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Intramolecular Photochemical Cross-Coupling Reactions of 3-Acyl-2-haloindoles and 2-Chloropyrrole-3-carbaldehydes with Substituted Benzenes

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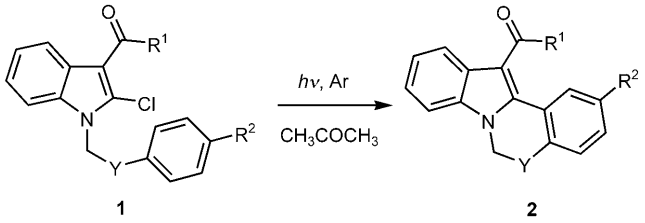
Abstract: Highly efficient syntheses of indolo[2,1-*a*]isoquinolines, indolo[2,1-*a*][2]benzazepines, pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]benzazepines in excellent yields have been achieved by the intramolecular photochemical cross-coupling reactions of 3-acyl-2-halo-*N*-(ω-arylalkyl)indoles and 2-chloro-*N*-(ω-arylalkyl)pyrrole-3-carbaldehydes in acetone. A new heterocyclic ring system – pyrrolo-[1,2-*d*][1,4]benzoxazepine – has also been constructed for the first time in this work by the photocyclization of 2-chloro-*N*-(2-phenoxyethyl)pyrrole-3-carbaldehyde.

Keywords: 2-chloro-*N*-(ω-arylalkyl)indole-3-carbaldehydes; 2-chloro-*N*-(ω-arylalkyl)pyrrole-3-carbaldehydes; cross-coupling; indolo[2,1-*a*][2]benzazepines; indolo[2,1-*a*]isoquinolines; photocyclization

The construction of aryl-aryl bonds has attracted much attention in the past decades because biaryls are common structural components of many pharmaceutically and biologically active compounds.[1] Aryl-aryl bonds could be formed through a large variety of palladium- or nickel-catalyzed cross-coupling reactions. These reactions involve the inter- and intramolecular coupling of a nucleophilic arylated organoelement reagents [boron (Suzuki),[2] magnesium (Kumada),[3] silicon (Hiyama),[4] tin (Stille),[5] or zinc (Negishi)[6]] with an electrophilic reagent such as aryl halides or triflates. Such versatile cross-coupling reactions have been highly successful in synthetic chemistry, but some limitations remain. Thus, activating groups must be present on both arene coupling partners, rather harsh conditions and/or stoichiometric amounts of expensive or moisture-sensitive organometallic compounds are required. The direct arylation by functionalization of an aryl C–H bond, where hydrogen is replaced by the aryl group, has also emerged, for example, Bu_3SnH-mediated aryl radicals substitution.[7] But there are also many disadvantages associated with tributyltin hydride such as serious toxicity and problems of separation of tin residues from organic products.[8–10] Thus, the search for alternative methodologies has long been an attractive topic. Less toxic and more expensive silanes[9] and germanes[10] have been used as substitutes for Bu_3SnH. Alternatives were reported including intramolecular aryl radical cyclizations mediated by the indium(III) chloride-sodium borohydride system[11] or by samarium(II) iodide (SmI_2)-HMPA in THF.[12] Nevertheless, the simplest and most environmentally friendly protocol has to be the generation of the σ-aryl or heteroaryl radical by UV-induced homolytic cleavage of an aryl halide with subsequent intramolecular substitution onto a nearby aromatic ring. Recently Albini reported the metal-free intermolecular photocoupling reactions of amino- or hydroxy-substituted aryl halides with polyalkylbenzenes.[13] In comparison, the intramolecular photocoupling reactions which are used to construct polycyclic systems have been studied more extensively[14]. It is found, however, that the substrates used in the synthesis of polycycles are *o*-haloaryl-substituted arenes, few haloheteroaryl-substituted substrates were considered in this synthetic strategy.[15] Therefore we are interested in the photocoupling reactions of 1-aza-2-chloroarene-3-carbaldehydes with regard to the synthetic method, the reaction mechanism and a few of works have been carried out recently.[16] As a new progress in this program, we

report here a highly efficient synthesis of indolo[2,1-*a*]isoquinolines and the like (Scheme 1).

We found that the simple irradiation of 2-chloro-*N*-(ω-arylalkyl)-3-acylindoles **1** in acetone could afford



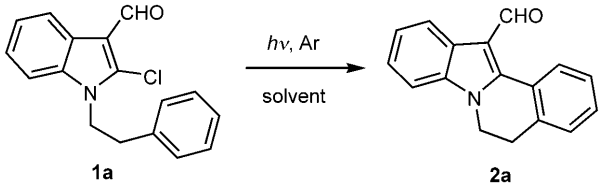
Scheme 1. Photocyclization of 2-chloro-*N*-(ω-arylalkyl)-3-acylindoles in acetone.

tetracyclic [2,1-*a*] fused heterocycles **2** in excellent yields (Scheme 1). Whereas the Bu_3SnH-mediated aryl radical cyclization of similar precursors was often accompanied with halogen-reduced uncyclized products.[7b]

Indolo[2,1-*a*]isoquinolines and indolo[2,1-*a*][2]benzazepines are well known for their potent biological and pharmacological activities.[17] Different methods for the synthesis of these compounds have been reported. The usual methods for the synthesis of indolo-[2,1-*a*]isoquinolines are ring closure of the indole ring of functionallized isoquinolines, for example, nickel-mediated intramolecular coupling of tetrahydroisoquinoline with aryl chlorides,[18] Bu_3SnH-mediated intramolecular coupling of dihydroisoquinolines aryl bromides,[7a] and ring closure of the isoquinoline ring of functionallized indoles, for example, the norbornene-mediated palladium-catalyzed tandem alkylation and arylation of *N*-(2-bromoethyl)indoles,[19] and Bu_3SnH-mediated intramolecular coupling of 2-bromo-*N*-(ω-arylalkyl)indole-3-carbaldehydes.[7b] In comparison with these methods, the advantages of our new synthesis over the Bu_3SnH-mediated cyclization of 1-(ω-arylalkyl)-2-bromoindoles-3-carbaldehydes are not only the high yields with no reductive products found, but also the simple and environmentally friendly protocol.

We first investigated the photoreaction of 2-chloro-*N*-(2-phenylethyl)indole-3-carbaldehyde (**1a**) in different solvents. It was found that the photocyclization reaction in acetonitrile, ethyl acetate or dichloromethane was slow and the addition of acetone could efficiently accelerate the reaction and increase the yield as shown in Table 1. This result may be ascribed to the photosensitization effect of acetone because the E_T of acetone ($E_T = 326\ kJ\ mol^{-1}$)[20a] is higher than that of indole-3-carbaldehyde ($E_T = 275\ kJ\ mol^{-1}$).[20b] Therefore acetone was selected as solvent in all photocyclization reactions of **1a–o**.

Table 1. Photocyclization of **1a** in different solvents.[a]



Entry	Solvent	Time [h]	Conversion [%][b]	Yield [%][c]
1	MeCN	16	80	84
2	AcOEt	16	82	84
3	CH_2Cl_2	16	86	86
4	CH_2Cl_2 + 10% Me_2CO	14	92	92
5	Me_2CO + 0.1 N aqueous Na_2CO_3	8	99	95

[a] Compound **1a** (0.283 g, 1 mmol) was dissolved in different solvents (2 × 50 mL). The solution was irradiated at $\lambda \geq 300$ nm with a medium-pressure mercury lamp (500 W) under an argon atmosphere at ambient temperature.

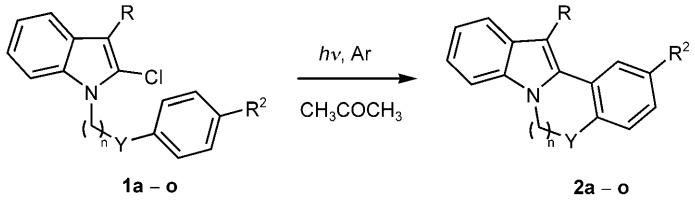
[b] Conversion was calculated on the basis of **1a**.

[c] Yield of isolated product based on consumed **1a**.

It is noticeable that the photoreactions of substrates **1a–e** bearing a phenylalkyl or a phenylalkenyl group all afforded the corresponding cyclization products **3a–e** in excellent yields (Table 2, entries 1–5), and no intramolecular indolyl-alkenyl coupling products were detected. Photoreactions of substrates **1f** and **1j** with an electron-withdrawing group on the phenyl group did not give positive results (entries 6 and 10). In contrast, an electron-donating group on the phenyl group in **1g, 1h** and **1i** could lead to an increase in both the yields of the products and the rate of the photoreactions (entries 7–9). However, an attempt to extend the range of substrates to 1-benzyl-2-chloroindole-3-carbaldehyde was unsuccessful (Table 2, entry 11), which was consistent with that observed in the Bu_3SnH-mediated cyclization of 1-benzyl-2-bromoindole-3-carbaldehyde.[7b] With 2-chloro-*N*-(ω-arylalkyl)-3-acetylindoles **1l–n** as substrates (Table 2, entries 12–14), similar results were obtained. Comparatively, the rate of photoreaction of 2-chloro-3-methyl-1-phenethylindole (**1o**) was much slow although the corresponding cyclization product **2o** (Table 2, entry 15) could also be obtained after long irradiation. In fact, no cyclization product **2o** was detected after long irradiation of the same substrate **1a** in dichloromethane at $\lambda \geq 300$ nm. These results indicated that acetone could catalyze the cyclization reaction and the presence of an acyl group was favorable for the cyclization reaction.

The photoreactions of different halogen-substituted 1-phenethylindoles (**1a, 1a-2** and **1a-3**) were investigated as shown in Table 3. Contrary to expected reac-

Table 2. Photocyclization of 2-chloro-*N*-(ω-arylalkyl)-3-acylindoles.[a]



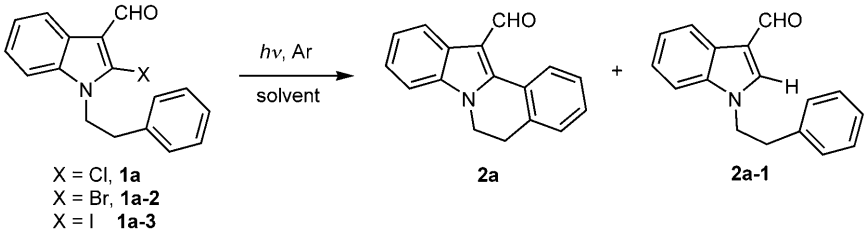
Entry	Substrate	n	Y	R	R^2	Time [h]	Conversion [%][b]	Product	Yield [%][c]
1	**1a**	1	CH_2	CHO	H	10	99	**2a**	95
2	**1b**	1	CH_2CH_2	CHO	H	10	86	**2b**	90
3	**1c**	1	$CHCH_3$	CHO	H	10	99	**2c**	94
4	**1d**	1	C=CH_2	CHO	H	10	89	**2d**	88
5	**1e**	1	CH=CH	CHO	H	12	96	**2e**	96
6	**1f**	1	C=O	CHO	H	16	0	**2f**	0
7	**1g**	1	$CONCH_3$	CHO	H	10	86	**2g**	92
8	**1h**	1	CH_2O	CHO	H	10	94	**2h**	95
9	**1i**	1	CH_2O	CHO	OCH_3	8	96	**2i**	96
10	**1j**	1	CH_2O	CHO	NO_2	10	0	**2j**	0
11	**1k**	0	CH_2	CHO	H	16	0	**2k**	0
12	**1l**	1	CH_2	$COCH_3$	H	12	90	**2l**	87
13	**1m**	1	CH_2CH_2	$COCH_3$	H	12	84	**2m**	84
14	**1n**	1	CH_2O	$COCH_3$	H	10	93	**2n**	95
15	**1o**	1	CH_2	CH_3	H	16	34	**2o**	91

[a] Compound **1a–o** (1.0 mmol) was dissolved in acetone (2×50 mL) containing 0.1 N aqueous Na_2CO_3 (2 mL). The solution was irradiated at $\lambda \geq 300$ nm with a medium-pressure mercury lamp(500 W) under an argon atmosphere at ambient temperature.

[b] Conversion was calculated on the basis of the substrate.

[c] Yield of isolated product based on the consumed substrate.

Table 3. Photoreactions of different halogen-substituted-*N*-phenethylindole-3-carbaldehydes.[a]



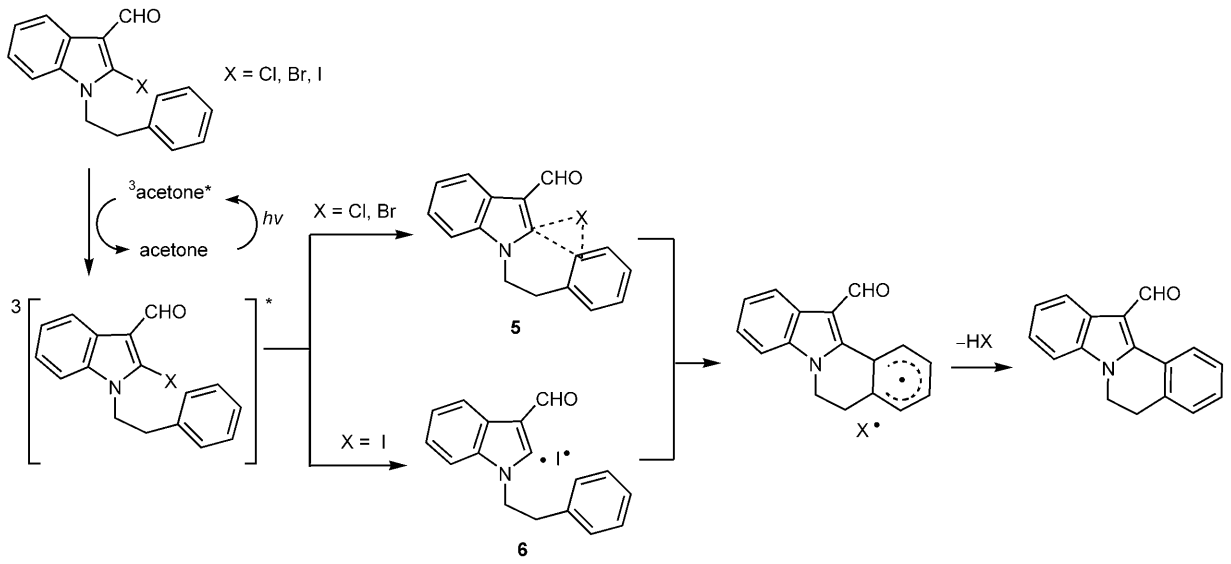
Entry	Substrate	Solvent	X	Y	Time [h]	Conversion [%][b]	Product	Yield [%][c]	
								2a	**2a-1**
1	**1a**	Me_2CO	Cl	CH_2	10	99	**2a**	95	
2	**1a-2**	Me_2CO	Br	CH_2	16	82	**2a**	92	
3	**1a-3**	Me_2CO	I	CH_2	16	62	**2a**	90	
4[d]	**1a**	CH_2Cl_2 + 50% C_6H_{12}	Cl	CH_2	16	80	**2a**	83	trace
5[d]	**1a-2**	CH_2Cl_2 + 50% C_6H_{12}	Br	CH_2	16	58	**2a + 2a-1**	70	5
6[d]	**1a-3**	CH_2Cl_2 + 50% C_6H_{12}	I	CH_2	16	45	**2a + 2a-1**	44	23

[a] Substrate (1.0 mmol) was dissolved in acetone (2×50 mL) containing 0.1 N aqueous Na_2CO_3 (2 mL). The solution was irradiated at $\lambda \geq 300$ nm with a medium-pressure mercury lamp (500 W) under an argon atmosphere at ambient temperature.

[b] Conversion was calculated on the basis of the substrate.

[c] Yield of isolated product based on the consumed substrate.

[d] Substrate (1.0 mmol) was dissolved in dichloromethane (2×25 mL) and cyclohexane (2×25 mL). The solution was irradiated at $\lambda \geq 300$ nm with a medium-pressure mercury lamp (500 W) under an argon atmosphere at ambient temperature.



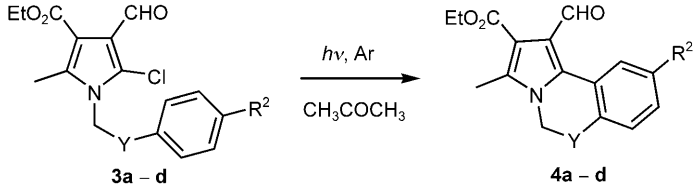
Scheme 2. A plausible photoreaction mechanism of 2-halogen-*N*-(2-phenylethyl) indole-3-carbaldehydes in acetone.

tivity of **1a-3** > **1a-2** > **1a** based in a simple C–X bond homolysis mechanism (the C–X bond dissociation energies D_{C-X} for C–Cl, C–Br and C–I are 339, 289, 222 kJ mol^{-1}, respectively[21]), the observed reactivity is **1a** > **1a-2** > **1a-3** in acetone because the time needed to complete the photoreactions of **1a, 1a-2** and **1a-3** increased greatly. Another unmatchable point to these results is the fact that the excited energy of **1a** (E_T = 275 kJ mol^{-1})[20b] is insufficient to cleave C–Cl and C–Br bonds effectively. These results rule out a simple homolysis mechanism for **1a** and **1a-2** and show the presence of some factor which provides a much lower energy path for cyclization. We believe this factor to be a type of anchimeric assistance whereby the phenyl ring can, through its π-cloud, complex the developing radical centres in the stretching C–X bond and thus lower the transition state energy for reaction as depicted in Scheme 2. Chlorine and bromine atoms are electron-deficient species with high electron affinities[22] and their complexation by aromatic molecules is well known and the anchimeric assistance to C–X bond cleavage by radical complexation has also proved by dynamic methods[23a] and flash photolysis studies.[23b,c] The mechanism affords an explanation why the chloro-compound cyclizes faster than the bromo-compound even though $D_{C-Cl} > D_{C-Br}$, since the transition state **5** is reached earlier along the reaction coordinate for X = C1 than for X = Br due to the higher electron affinity of the chlorine atom. Photocyclization of **1a-3** may probably proceed *via* homolysis of the C–I bond to give a free indolyl radical and an iodine atom and subsequent coupling of the indolyl radical with an aryl group. The electron transfer mechanism for photocyclizations of **1a**, **1a-2** and **1a-3** can also be ruled out because the reported dissociation rates for radical-anions from halobenzenes are iodobenzene > bromobenzene > chlorobenzene,[24] which is also contrary to our observations. The photoreactions of **1a, 1a-2** and **1a-3** in cyclohexane were also examined to detect if the free indolyl radical could be formed (Table 3, entries 4–6). The great amount of reductive deiodination product **2a-1** could be separated besides the cyclization product **2a** in the photoreaction of **1a-3**. Compound **2a-1** was obviously derived from the H-abstraction of a free indolyl radical from the solvent. In comparison, **1a** and **1a-2** gave the photocyclization product **2a** as the main product. These results further confirmed the radical complexation mechanism for the photocyclization of **1a** and **1a-2**.

In order to expand the scope of this photocyclization reaction, we further investigated the photoreactions of 2-chloro-*N*-(ω-arylalkyl)pyrrole-3-carbaldehydes in acetone. As shown in Table 4, the results of the photoreactions were very similar to those of 2-chloro-*N*-(ω-arylalkyl)indole-3-carbaldehydes. All products were fully identified by ^{1}H, ^{13}C NMR and MS, and the structure of **4a** was further confirmed by X-ray crystallography (Figure 1).[25]

In summary, highly efficient syntheses of indolo[2,1-*a*]isoquinolines, indolo[2,1-*a*][2]benzazepines, pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]benzazepines have been developed. To the best of our knowledge, this is the first report for the synthesis in excellent yields of these compounds *via* photoinduced dehalogenation and cyclization of 2-halo-*N*-(ω-arylalkyl)indole-3-carbaldehydes and 2-chloro-*N*-[3-(ω-arylalkyl)]pyrrole-3-carbaldehydes in acetone. The advantages of this reaction over the Bu_3SnH-mediated cyclization of 1-(ω-phenylalkyl)-2-bromoindoles-3-carbaldehydes are not only the high yields with no reductive products formed, but also the simple and en-

Table 4. Photocyclization of 2-chloro-*N*-(ω-arylalkyl)pyrroles-3-carbaldehydes.[a]



Entry	Substrate	Y	R^2	Time [h]	Conversion [%][b]	Product	Yield [%][c]
1	**3a**	CH_2	H	6	99	**4a**	95
2	**3b**	CH_2CH_2	H	8	90	**4b**	91
3	**3c**	CH_2O	H	8	95	**4c**	93
4	**3d**	CH_2O	OCH_3	6	97	**4d**	94

[a] Compound **3a–d** (1.0 mmol) was dissolved in acetone (2×50 mL) containing 0.1 N aqueous Na_2CO_3 (2 mL). The solution was irradiated at $\lambda \geq 300$ nm with a medium-pressure mercury lamp (500 W) under an argon atmosphere at ambient temperature.
[b] Conversion was calculated on the basis of the substrate.
[c] Yield of isolated product based on the consumed substrate.

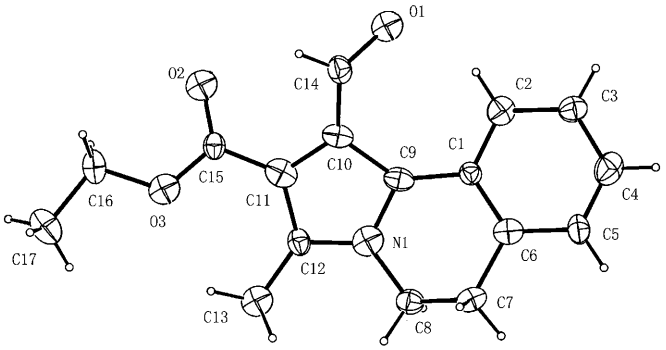


Figure 1. X-ray crystal structure of **4a.**

vironmentally friendly protocol. The pyrrolo[1,2-*d*]-[1,4]benzoxazepine ring system was first constructed in this work by the photocyclization of 2-chloro-*N*-(2-phenoxyethyl)pyrrole-3-carbaldehyde. Further investigations into the detailed mechanism are currently underway in our laboratory.

Experimental Section

Photochemical Reaction; General Procedure

Compound **1a** (0.283 g, 1 mmol) was dissolved in 2×50 mL acetone containing 0.1 N aqueous Na_2CO_3 (2 mL). The solution was deaerated by bubbling Ar for 30 min and irradiated at $\lambda \geq 300$ nm with a medium-pressure mercury lamp (500 W) at ambient temperature. The progress of reaction was monitored by TLC at regular intervals. After the solvent had been removed under reduced pressure, the residue was separated by column chromatography on silica gel eluted by hexane-ethyl acetate 10:1 (v/v) to afford product **2a.** The solid was further purified by recrystallization from ethyl acetate.

Acknowledgements

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[25] CCDC 740699 contains the supplementary crystallographic data for compound **4a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

