One-Pot Synthesis of Indolo[2,3-*c*]quinolin-6-ones by Sequential Photocyclizations of 3-(2-Azidophenyl)-*N*-phenylacrylamides

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Abstract: A one-pot synthesis of indolo[2,3-*c*]quinolin-6(7*H*)-ones was achieved by sequential photocyclizations of 3-(2-azidophenyl)-*N*-phenylacrylamides in moderate to high yields. The reactions proceeded via photochemical cyclization of aryl azides to form *N*-phenylindol-2-carbamides and subsequent 6 π -electrocyclic reaction and oxidative aromatization to afford the corresponding indolo[2,3-*c*]quinolin-6(7*H*)-ones.

Key words: indolo[2,3-*c*]quinolin-6(7*H*)-ones, photocyclization, 3-(2-azidophenyl)-*N*-phenylacrylamides, aryl azides, 6 π -electrocyclic reaction

Indoloquinolines are present in many natural alkaloids¹ and pharmaceuticals² possessing important biological activities, such as alkaloid cryptolepine (**A**; Figure 1) (5-methyl-5*H*-indolo[3,2-*b*]quinoline), cryptotackieine (**B**) (5-methyl-5*H*-indolo[2,3-*b*]quinoline) and cryptosanguinolentine (**C**) (5-methyl-5*H*-indolo[3,2-*c*]quinoline), all having potent antiplasmodial and antimalarial activities.^{1–3} Isonocryptolepine (indolo[2,3-*c*]quinoline) (**D**), a synthetic analogue of the above natural products, also shows low resistant activity to chloroquine and pyrimethamine, but has much better selectivity index (cytotoxicity/antiplasmodial activity ratio) than cryptolepine, which makes it a better compound for further validation of the indoloquinolines as a potential antiplasmodial drugs. The indoloquinoline alkaloids have been used extensively as lead compounds for the discovery of new antiplasmodial substances.

Many reports have been found for the synthesis of indoloquinoline alkaloids,^{1–4} but for the unnatural isonocryptolepine (indolo[2,3-*c*]quinoline) derivatives, especially indolo[2,3-*c*]quinolin-6(7*H*)-ones which was found to possess antitumor activities,⁵ only a few of synthetic methods were found in literature,⁶ for example, Pd(OAc)₂-catalyzed intramolecular Heck reaction of *N*-

(2-iodophenyl)-1*H*-indole-2-carboxamides^{6a} or of 3-(2-bromophenylamino)quinolines,^{6b} photostimulated intramolecular S_{RN}1 reactions of *N*-(2-chlorophenyl)-1*H*-indole-2-carboxamides,^{6c} and cyclocondensation of 3-formaloxindoles with phenylhydrazines,^{6d} and oxidative photochemical cyclization of *N*-phenylindole-2-carboxamides.^{6e} However, all these methods generally required either an indole or a quinoline as the precursor and then in order to reach to indolo[2,3-*c*]quinolin-6(7*H*)-ones structure, construction of another ring.

We have been long interested in the synthesis of polycyclic heterocycles by one-pot multistep reactions. Recently, we reported a new synthesis of indolo[3,2-*c*]quinolin-6-ones by the photoreaction of 3-(2-azidobenzylidene)indol-2-ones.⁷ In this route, photocyclization of 3-(2-azidobenzylidene)indol-2-ones first lead to formation of indole ring and subsequent ring expansion of indol-2-one afford the quinoline ring. Here, we report a new method for the synthesis of indolo[2,3-*c*]quinolin-6(7*H*)-ones (isonocryptolepinone) by a one-pot two-step photocyclization of 3-(2-azidophenyl)-*N*-phenylacrylamides (Scheme 1).

The reactions proceeded via photochemical cyclization of aryl azides **1** to form the corresponding indole ring **2** first and then photochemical 6 π -electrocyclic reaction to form the cyclic dihydroquinolin-2-one intermediate which is aromatized by oxidative dehydrogenation to give the product indolo[2,3-*c*]quinolin-6(7*H*)-ones **3**.

We first optimized the photoreaction conditions using 3-(2-azidophenyl)-*N*-phenylacrylamide (**1a**) as a model substrate which was prepared by the Wittig reaction of 2-azidobenzaldehyde with triphenyl phenylcarbamoylmethyl phosphonium salt according the reported procedure (Scheme 2).^{8a,b}

Figure 1

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Scheme 1 One-pot two-step photocyclization of 3-(2-azidophenyl)-*N*-phenylacrylamides

The reaction of **1a** was examined in different oxygen-saturated solvents (Scheme 3) in a Pyrex flask ($\lambda \geq 280$ nm) because it was suggested that the irradiation of aromatic amide systems with the 254 nm light largely induced photo-Fries rearrangement,⁹ but the irradiation with $\lambda \geq 300$ nm light rather promoted cyclization.^{6e}

Scheme 2 The procedure for the preparation of **1a**

As shown in Table 1, the reaction efficiency was not satisfactory in nonpolar solvent benzene or polar solvent acetonitrile because of the low solubility of substrate **1a** in benzene and no **3a** was formed in acetonitrile except for the indole-2-carbamide **2a**. Thus, the photoreaction was then examined in a mixture of solvents. It was observed that the photoreaction efficiency of **1a** increased in solvent mixture and reached its highest value in a 9:1 mixture of benzene and dichloromethane. This result was probably ascribed to the solvent effects on the two photocyclizations because the weak polar solvents such as benzene, cyclohexane and dioxane favored the oxidative photocyclization of amide systems,^{6e,10} whereas polar solvents such as dichloromethane and acetonitrile were favorable to the photochemical cyclization of aryl azides⁷ and photo-Fries rearrangement.⁹ The addition of small quantity of dichloromethane to benzene not only enhanced the reaction of aryl azides, but also increased the solubility of substrates. Therefore, irradiation of substrates **1** in a mixture of solvents benzene and dichloromethane (9:1) in Pyrex flask was selected as the optimal conditions for the synthesis of indolo[2,3-*c*]quinolin-6(7*H*)-ones.

Scheme 3 Photoreaction of **1a** in different solvents

Table 1 Optimization of Reaction Conditions for the Synthesis of **3a**^a

Entry	Solvent	Time (h)	Conv. (%) ^b	Yield (%) ^c
1	MeCN	20	93	0 ^d
2	benzene	20	83	75 ^e
3	benzene–acetone (5:1)	20	70	30
4	benzene–EtOH (5:1)	16	82	45
5	benzene (5:1)	15	85	68
6	benzene–CH ₂ Cl ₂ (2:1)	14	89	66
7	benzene–CH ₂ Cl ₂ (5:1)	12	90	70
8	benzene–CH ₂ Cl ₂ (9:1)	11	96	76
9	benzene–CH ₂ Cl ₂ (15:1)	13	91	70

^a Reaction conditions: compound **1a** (128 mg, 0.5 mmol) was dissolved in anhyd benzene (54 mL) and anhyd CH₂Cl₂ (6 mL). The solution was bubbled with oxygen for 10 min and irradiated at $\lambda \geq 280$ nm with a medium-pressure mercury lamp (500 W) at ambient temperature.

^b Conversions calculated on the basis of substrate.

^c Yields of isolated product based on consumed substrate.

^d No **3a** was separated except for the *N*-phenyl-2-indolecarbamide (**2a**).

^e The substrate **1a** was not dissolved completely because of its low solubility in benzene.

We then examined the photocyclization of a group of 3-(2-azidophenyl)-*N*-phenylacrylamides with different substituents on both azidobenzene ring and aniline ring under the optimized conditions.¹¹ The photoreactions of all these substrates (**1b–p**) afforded the corresponding cyclization products (**3b–p**) in moderate to high yields after irradiations for 5–25 hours at room temperature (Table 2). All products were fully identified by ¹H NMR, ¹³C NMR, HRMS and IR.¹¹ It can be observed from Table 1 that the

Scheme 4 A plausible photoreaction mechanism of **1a**

photoreaction efficiency was different for the substrates with different substituents. The electron-donating groups, such as the methoxy and methyl groups (**1f** and **1g**) on the aniline ring, retarded the photoreaction of **1f** and **1g** and more time was needed to reach the high conversion (entries 6 and 7; 18 h and 16 h, respectively). In contrast, electron-attracting groups, such as chlorine atom (**1h**, **1i**) and carboxylate group (**1j**) had no significant effects on the photoreaction rate of **1h–j** (entries 8–10) in comparison with **1a**, but decreased the yields of **3h–j** greatly (entry 10). Moreover, the *ortho*-ethoxycarbonyl group in **1k** led to a significant decrease in both the reaction rate and the yield of product **3k** (entry 11). These results were probably derived from the decrease of pericyclic reaction probability of the intermediate product **2k** and the increase of photo-Fries rearrangement products of **2k** because one *ortho*-position was blocked in **2k**. In fact, small quantities of

decomposition product methyl 2-aminobenzoate and photo-Fries rearrangement products could be separated from the reaction mixture besides **2k** and **3k** after irradiation of **1k** for 25 hours. This kind of result was also reported in the photocyclization of benzanilides under the irradiation at $\lambda \geq 280$ nm.^{9b} On the other hand, the substituents on the azidophenyl ring also had some effects on the photoreactions of **1m–p**. For example, *meta*-chlorine atom in **1l,m** (entries 13 and 14) accelerated the photoreaction in comparison to that of **1b,c** (entries 2 and 3). Differently, *para*-ethoxycarbonyl group led to the decrease of both the reaction rate of **1l,m** and the yield of products **3l,m** (entries 13 and 14) as compared with the reactions of **1d,e** (entries 4 and 5); the alkoxy groups in **1l** lowered the yield of **3l** (entry 12) as compared with that of **3d** (entry 4) although the reaction times needed were similar.

Table 2 Photocyclization of (*E*)-3-(2-Azidophenyl)-*N*-phenylacrylamides in Benzene–Dichloromethane^a

Entry	Substrate	Time (h)	Conv. (%) ^b	Product	Yield (%) ^c
1	1a	11	96	3a	76
2	1b	15	92	3b	68

Table 2 Photocyclization of (*E*)-3-(2-Azidophenyl)-*N*-phenylacrylamides in Benzene–Dichloromethane^a (continued)

Entry	Substrate	Time (h)	Conv. (%) ^b	Product	Yield (%) ^c
3	1c 	10	94	3c 	60
4	1d 	6	98	3d 	78
5	1e 	5	99	3e 	85
6	1f 	18	92	3f 	75
7	1g 	16	90	3g 	65
8	1h 	11	96	3h 	80
9	1i 	12	96	3i 	83
10	1j 	9	95	3j 	52

Table 2 Photocyclization of (*E*)-3-(2-Azidophenyl)-*N*-phenylacrylamides in Benzene–Dichloromethane^a (continued)

Entry	Substrate	Time (h)	Conv. (%) ^b	Product	Yield (%) ^c
11	1k 	25	93	3k 	40
12	1l 	5	96	3l 	60
13	1m 	8	95	3m 	57
14	1n 	7	95	3n 	56
15	1o 	9	95	3o 	50
16	1p 	9	94	3p 	52

^a Reaction conditions: compound **1** (0.5 mmol) was dissolved in anhyd benzene (54 mL) and anhyd CH₂Cl₂ (6 mL). The solution was bubbled with oxygen for 10 min and irradiated at $\lambda \geq 280$ nm with a medium-pressure mercury lamp (500 W) at ambient temperature.

^b Conversions calculated on the basis of substrate.

^c Yields of isolated product based on consumed substrate.

The intermediate products *N*-phenylindol-2-carbamides **2**, produced in the first photocyclization of **1a–p** (Scheme 1), were monitored in the progress of photoreactions. It was found that no intermediate products **2** were detected in most cases except for the photoreaction of **1c**, **1d**, **1e** and **1k** in which a small quantity of intermediate **2c**, **2d**, **2e** and **2k**, respectively, could be separated. It meant that the oxidative photocyclization of intermediates **2** (the second photocyclization) proceeded more quickly than the photocyclization of **1** in most cases; only for **1c**, **1d**, **1e** and **1k**, the photocyclization of intermediates **2c**, **2d**, **2e** and **2k** was slower than the photocyclization of **1c**, **1d**, **1e** and **1k**.

A reasonable mechanism to account for the formation of indolo[2,3-*c*]quinolin-6(7*H*)-ones is presented in Scheme 4. Photocyclization of azide **1a** is believed to occur via at-

tack of nitrene **1a** to the β -position of the adjacent double bond to form a zwitterion **IIa**¹⁰ and the subsequent shift of hydrogen atom from β -carbon to nitrogen atom to give the intermediate aryl anilide **2a**. Photochemical 6π -electrocyclic reaction of **2a** forms the cyclic intermediate (**IVa**) which then is dehydrogenated by oxygen to give the final product **3a**.^{10a,12}

In summary, we have developed an efficient method for the synthesis of indolo[2,3-*c*]quinolin-6(7*H*)-ones, indolo[2,3-*c*]pyrrolo[3,2,1-*i,j*]quinolin-7-ones and indolo[2,3-*c*]pyrido[3,2,1-*i,j*]quinolin-8-ones by a one-pot photocyclization of 3-(2-azidophenyl)-*N*-phenylacrylamides. The reactions proceed by two sequential cyclization reactions, namely photocyclization of 2-azidocinnamides and 6π -electrocyclic reaction of the formed intermediate aryl anilides.

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- (11) **Typical Experimental Procedure:** A solution **1a** (128 mg, 0.5 mmol) in a mixture of anhyd benzene (54 mL) and anhyd CH₂Cl₂ (6 mL) was bubbled with oxygen for 10 min and irradiated at $\lambda \geq 280$ nm with a medium-pressure mercury lamp (500 W) in three 25-mL Pyrex flasks at ambient temperature. The progress of reaction was monitored by TLC at regular intervals. After the solvent was removed under reduced pressure, the residue was separated by silica gel column chromatography eluted with hexane–EtOAc (5:1) to yield the product **3a**.
Selected spectroscopic data for compounds: **3a**: pale yellow solid; mp 294–298 °C. IR (KBr): 3430, 3147, 2921, 1655, 1617, 735 cm⁻¹. ¹H NMR (400 MHz, DMSO): δ = 7.30–7.36 (m, 2 H), 7.41 (td, J = 8.4, 1.6 Hz, 1 H), 7.45–7.52 (m, 2 H), 7.64 (d, J = 8.0 Hz, 1 H), 8.45 (d, J = 8.0 Hz, 1 H), 8.48 (d, J = 8.4 Hz, 1 H), 11.86 (s, 1 H), 12.35 (s, 1 H). ¹³C NMR (100 MHz, DMSO): δ = 155.67, 138.81, 134.93, 127.59, 125.88, 125.62, 122.97, 122.31, 122.29, 122.22, 120.64, 118.17, 118.01, 116.06, 113.02. ESI–HRMS: m/z [M + H]⁺ calcd for C₁₅H₁₁N₂O: 235.0871; found: 235.0870.
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