One-pot synthesis of benzo[*c*]carbazoles by photochemical annulation of 2-chloroindole-3-carbaldehydes†

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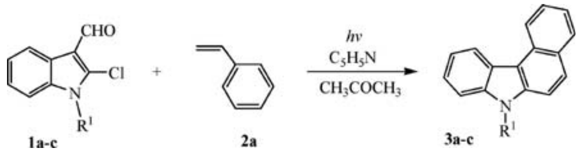
A novel and efficient procedure for the synthesis of benzo[*c*]-carbazoles has been achieved in moderate to high yields by the one-pot photochemical annulations of 2-chloroindole-3-carbaldehydes by styrenes *via* photodechlorination-initiated coupling of 2-chloroindole-3-carbaldehydes with styrenes, electrocyclic reactions and deformylative aromatization in the presence of pyridine.

Photoarylation of alkenes, alkynes and arenes by aryl halides has received great attention in recent years,[1] due to the wide-ranging application in the metal-free synthesis of aryl-substituted alkylamines, alkanols, alkynes, ketones, aldehydes and biaryls. Albini and co-workers were engaged in the extensive research on the inter- and intermolecular photoarylation of electron-rich alkenes, alkynes and arenes by amino- and alkoxyl-substituted aryl halogens.[1a–d] Comparatively, investigation on the photoarylation of alkenes by halogenated heteroaromatics was rare.[2] We are interested in the photocoupling reactions of halogenated heteroaromatics with olefins in relation to the synthetic method and the reaction mechanism. We envisioned that the photoreaction of 2-chloro-1-phenylindole-3-carbaldehyde (**1a**) with styrene (**2a**) would serve as an attractive synthetic route to a polycyclic compound indolo[1,2-*a*]quinoline-7-carbaldehyde by photodissociation of the C–X bond and subsequent addition of the σ-indolyl radical to **2a** and the annulation of the adduct radical on the 1-phenyl group. Contrary to our expectation, the main product obtained was not indolo[1,2-*a*]quinoline-7-carbaldehyde, but benzo[*c*]carbazole (**3a**) which seemed to be derived from cycloaddition of the σ-indolyl radical with **2a** and subsequent deformylation as shown in Scheme 1.



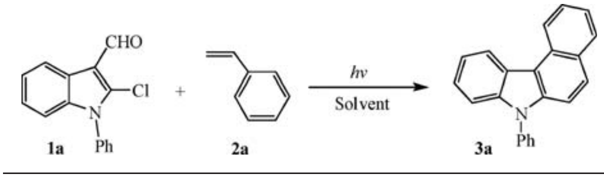
Scheme 1

Procedures for the facile synthesis of benzo[*c*]carbazoles are of interest since a number of biologically active alkaloids contain this unit[3] and some substituted benzo[*c*]carbazoles possess potential kinase inhibitory[4a] and antitumor activities.[4b,c] Several strategies have been reported for the construction of benzo[*c*]carbazole systems. For example, Bu_3SnH-mediated radical cyclization of 1-(3-iodioindol-2-yl)-2-phenylethene, palladium-catalyzed cyclization of 1-(2-nitrophenyl)naphthalenes driven by CO as the stoichiometric reductant;[5b] microwave-enhanced reductive cyclization reaction of 1-(2-nitrophenyl)naphthalenes by triethyl phosphate.[5c] The formation of benzo[*c*]carbazoles by photo-;cyclization of 2-methyl-3-(2′-acetylphenyl)indoles assisted by $t\text{-BuO}^-K^+$,[5d] and photocyclization of 2-phenylaminonaphthalenes in the presence of oxygen[5e] has also been reported, but there are no procedures for a direct synthesis of benzo[*c*]carbazoles by the photocycloaddition of indoles with olefins. Herein we describe the first construction of benzo[*c*]carbazoles by the novel photochemical annulation of readily available 2-chloroindole-3-carbaldehydes[6] with styrenes (Scheme 1).

We first optimized photoreaction conditions using 2-chloro-1-phenylindole-3-carbaldehyde (**1a**) as a model reactant. No great difference was found for the reaction of **1a** and **2a** in the presence or absence of oxygen in CH_2Cl_2 solutions, but the photoreaction was greatly affected by solvents and bases as shown in Table 1. The conversion of **1a** and the yield of **3a** in CH_2Cl_2 were low and the solution turned dark in a short time while in acetone a little improvement was observed. This result may be derived from the sensitization effect of acetone to **1a** because E_T = 326 kJ mol^{-1},[7a] of acetone is higher than that for **1a** (E_T = 275 kJ mol^{-1},[7b]). The conversion of **1a** and yield of **3a**, however, were increased greatly by the addition of base such as pyridine or sodium carbonate because the solution could be irradiated for much longer time without turning dark. Obviously pyridine or sodium carbonate retarded the oligomerization of indole derivatives induced by HCl and light. Therefore acetone with the addition of pyridine was selected as the solvent in all photoreactions.

Having established the optimal photoreaction conditions, we then examined a variety of 2-chloroindole-3-carbaldehydes and styrenes to explore the generality of this new one-pot

Table 1 Optimization of photoreaction conditions of **1a** with **2a**



Entry	Solvent	t/h	Conv.[a] (%)	Yield[b] (%)
1	CH_2Cl_2	8	51	20
2	CH_3COCH_3	12	69	32
3	CH_2Cl_2–pyridine	16	77	52
4	CH_3COCH_3–pyridine	16	95	70
5	CH_3COCH_3–Na_2CO_3	20	87	53

[a] Conversion based **1a**. [b] Isolated yield.

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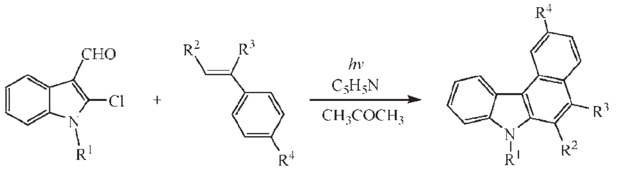
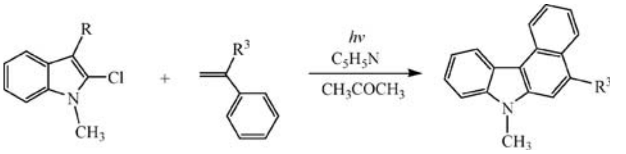
Table 2 Photoreaction of 2-chloroindole-3-carbaldehydes with styrenes



Entry		R^1	R^2	R^3	R^4	Prod.	t/h	Conv.[a] (%)	Yield[b] (%)
1	**1a**	Ph	H	H	H	**3a**	16	95	70
2	**1a**	Ph	H	Me	H	**3b**	12	90	41
3	**1a**	Ph	H	Ph	H	**3c**	24	96	82
4	**1a**	Ph	Me	H	MeO	**3d**	12	92	36
5	**1b**	Me	H	H	H	**3e**	12	69	54
6	**1b**	Me	H	Me	H	**3f**	12	71	35
7	**1b**	Me	H	Ph	H	**3g**	30	91	65
8	**1b**	Me	Me	H	MeO	**3h**	36	95	45
9	**1c**	H	H	H	H	**3i**	16	60	48
10	**1c**	H	H	Me	H	**3j**	24	65	37
11	**1c**	H	H	Ph	H	**3k**	30	88	56
12	**1c**	H	Me	H	MeO	**3l**	12	82	33

[a] Conversion based **1a–c**. [b] Isolated yield.

Table 3 Photoreaction of 2-chloroindoles with different substituents at 3-position with styrenes



Entry		R	R^3	Prod.	t/h	Conv.[a] (%)	Yield[b] (%)
1	**1d**	COMe	H	**3e**	24	85	53
2	**1d**	COMe	Me	**3f**	20	88	46
3	**1d**	COMe	Ph	**3g**	20	85	48
4	**1e**	H	H	**3e**	36	46	32
5	**1e**	H	Me	**3f**	36	49	37
6	**1f**	Et	Me	**3e**	36	37	25
7	**1g**	CO_2Et	Me	—	48	—	—

[a] Conversion based **1d–f**. [b] Isolated yields.

photochemical annulation reaction.‡ The reactions were conducted under the above reaction conditions for 12–60 h and the expected benzo[*c*]carbazoles were obtained as major products in all cases (Table 2). All products were fully identified by ^{1}H, ^{13}C NMR and MS, and the structure of **3h** was further confirmed by X-ray crystallography (Fig. 1).§ It is noteworthy that the conversion of **1a–c** and the yields of **3a–l** are increased when irradiation is prolonged and the presence of substituents (R^1 = Ph, Me) in **1a** and **1b** is favourable for longer irradiation; substituents (R^2, R^3 = Me) in **2b** and **2d** are unfavourable to the yields of benzo[*c*]carbazoles.

To investigate the scope and the mechanism of the photochemical process, we have tested the reactivity of other reactants with different substituents at the 3-position of 2-chloroindole under similar conditions. It is observed from Table 3 that the photoreaction of **1d**, **1e** and **1f** with **2a** or **2b** can all produce benzo[*c*]carbazoles in moderate yields from dechlorination, cyclization and deacetylation or dealkylation. Comparatively, the time needed for the photoreaction of **1d** is relatively short, but much more time is needed for the reaction of **1e** or **1f** to attain high conversions. It seems reasonable to ascribe the differences to carbonyl compounds **1a–d** having longer triplet lifetimes than **1e** and **1f**. In the case of **1g**, no reaction can be detected even after prolonged irradiation.

We analyzed the reaction mixtures and found that some non-cyclization adducts of **1a–d** with **2a–d** were produced besides the cyclization products **3a–l**. For example, 1-methyl-2-(2-phenyl-2-propenyl)indole-3-carbaldehydes (**4f**) and 2-(2,2-diphenylethenyl)-3-carbaldehydes (**4k**) were separated from the reaction mixture of **1b** with **2b** and **1c** with **2c**, respectively (Scheme 2). Irradiation of **4k** gave the cyclization product benzo[*c*]carbazole **3k** (Scheme 3), but no change could be detected after prolonged irradiation of the other non-cyclization adduct **4f**. These results illustrate that **4k** may be the intermediate of multiple photoreaction and its photocyclization is a key step in the formation of benzo[*c*]carbazole **3k**. No reports for electrocyclic reaction with the elimination of a formyl or a alkyl group have been found in the literature, but deformylative or dealkylative aromatization have been reported in the formation of heteroaromatics, such as 3-benzoylpyrrole from deformylation of 3-formyl-3-benzoylpyrrole;[8] 2,6-dimethylpyridine-3,5-dicarboxylate from dealkylation of 4-alkyl-substituted Hantzsch 1,4-dihydropyridines.[9]

The UV spectrum of **1b** shows three absorptions at λ_{max} = 226 nm (K band), 246 nm (K band) and 298 nm (R band). Pyrex can filter the K bands and the triplet state of **1b** is only produced from the absorption of the R band or energy transfer from the triplet of acetone. E_T of **1b** should be near that of indole-3-aldehyde which shows E_T = 275 kJ mol^{-1},[7b] since **1b**

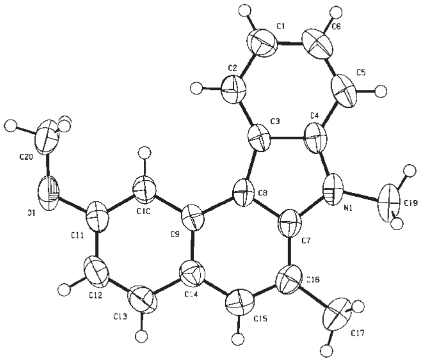
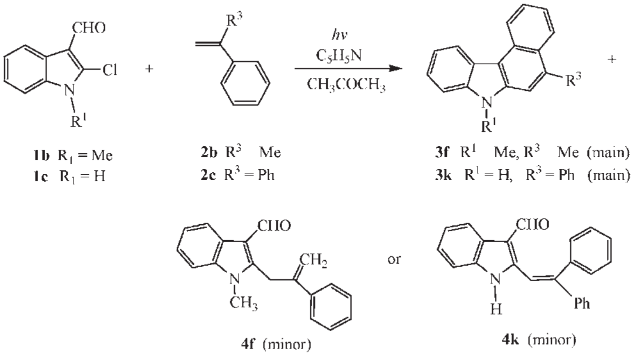
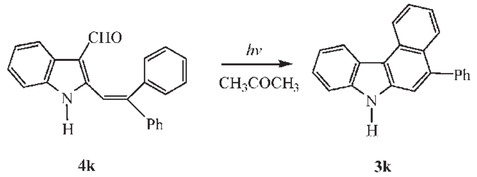


Fig. 1 X-Ray crystal structure of **3h**.



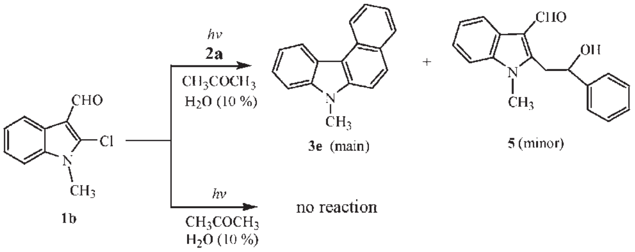
Scheme 2



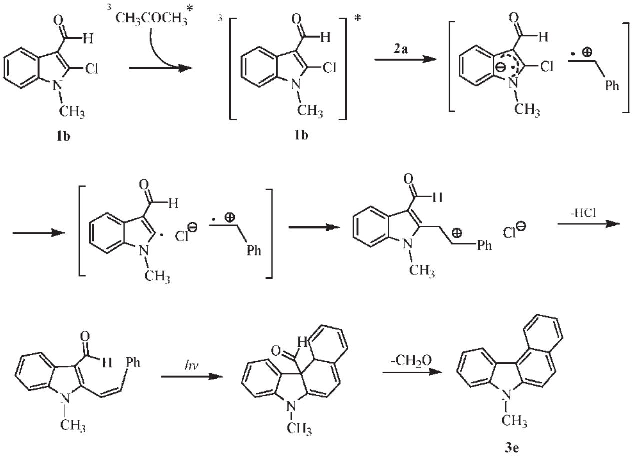
Scheme 3

has a similar absorption, fluorescence emission and phosphorescence emission spectra to those of indole-3-carbaldehyde.[7b,10] This energy is insufficient for homolytic fission of the C–Cl bond in **1b** as compared with the estimation of D'Auria that the dissociation energy of the C–Br bond in 5-bromofuran-2-carbaldehyde is 70 kcal mol^{-1}.[2c] Thus it could be supposed that the photoreaction of **1b** with **2a** is initiated not by the direct C–Cl fission but by the formation of an exciplex and subsequent single electron transfer which promotes the cleavage of C–Cl bond. Support for this proposal is the difference of photoreaction of **1b** in aqueous acetone in the presence of **2a** and in the absence of **2a** under irradiation of $\lambda \geq 300$ nm as shown in Scheme 4.

That no substitution reaction took place for **1b** in aqueous acetone or in methanol in the absence of **2a** indicated that there was no σ-indolyl cation produced under direct photolysis; Comparatively in the presence of **2a**, the photoreaction of **1a** with **2a** could proceed smoothly to produce **3a** in both solvents. A reasonable explanation as to the difference is the electron transfer from **2a** to excited **1b** can promote the fission of a C–Cl bond. The minor product **5** in aqueous acetone seems to be derived from the combination of a carbocation with water. This carbocation may be the coupling product of the σ-indolyl radical from dechlorination of the anion radical of **1b** with the cation radical of **2a**.



Scheme 4



Scheme 5

According to the above experimental results, a possible mechanistic rationalization for the formation of benzo[*c*]carbazole **3e** is depicted (Scheme 5).

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Notes and references

‡ *Typical experimental procedure*: **1a** (0.256 g, 1.0 mmol) and styrene **2a** (0.104 g, 2.25 mmol) and pyridine (0.119 g, 1.5 mmol) were dissolved in 25 mL dry acetone. The solution was distributed into five 10 mL Pyrex tubes and deaerated by bubbling Ar for 30 min and irradiated at $\lambda \geq 300$ nm with a high-pressure mercury lamp (500 W) 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 column chromatography on silica gel eluted by hexane–ethyl acetate 10 : 1 (v/v) to afford product **3a**. The solid was further purified by recrystallization from methanol.

§ *Crystal data* for **3h** (recrystallized from acetone–hexane). $C_{19}H_{17}NO$, $M_r = 275.34$, monoclinic, space group $P2_1/c$, $a = 11.209(3)$, $b = 7.292(2)$, $c = 18.864(4)$ Å, $\beta = 114.178(13)°$, $V = 1406.6(6)$ Å^3, colorless plates, $D_c = 1.300$ g cm^{-3}, $T = 293(2)$ K, $Z = 4$, μ(Mo-Kα) = 0.71073 mm^{-1}, $2\theta_{max} = 51°$, 2600 reflections measured, 1984 unique ($R_{int} = 0.1591$) which were used in all calculations. The final $wR(F^2)$ was 0.0720 (for all data), $R1 = 0.0583$.

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