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Photoreaction of *N*-(2-Halophenyl)cyclohexanecarboxamide: Synthesis of 2-Alkylbenzoxazole

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The photochemical behavior of haloarene tethered to alkyl by an amide bone (**1, 2**) was studied. The photoreaction of *N*-(2-bromophenyl) cyclohexanecarboxamide (**1b**) in basic medium afforded intramolecular substituted product, 2-cyclohexylbenzoxazole (**4**) and reduced product, *N*-phenylcyclohexanecarboxamide (**5**) in 33 and 26 % yields, respectively. The chloro analogue (**1a**) produced photo-Fries type and photosubstituted products (**6, 4**), whereas the iodo analogue produced extensively photoreduced product **5**. *N*-(2-bromophenyl)-*N*-methylcyclohexanecarboxamide (**2**), which can not exist as imidol form, produced a photocyclized product, supporting an imidol form is involved in the intramolecular photosubstitution. Since the photoreduction but the photosubstitution reaction is retarded by the presence of oxygen, a triplet state for the photoreduction and a singlet state for the photosubstitution are involved.

key words: 2-cyclohexylbenzoxazole, *N*-(2-halophenyl)cyclohexanecarbox amide, intramolecular photosubstitution, photoreduction, photo-Fries type

INTRODUCTION

The photochemistry of haloarene tethered to an arene by an amide bond is diverse depending upon the reaction condition and haloarene species. In the photoreaction of the haloarene, intramolecular cyclization, reduction, and Fries-type reactions are well known [1-5], but intramolecular substitution reaction with the carbonyl oxygen of the amide bond is not much known. Recently, we reported that 2-pyridylbenzoxazole and 2-phenylbenzoxazole could be formed by an intramolecular photosubstitution of *N*-(2-halophenyl)pyridinecarboxamide and 2′-bromobenzanilide with their carbonyl oxygens of the amide bonds, respectively [6, 7]. The reaction is novel because the carbonyl oxygen substitutes the aryl halide to give a five-membered heterocyclic ring compounds. As an extension of our work in this area, we disclose herein the synthesis of 2-alkylbenzoxazole via intramolecular photosubstitution of *N*-(2-halophenyl)cyclohexanecarboxamide with its carbonyl oxygen of the amide bond.

RESULTS AND DISCUSSION

N-(2-halophenyl)cyclohexanecarboxamides (**1a, 1b, 1c**) were prepared by acylation of 2-haloanilide with cyclohexanecarbonyl chloride in pyridine. *N*-(2-bromophenyl)-*N*-methylcyclohexanecarboxamide (**2**) was prepared by methylation of *N*-(2-bromophenyl)cyclohexanecarboxamide (**1b**) with methyl iodide in basic acetone [8]. The cyclohexanecarboxamides (**1, 2**) have been identified by the spectral properties(^{1}H NMR, UV, IR, mass spectra) and element analysis.

When an acetonitrile solution (450 mL) of *N*-(2-bromophenyl)cyclohexanecarboxamide (**1b**, 0.5 mmole) containing 50 mL of aqueous 2 M NaOH was irradiated by a Hg lamp (450 W, medium pressure) under nitrogen for 40 min, a photosubstituted product, 2-cyclohexylbenzoxazole (**4**) and a photoreduced product, *N*-(phenyl)cyclohexanecarboxamide (**5**), were obtained in 33 and 26% yields, respectively. When a plain acetonitrile solution of **1b** was used (without base), the same products (**4** and **5**) were obtained in the similar yields as above. The photosubstitution reaction shows that 2-alkylbenzoxazole can be readily synthesized by the photoreaction of *N*-(2-bromophenyl)alkanecarboxamide. The photoreduction for the haloarene has been known [7, 9-11].

The products were identified by their spectral properties (NMR, IR, and MS) and element analysis. 2-Cyclohexylbenzoxazole, for instance, was identified by the ^{1}H NMR. Four aromatic protons appear at a range of δ 7.3-7.7, whereas eleven aliphatic proton appear at a range of δ 1.3-2.2: methine proton occurs as three triplet; two neighbor axial hydrogens split the methine proton as triplet with J = 11.0 Hz and two neighbor equatorial protons again split the

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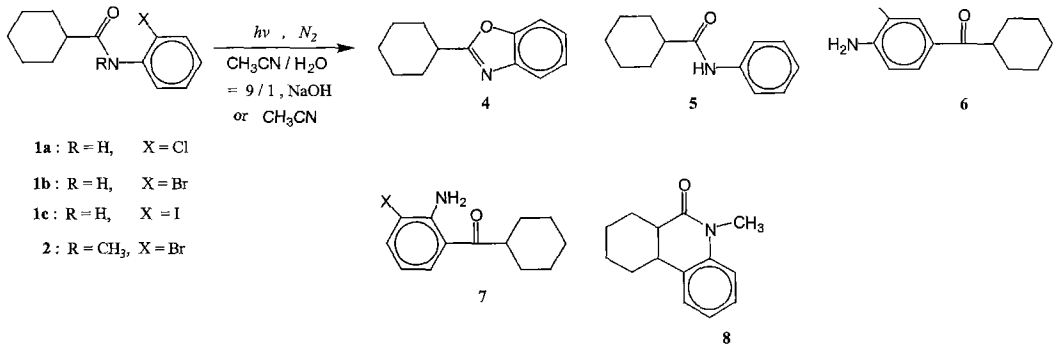
Table 1. The photoreaction of *N*-(2-halophenyl)cyclohexanecarboxamide in basic aqueous acetonitrile solution (CH_3CN/2*N* NaOH = 450 mL/50 mL).

starting compd	reaction time(min)	recovered starting compd	isolated products	yields	mp
			4	15(6)* %	32-33 ℃
1a	50	4 %	**6**	6(20)* %	–
			7	0(14)* %	80-82 ℃
			4	33(30)* %	32-33 ℃
1b	40	15 %	**5**	26(24)* %	144-145 ℃
			4	3 %	32-33 ℃
1c	25	5 %	**5**	54 %	144-145 ℃
2	120	9 %	**8**	36 %	–

* in acetonitrile



Scheme 1.

methine proton as triplet with J = 3.9 Hz.

The pertinent results of the synthetic reactions are shown in Table 1 and Scheme 1. Chloro analogue **1a** produced a photosubstituted product **4** (15%) and a photo-Fries type product **6** (6%). The reactivities of **1a** and **1b** are similar to the 2′-chlorobenzanilide [7]. In plain acetonitrile (without base) **1a** produced more photo-Fries type products **6** and **7** and less photosubstituted product **4**, compared to those from the basic conditions. Iodo analogue **1c** mainly afforded the reduced product **5**. Interestingly, *N*-(2-bromophenyl)-*N*-methylcyclohexanecarboxamide, which can not exist as imidol form, produced a photocyclized product, but not the photosubstituted product. This result supports the report which imidol form is involved in the photosubstitution [6].

The quantum yield for the photoreaction of **1** was measured and is shown in Table 2. The quantum yield of the photosubstitution in Table 2 ranges from a value of 7×10^{-4} for **1c** to 4×10^{-3} for **1b**. The reduction quantum yield is similar to the photosubstitution. The quantum yields of the photosubstitutions of **1a**, **1b**, and **1c** was not reduced in the presence of oxygen as a triplet quencher, whereas that of reduction was reduced in the presence of oxygen. The results imply that the singlet excited state is involved for the substitution, but a triplet state for the reduction. The photoreduction reactivities of **1a**, **1b**, **1c** indicate the radical reaction.

Table 2. Quantum Yield on the Photosubstitution and Photoreduction of *N*-(2-halophenyl)cyclohexanecarboxamide with and without Oxygen †.

substrate	photosubstitution (Φ)		photoreduction (Φ)	
	with Ar	with O_2	with Ar	with O_2
1a	0.001	0.001	–	–
1b	0.004	0.004	0.005	0.0003
1c	0.0007	0.0006	0.006	0.0006

†in acetonitrile containing 2.0N aq NaOH(9/1) with monochromatic light

‡less than 1×10^{-4}

EXPERIMENTAl SECTION

General procedure for the synthesis of N-(2-halophenyl)cyclohexane carboxamide

The desired 2-haloaniline (for 2-chloroaniline 2.1 mL, 20 mmole) was stirred in 20 mL pyridine and one equivalent cyclohexanecarbonyl chloride (2.7 mL) was added dropwise at ice bath temperature for 2 min. The mixture was stirred in ice bath for 2 hrs and in room temperature for 3 hrs. When 250 mL of water added, a white solid was isolated typically in 92% yield.

*N-(2-chlorophenyl)cyclohexanecarboxamide (**1a**):*

Yield 92%; mp (crystallized from aectone/H_2O) 107-108 ℃; UV (λ_{max} in acetonitrile) 245 nm (ε_{245}=1.7×10^4 L/mol.cm); IR (CHCl3) 3281, 3188, 1658 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J=8.4 Hz, 1H), δ 7.72 (br. s, J=7.8 Hz, 1H), δ 7.38 (dd. J=7.8 Hz, 1H), δ 7.30 (t, J=10.5 Hz, 1H), δ 7.06 (t, J=7.8 Hz, 1H), δ 2.34 (tt, J=8.1 Hz, 1H), δ 2.04-1.24 (m, 10H); MS m/z (rel. intensity) 239 (3, M$^+$+2), 237 (10, M$^+$), 202 (16, M$^+$-Cl). Analytical Cal. for $C_{13}H1_6NOCl$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.37; H, 6.83; N, 5.69.

*N-(2-bromophenyl)cyclohexanecarboxamide (**1b**):*

Yield 78%; mp (crystallized from cyclohexane) 115-116 ℃; UV (λ_{max} in acetonitrile) 245 nm (ε_{245}=1.2×10^4 L/mol.cm); IR ($CHCl_3$) 3281, 3188 , 1658 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J=8.4 Hz, 1H), δ 7.72 (br. s, 1H), δ 7.55 (dd. J=8.1 Hz, 1H), δ 7.34 (t, J=8.4 Hz, 1H), δ 7.00 (t, J=8.1 Hz, 1H), δ 2.37 (tt, J=11.4 Hz, 1H),δ 2.05-1.25 (m, 10H); MS m/z (rel. intensity) 283 (3, M$^+$+2), 281 (3, M$^+$), 202 (18, M$^+$-Br). Analytical Cal. for $C_{13}H_{16}NOBr$: C, 55.33; H, 5.72; N, 4.96. Found: C, 55.52; H, 5.71; N, 4.87.

*N-(2-iodophenyl)cyclohexanecarboxamide (**1c**):*

Yield 97%; mp (crystallized from cyclohexane) 134-135 ℃; UV (λ_{max} in acetonitrile) 242 nm (ε_{242}=1.1×10^4 L/mol.cm); IR ($CHCl_3$) 3269, 3188, 1656 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J=8.4 Hz, 1H), δ 7.78 (dd, J=7.8 Hz, 1H), δ 7.52 (br. s, 1H), δ 7.36 (t, J=8.4 Hz, 1H), δ 6.86 (dt, J=7.8 Hz, 1H), δ 2.37 (tt, J=11.7 Hz, 1H), δ 2.08-1.24 (m, 10H); MS m/z (rel. intensity) 329 (8, M$^+$), 202 (100, M$^+$-I). Analytical Cal. for $C_{13}H_{16}NOI$: C, 47.43; H, 4.90; N, 4.25. Found: C, 47.71; H, 5.12; N, 4.02.

*N-(2-Bromophenyl)-N-methylcyclohexanecarboxamide (**2**)*

N-(2-Bromophenyl)-*N*-methylcyclohexanecarboxamide (**2**) was prepared by the method of Johnstone [8]: to a solution of *N*-(2-bromophenyl)cyclohexanecarboxamide (1.4g, 5 mmole) in acetone (30 mL) at 50 ℃, was added potassium hydroxide (powder, 1.1 g) and methyl iodide (1.3 mL, 20 mmole), mixture was reflexed for 15 min and the excess methyl iodide and acetone were evaporated. The reaction mixture was extracted with chloroform/H_2O. When the chloroform layer was evaporated, a white solid was isolated . Recrystallization from n-hexane gave 2 g *N*-(2-bromophenyl)-*N*-methylcyclohexanecarboxamide (87%, yield)

*N-(2-bromophenyl)-N-methylcyclohexanecarboxamide (**2**):*

Yield 87%; mp (crystallized from n-hexane) 112-114 ℃; UV λ_{max} in acetonitrile) 267 nm (ε_{267}=1.5×10^3 L/mol.cm); IR ($CHCl_3$) 1656 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J=8.52 Hz, 1H), δ 7.41 (dt, J=7.0 Hz, 1H), δ 7.27 (m, 2H), δ 3.17 (s, 3H), δ 1.96 (tt, J=11.52 Hz, 1H), δ 1.79-1.43 (m, 10H); MS m/z (rel. intensity) 298 (5, M$^+$+2), 296 (6, M$^+$), 216 (86, M$^+$-Br). Analytical Cal. for $C_{14}H_{18}NOBr$: C, 56.77; H, 6.13; N,4.73. Found: C, 56.84; H, 6.22; N, 4.60.

*Preparative Photoreaction. Photoreaction of N-(2-bromophenyl)cyclohexanecarboxamide (**1b**) in a basic medium. General Procedure.*

To a large (500 mL) quartz immersion well photolysis unit with provision for circulation of nitrogen were added 450 mL of acetonitrile, 50 mL aqueous NaOH (2 M) and 0.5 mmole (0.14 g) of *N*-(2-bromophenyl) cyclohexanecarboxamide (**1b**). With nitrogen circulation, the solution was irradiated with a 450 W mercury lamp (medium pressure) at 110 V at room temperature for 40 min. After reaction acetonitrile and water layers were separated. The water layer was extracted with ethyl acetate. After evaporation of the organic solvent (acetonitrile and ethyl acetate portion) preparative TLC for the residue gave R_f values in THF/n-hexane (1/8) of 0.14, 0.39, and 0.49. They were identified as *N*-phenylcyclohexanecarboxamide (**5**), starting material and 2-cyclohexylbenzoxazole (**4**), respectively.

*N-Phenylcyclohexanecarboxamide (Rf 0.14, **5**):*

Yield 26%; mp (crystallized from acetone/H_2O) 144-145 ℃; IR ($CHCl_3$) 3244, 3132, 1658 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J=8.1 Hz, 2H), δ 7.34 (t, J=7.5 Hz, 2H), δ 7.15 (br. s, 1H), δ 7.12 (t, J=7.5 Hz, 1H), δ 2.27 (tt, J=11.7 Hz, 1H), δ 1.98-1.27 (m, 10H); MS m/z (rel. intensity) 203 (8, M$^+$), 93 (100), 83 (36). Analytical Cal. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.70; H, 8.34; N, 6.93.

*2-Cyclohexylbenzoxazole (R_f 0.49, **4**):*

Yield 33%; mp 32-33 ℃; IR ($CHCl_3$) 3058, 1611 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70 (m, J=8.4 Hz, 1H), δ 7.49 (m, 1H), δ 7.32 (m, 2H), δ 3.01 (tt, J=11.4 Hz, 1H), δ 2.20-1.26 (m, 10H); MS m/z (rel. intensity) 201(17, M$^+$), 172 (10), 146 (100). Analytical Cal. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.40: H, 7.60; N, 6.78.

*Photoreaction of N-(2-chlorophenyl)cyclohexanecarboxamide (**1b**) in a basic medium:*

The procedure was the same as above. The reaction time was 50 min. The products were 2-chloro-4-(cyclohexanecarbonyl)aniline (R_f 0.13, 6%), *N*-(2-chlorophenyl)cyclohexanecarboxamide (R_f 0.38, 4%), and 2-cyclohexylbenzoxazole (R_f 0.49, 15%).

*2-chloro-4-cyclohexanecarbonylaniline (R_f 0.13, **6**):*

Yield 6%; mp (crystallized from cyclohexane) 80-82 ℃; IR ($CHCl_3$) 3230, 3067, 1670 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), δ 7.72 (d, J=8.5 Hz, 1H), δ 6.76 (d, J=8.5 Hz, 1H), δ 4.49 (br. s, 2H), δ3.16 (t, J=10.5 Hz, 1H), δ 1.85-1.25 (m, 10H); MS m/z (rel. intensity) 239 (3, M$^+$+2), 237 (10, M$^+$), 202 (7, M$^+$-Cl). Analytical Cal. for $C_{13}H_{16}NOCl$:

C, 65.68; H, 6.78; N, 5.89. Found: C, 65.60; H, 6.80; N, 5.70.

*Photoreaction of N-(2-iodophenyl)cyclohexanecarboxamide (**1c**) in a basic medium:*

The procedure was the same as above. The reaction time was 25 min. The products were *N*-phenylcyclohexanecarboxamide (R_f 0.23, 54%) and 2-cyclohexylbenzoxazole (R_f 0.46, 3%).

*Photoreaction of N-(2-bromophenyl)-N-methylcyclohexanecarboxamide (**2**) in a basic medium:*

The procedure was the same as above. The reaction time was 2 hrs. The products were *N-(2-bromophenyl)-N-methylcyclohexanecarboxamide* (R_f 0.14, 9%) and 5-methyl-6a,7,8,9,10,10*a*-hexahydro-5H-phenanthridin-6- one (R_f 0.33, 36%).

5-methyl-*6a,7,8,9,10,10a-haxahydro-5H-phenanthridin-6-one (R_f 0.33, **8**):*

Yield 36%; IR ($CHCl_3$) 3074, 2954, 1663 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J=7.5 Hz, 1H), δ 7.30 (t, J=7.8 Hz, 1H), δ 7.07 (t. J=7.5 Hz, 1H), δ 6.86 (t, J=7.8 Hz, 1H), δ 3.20 (s, 3H), δ 1.97-1.54 (m, 10H); MS m/z (rel. intensity) 215 (47, M^+), 160 (100), 91 (45).

Photoreac*tion of N-(2-chlorophenyl)cyclohexanecarboxamide (**1a**) in acetonitrile*:

When the solution of *N*-(2-chlorophenyl)cyclohexanecarboxamide (**1a**, 0.5 mmole, 0.12 g) in acetonitrile (500 mL) was treated as above, the products were 2-chloro-4-(cyclohexanecarbonyl)aniline (R_f 0.13, 20%), *N*-(2-chlorophenyl)cyclohexanecarboxamide (R_f 0.38, 4%), 2-cyclohexyl benzoxazole (R_f 0.49, 6%), and 2-chloro-4-(cyclohexanecarbonyl)aniline (R_f 0.62, 14%).

*2-chloro-4-(cyclohexanecarbonyl)aniline (R_f 0.62, **7**):*

Yield 14%; IR ($CHCl_3$) 3340, 3056, 1656 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.0 Hz, 1H), δ 7.41 (d, J=7.6 Hz, 1H), δ 6.62 (t, J=7.5 Hz, 1H), δ 6.85 (br. s, 2H), δ 3.29 (t, J=11.0 Hz, 1H), δ 1.87-1.22 (m, 10H); MS m/z (rel. intensity) 239 (3, M^++2), 237 (10, M^+), (7, M^+-Cl).

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