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A new photochemical synthesis of benzoxazolo[3,2-*b*]isoquinolin-11-one and isoquinolino[3,2-*b*][1,3]benzoxazin-11-one

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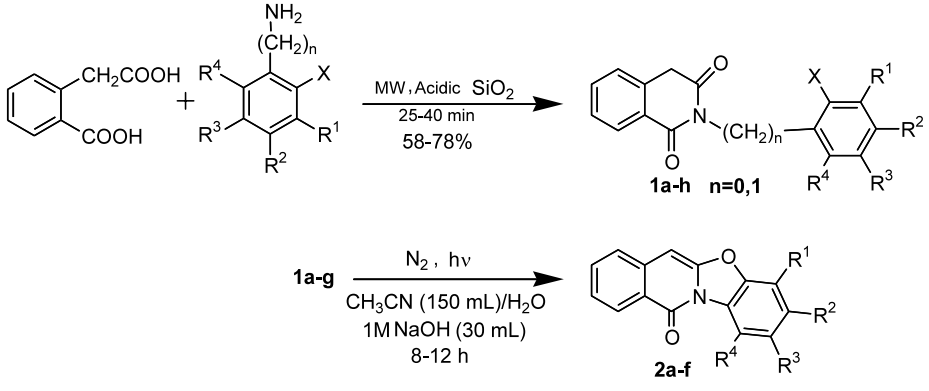
Abstract—Photocyclization of substituted tetrahydroisoquinoline-1,3-diones, under base-mediated conditions, afforded benzoxazolo[3,2-*b*]isoquinolin-11-ones and an isoquinolino[3,2-*b*]benzoxazin-11-one.

Tetrahydroisoquinolines constitute a class of compounds attracting increasing interest due to their biological activities. They are important key intermediates for the synthesis of isoquinoline alkaloids.[1,2] Isoquinoline fused heterocyclic compounds are also highly important showing significant biological activity.[3]

A few methods have been reported for the synthesis of oxazoloisoquinoline analogues.[4,5] Xu et al,[6] reported the synthesis of benzoxazolo[3,2-*b*]isoquinolin-11-ones and isoquinolino[2,3-*a*][3,1]benzoxazine-5,12-dione from homophthalic anhydride. Recently, photocyclization of *N*-(2-halophenyl)-pyridine carboxamides to 2-pyridyl benzoxazoles has been reported.[7]

In continuation of our interest in the photochemical synthesis of benzothiazoles,[8,9] we have recently reported[10] the photocyclization of triazole-3-thiones to triazolo[3,4-*b*]-1,3-(4*H*)-benzothiazines, under basic conditions. To the best of our knowledge there is no report on the photochemical synthesis of isoquinoline-fused benzoxazole and benzoxazine systems. We report here our preliminary results on the photocyclization of substituted tetrahydroisoquinoline-1,3-diones to benzoxazolo[3,2-*b*]isoquinolin-11-ones and an isoquinolino[3,2-*b*][1,3]benzoxazin-11-one, under basic conditions.

The required starting materials, tetrahydroisoquinoline-1,3-diones **1a**–**h**, were prepared by using the recently emerging solvent free microwave technique. Microwave irradiation of homophthalic acid and substituted anilines/benzylamine in acidic silica gel afforded the isoquinoline-1,3-diones **1a**–**h** in good yields (Scheme 1).



Scheme 1.

Keywords: photocyclization; basic conditions; photohydrolysis.

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The structures of compounds **1a–h** were confirmed by spectral data. Further, the structure of compounds **1b**, **1f** and **1h** were confirmed by single-crystal X-ray diffraction.[11]

Irradiation of the quinoline **1a** under aqueous basic conditions (CH_3CN/1 M NaOH, two-phase) in a multilamp reactor (MLR) (254 nm) under nitrogen furnished the benzoxazolo[3,2-*b*]isoquinolin-11-one **2a** in good yield (Scheme 1). Similarly, photolysis of compounds **1b–f** also gave the corresponding benzoxazolo[3,2-*b*]isoquinolin-11-ones **2b–f** as the sole products (Table 1). Irradiation of the bromo analogue **1g** also afforded the oxazole **2a**. A model reaction of **1a** under dark conditions gave no product; starting material **1a** was isolated.

The photosubstitution reaction described here involves intramolecular replacement of the halogen atom present in the *N*-phenyl moiety of the isoquinoline-1,3-diones **1a–g** by the carbonyl oxygen (C_3–CO) under the basic conditions.

Next, the irradiation of the *N*-benzyl derivative **1h** was carried out using CH_3CN/1 M NaOH in a MLR under nitrogen to afford the *N*-(2-chlorobenzyl)-2-methyl benzamide **3** involving hydrolysis followed by decarboxylation (Scheme 2), instead of the expected isoquinolinobenzoxazine **4**. Whereas, irradiation of **1h** using the CH_3CN/3 M NaOH (two-phase) conditions afforded the expected isoquinolino[3,2-*b*][1,3]benzoxazin-11-one **4** (Table 1) as the only product.

The formation of product **3** is probably due to ineffective deprotonation of the benzyl derivative **1h** in 1 M NaOH. Obviously, an increase in the concentration of base (3 M NaOH) facilitates the deprotonation considerably, which leads to intramolecular substitution of the *o*-chlorine of the *N*-benzyl isoquinoline **1h**.

The structures of the photoproducts **2a–f**, **3** and **4** were consistent with the spectral data.[12] Furthermore, the structure of the compound **2c**[13] was confirmed by single-crystal X-ray diffraction.

In conclusion, it has been observed that irradiation of tetrahydroisoquinolines **1a–g** under base-mediated conditions afforded the respective benzoxazolo isoquinolines. Photolysis of isoquinoline **1h** gave the decarboxylated or cyclized product depending on the concentration of the base employed.

A mechanistic study and experimental details will be published elsewhere.

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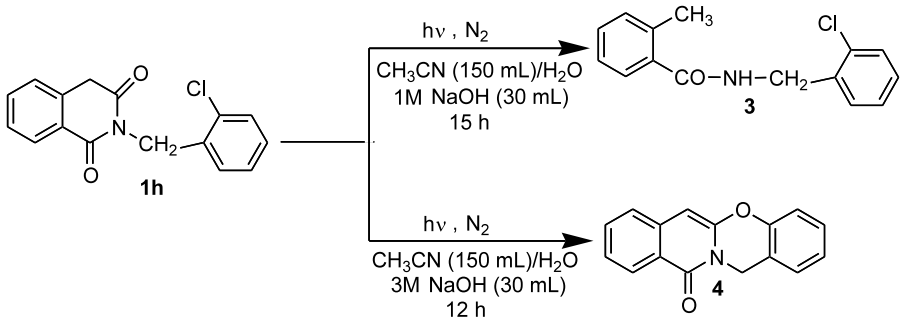
Table 1. Photolysis of tetrahydroisoquinolines **1a–h**

1	X	R^1	R^2	R^3	R^4	*n*	Irradiation time (h)	Product	Product yield (%)	Mp (°C)
a	Cl	H	H	H	H	0	12	**2a**	41	200–202 (204–206)[6]
b	Cl	Cl	H	H	H	0	7	**2b**	43	188–190
c	Cl	H	Cl	H	H	0	8	**2c**	48	205–207
d	Cl	H	H	Cl	H	0	9	**2d**	46	213–215 (211–212)[6]
e	Cl	H	H	H	Cl	0	10	**2e**	40	183–185
f	Br	H	CH_3	H	H	0	7	**2f**	52	200–202
g	Br	H	H	H	H	0	8	**2a**	50	198–200
h	Cl	H	H	H	H	1	12	**4**	47	210–212



Scheme 2.

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12. Spectral data of compound **3**: Yield: 69%; mp: 100–102°C; UV: 210 nm (CH_3OH); IR (KBr): 3296, 3060, 1641, 1535 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H, CH_3), 4.68 (d, 2H, $J=6$ Hz, CH_2), 6.25 (bs, 1H, NH), 7.20–7.44 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.71 (CH_3), 41.80 (CH_2), 125.64, 126.67, 127.08, 128.99, 129.52, 129.90, 130.27, 130.97, 133.61, 135.52, 135.98, 136.16, 169.80; MS, m/z (%): (259 (M^+), 261-trace), 224 (100), 125 (10), 119 (56), 91 (53), 77 (12). Analysis: $C_{15}H_{14}NOCl$ (259.73): calcd C, 69.36; H, 5.43; N, 5.39. Found: C, 69.00; H, 5.07; N, 5.65. Spectral data of compound **4**: UV: 232 nm (CH_3OH); IR (KBr): 1689, 1647, 1601, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.16 (s, 2H, CH_2), 6.21 (s, 1H, C_6-CH), 7.12–7.60 (m, 7H, ArH), 8.33 (d, $J=7.8$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.67 (CH_2), 87.79 (C_6-CH), 115.87, 118.39, 122.11, 124.23, 124.75, 125.25, 126.81, 127.95, 129.17, 132.82, 137.59, 147.20, 151.50, 161.88; MS, m/z (%): 249 (M^+, 100), 248 (28), 220 (15), 193 (6), 165 (10), 143 (98), 115 (73), 114 (5), 106 (12), 89 (18). Analysis: $C_{16}H_{11}NO_2$ (249.26): calcd C, 77.09; H, 4.44; N: 5.61. Found: C, 77.37; H, 4.68; N, 5.83.
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