but **1'** in **1o** because of steric hindrance. Then photoreactions of **1o** and **1p** were studied.



	R^1	R^2	Yield/%
a :	H	H	70
b :	Me	H	30
c :	H	Me	84
d :	Ph	H	-

Fig. 1.

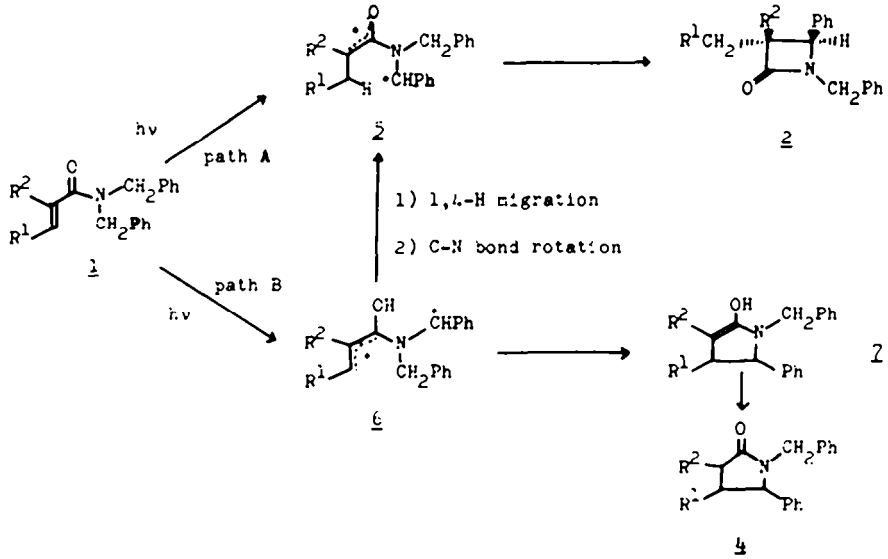
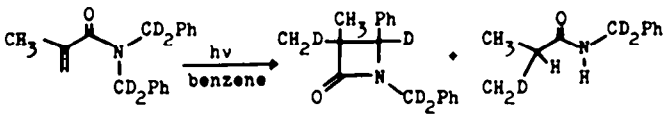
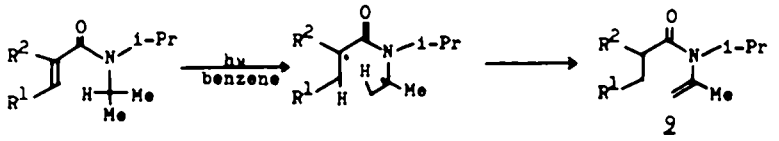


Fig. 2.



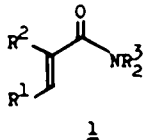
1c-d_4 2c-d_4 3c-d_3

Fig. 3.



	R^1	R^2	Yield of 3
e ;	H	H	30 %
f ;	H	Me	53
g ;	Me	H	-
h ;	Ph	H	-

Fig. 4.



	R^1	R^2	R^3
i;	H	H	Et
j;	Me	H	Et
k;	H	Me	Et
l;	Ph	H	Et
m;	H	H	Me
n;	H	Me	Me

Fig. 5.

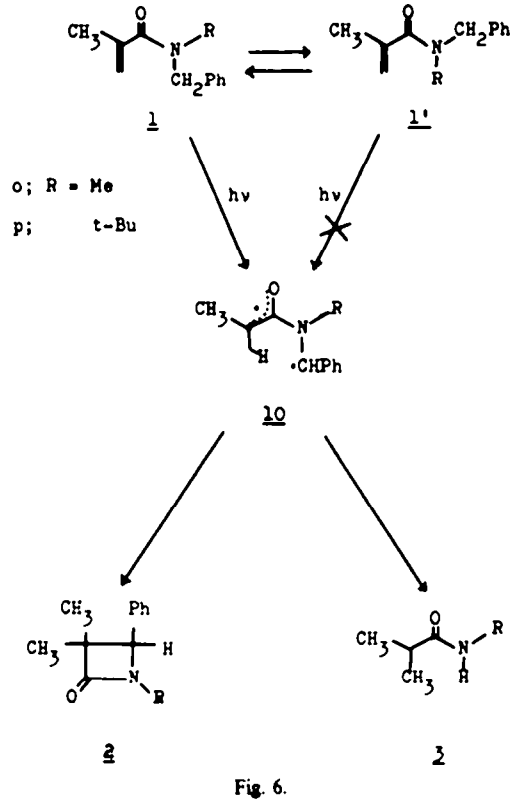


Fig. 6.

Benzene-sensitized irradiation of **1o** gave the corresponding 1-methyl-2-azetidinone **2o** in a 10% yield. Sensitized irradiation of **1p** under the same conditions gave the 1-butyl-2-azetidinone **2p** (7.5%) and N-t-butylisobutyramide (**3p**, 19.5%). The products **2o**, **2p**, and **3p** resulted from hydrogen abstraction by the β-C atom. The abstraction took place easily in **1p** than **1o**.

These results indicate that ground-state conformation of the starting amides controlled intramolecular hydrogen abstraction by the β-C atom.

EXPERIMENTAL

IR spectra were recorded on a Hitachi EPI-2 spectrometer. NMR spectra were run on a Hitachi R-20 spectrometer using TMS as internal standard. Mass spectra were measured with a Shimazu LKB-9000 spectrometer. A Taika low-pressure mercury lamp was used as a irradiation source.

Starting materials

Starting α,β-unsaturated amides (**1a–1p**) were prepared according to previously described methods.[19–23]

N,N-*Di-dideuteriobenzylmethacrylamide* (**1c-d_4**). In the conventional way ethyl benzoate (3.6 g) was reduced by 1 g of $LiAlD_4$

to benzylalcohol-d_2 in a 82% yield, and then the alcohol was converted to benzylchloride in a 93% yield. The benzylchloride-d_2 was transformed to dibenzylamine-d_4 in a 27% yield according to the method of synthesis of dibenzylamine.[24] The amide **1c-d$_4$** was prepared from dibenzylamine-d_4 and acrylchloride in a 27% yield. IR (liq. film) 1630 cm^{-1}, NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 5.23 (m, 2H, olefinic protons) and 7.0–7.4 (m, 10H, aromatic protons).

General procedure for photochemical reactions of α,β-unsaturated amides (1). A benzene soln of 1 (100 mg/40 cc) was irradiated in a quartz vessel under N_2 with a low-pressure mercury lamp. After removal of the benzene, the residue was chromatographed on silica gel. Elution with a mixture of benzene and EtOAc afforded 2 and/or a 3.

(i) 1 - benzyl - 3 - methyl - 4 - phenyl - 2 - azetidinone (**2a**). IR (liq. film) 1755 cm^{-1}, NMR ($CDCl_3$) δ 1.24 (d, 3H, J 7.5 Hz, 3-CH_3), 3.04 (d of q, 1H, J_a 2.0 Hz and J_a 7.5 Hz, 3-H), 3.74 (d, 1H, J 15.0 Hz, N-CH_2Ph), 3.96 (d, 1H, J 2.0 Hz, 4-H), 4.81 (d, 1H, J 15.0 Hz, N-CH_2Ph), and 6.9–7.5 (m, 10H, aromatic protons). This photoproduct was identical with an authentic sample.[10,11]

(ii) 1 - benzyl - 3 - ethyl - 4 - phenyl - 2 - azetidinone (**2b**). IR (liq. film) 1760 cm^{-1}, NMR ($CDCl_3$) δ 0.93 (t, 3H, J 7.2 Hz, CH_2CH_3), 1.67 (q of d, 2H, J_a 7.2 Hz and J_a 7.0 Hz, CH_2CH_3), 2.94 (t of d, 1H, J, 7.0 Hz and J_a 2.1 Hz, 3-H), 3.69 (d, 1H, J 15.2 Hz, N-CH_2Ph), 4.05 (d, 1H, J 2.1 Hz, 4-H), 4.83 (d, 1H, J 15.2 Hz, N-CH_2Ph), and 7.0–7.4 (m, 10H, aromatic protons). The 2-azetidinone **2b** was identical with an unequivocally synthesized sample, which was prepared from benzylidenbenzylamine and ethyl 2-brom-n-butyrate. The synthesized 2-azetidinone was given as *cis-trans* 1:2 mixture. b.p. 145°/10^{-3} mmHg, IR (liq. film) 1755 cm^{-1}, NMR ($CDCl_3$, *cis* form) δ 0.77 (t, 3H, J 7.2 Hz, CH_2CH_3), 1.22 (q of d, 2H, J_a 7.2 Hz, and J_a 7.0 Hz, CH_2CH_3), 3.24 (t of d, 1H, J, 7.0 Hz and J_a 5.5 Hz, 3-H), 3.74 (d, 1H, J 15.2 Hz, N-CH_2Ph), 4.56 (d, 1H, J 5.5 Hz, 4-H), 4.87 (d, 1H, J 15.2 Hz, N-CH_2Ph) and 7.0–7.4 (m, 10H, aromatic protons). (Found for *cis-trans* 1:2 mixture: C, 81.47; H, 7.05; N, 5.19. $C_{18}H_{19}NO$ requires: C, 81.47; H, 7.22; N, 5.28%).

(iii) 1 - benzyl - 3,3 - dimethyl - 4 - phenyl - 2 - azetidinone (**2c**). IR (liq. film) 1755 cm^{-1}, NMR ($CDCl_3$) δ 0.75 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 3.76 (d, 1H, J 15.0 Hz, N-CH_2Ph), 4.13 (s, 1H, 4-H), 4.83 (d, 1H, J 15.0 Hz, N-CH_2Ph) and 7.1–7.3 (m, 10H, aromatic protons). This was identical with an authentic sample.[25]

(iv) N-benzylisobutyramide (**3c**). m.p. 89–90° (lit., 92°).[25] This was identical with an authentic material.[25]

(v) 1 - dideuteriobenzyl - 4 - deuterio - 3 - deuteriomethyl - 3 - methyl - 4 - azetidinone (**2c-d$_4$**). IR (liq. film) 1750 cm^{-1}, NMR ($CDCl_3$) δ 0.75 (s, 2.5H, 3-CH_3), 1.29 (s, 2.5H, 3-CH_3), 7.1–7.3 (m, 10H, aromatic protons), Mass *m/e*$^+$ 269 (M^+).

(vi) N - dideuteriobenzyl - 2 - deuteriomethylisobutyramide (**3c-d$_3$**). IR (KBr) 3350 and 1645 cm^{-1}, NMR ($CDCl_3$) δ 1.11 (d, 5H, J 6.8 Hz, CH_3 and $CDCH_2$), 2.3 (m, 1H, CH), 6.4 (bs, 1H, NH), and 7.25 (s, 5H, aromatic protons), Mass *m/e*$^+$ 180 (M^+).

(vii) N-isopropyl-n-propionamide (**3e**), IR (liq. film) 3320 and 1640 cm^{-1}. The amide was identical with an authentic sample.[26]

(viii) N-isopropylisobutyramide (**3f**) m.p. 99–101° (lit. 102°).[27] This amide was identical with an authentic material.[27]

(ix) 1,3,3 - trimethyl - 4 - phenyl - 2 - azetidinone (**2h**) b.p. 120°/5 mmHg, (lit. 117–121°/4.6 mmHg)[28] IR (liq. film) 1745 cm^{-1}, NMR ($CDCl_3$) δ 0.73 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.80 (s, 3H, N-CH_3), 4.28 (s, 1H, 4-H) and 7.05–7.35 (m, 5H, aromatic protons).

(x) 1 - t - butyl - 3,3 - dimethyl - 4 - phenyl - 2 - azetidinone (**2p**), m.p. 80–82°, (lit. 85.5–87°)[28] IR (KBr) 1740 cm^{-1}, NMR ($CDCl_3$) δ 0.70 (s, 3H, CH_3), 1.27 (s, 9H, C(CH_3)$_3$), 1.31 (s, 3H, CH_3), 4.28 (s, 1H, 4-H) and 7.1–7.3 (m, 5H, aromatic protons).

(xi) N-t-butylisobutyramide (**3p**), m.p. 117–118°, (lit. 119–120°).[29] This amide was identical with an authentic material.[29]

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