Organic &
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Cite this: *Org. Biomol. Chem.*, 2012, **10**, 232

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Photoinduced chlorine atom-transfer cyclization/photohydrolysis of 3-acyl-2-chloro-*N*-(ω-phenylalkynyl)pyrroles: a one-pot synthesis of benzoyl-substituted fused pyrroles†‡

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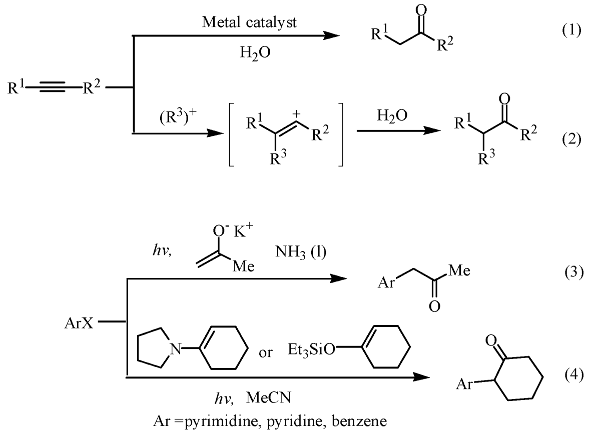
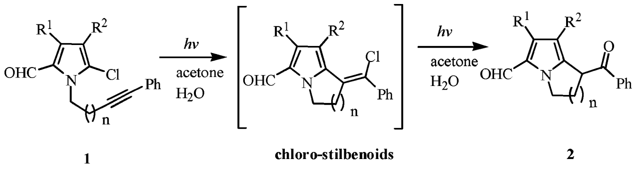
Received 13th June 2011, Accepted 26th September 2011
DOI: 10.1039/c1ob05954h

A one-pot synthesis of benzoyl-substituted fused pyrroles or indoles in moderate to high yields has been achieved by the photocyclization/photohydrolysis reactions of *N*-(ω-phenylalkynyl)-2-chloropyrrole-3-carbaldehydes or 3-acyl-*N*-(ω-phenylbutynyl)-2-haloindoles in wet acetone. The formation of all these products could be inferred by a two-step reactions, namely, photoinduced chlorine atom-transfer cyclization and subsequent photohydrolysis.

The transformation of alkynes to ketones is of prime interest considering the wide availability of alkynyl substrates and the fundamental importance of the carbonyl motif in modern organic synthesis.[1] The metal-catalyzed hydration reaction of alkynes is the generally used method and has been studied extensively in recent years (Scheme 1, eq 1).[2] Besides the metal-catalyzed hydration of alkynes, the addition of electrophilic agents such as alkyl cations to alkynes and subsequent capture of the vinyl cation by water has also supplied another useful method for the synthesis of α-alkyl-substituted ketones (Scheme 1, eq 2).[3] The photochemical reaction of aryl halides with pinacolone potassium enolate in liquid NH_3 *via* an $S_{RN}1$ mechanism (Scheme 1, eq 3)[4] or with enamines or silyl enol ethers by an S_N1 mechanism (Scheme 1, eq 4)[5] has also afforded two methods for the synthesis of aryl ketones. In our previous paper, we reported photoinduced halogen atom-transfer cyclization reactions of 2-chloro-1-(*ω*-alkenyl)indole-3-carbaldehyde.[6] Herein, we present a cascade process involving photoinduced chlorine atom-transfer cyclization of *N*-(ω-phenylalkynyl)-2-chloropyrrole-3-carbaldehydes and 3-acyl-*N*-(ω-phenylbutynyl)-2-chloroindoles and subsequent photohydrolysis of intermediate products, α-chlorostilbenoids, in acetone–water to give an access to various benzoyl substituted cyclic compounds (Scheme 2). Photohydrolysis of α-chlorostilbenoids has not been reported before in the literature, but the photoalcoholysis of *α*-chlorostilbene has been extensively studied.[7]



Scheme 1 Conventional synthesis of the ketones.



Scheme 2 Photoinduced chlorine atom-transfer cyclization/photohydrolysis of *N*-(ω-phenylalkynyl)-2-chloropyrrole-5-carbaldehydes.

We first investigated the effect of solvents on the photoreaction of 3,5-dichloro-1-(4-phenylbut-3-ynyl)pyrrole-2,4-dicarbaldehyde (**1a**) (Table 1). It was found that the photoreaction of **1a** could afford cyclization product **2a** in all selected wet solvents. The conversion of **1a** and the yield of the product **2a** depended on the solvent. In wet acetone, the conversion of **1a** and the yield

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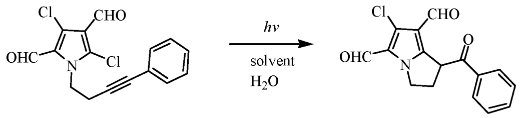
† Electronic supplementary information (ESI) available. CCDC reference number 807627. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05954h

‡ *Photochemical reaction*; *general procedure*: **1a** (0.160 g, 0.5 mmol) was dissolved in 25 mL acetone containing 0.1 mL H_2O. The solution was deaerated by bubbling Ar for 30 min and irradiated at $\lambda > 300$ nm with a medium-pressure mercury lamp (500 W) at ambient temperature. The progress of the 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 6 : 1 (v/v) to afford product **2a**.
Compound **2d** (CCDC 807627), $C_{16}H_{11}Cl_2NO_3$ $M_r = 336.16$, monoclinic, space group $P2_1/n$, $a = 6.393(13)$ Å, $b = 9.37(2)$ Å, $c = 26.44(6)$ Å, $\beta = 92.38(2)^\circ$, $V = 1582(6)$ Å^3. colorless block, $D_c = 1.411$ g cm^{-3}, $T = 296(2)$ K, $Z = 4$, μ(MoKα) = 0.71073 mm^{-1}, $2\theta_{max} = 25.10^\circ$, 7140 reflections measured, 2793 unique, ($R_{int} = 0.1683$) which were used in all calculations. The final $wR(F^2)$ was 0.2454 (for all data), $R_1 = 0.3128$.

Table 1 Photoreaction of **1a** in different solvents[a]



1a **2a**

Entry	Solvent	Time [h]	Convn [%][b]	Yield [%][c]
1	wet CH_2Cl_2	8	83	78
2	wet MeCN	8	83	80
3	wet Me_2CO	8	98	94

[a] 0.5 mmol **1a** was dissolved in different solvents (25 mL). The solution was irradiated at $\lambda > 300$ nm with a medium-pressure mercury lamp (500 W) under argon atmosphere at ambient temperature. [b] Conversion was calculated on the basis of **1a**. [c] Yield of isolated product based on consumed **1a**.

of the product **2a** were relatively higher than those obtained in wet methylene dichloride or wet acetonitrile. This result may be derived from the sensitization effect of acetone to **1a**. Therefore, acetone was selected as the solvent in all the photoreactions. In order to investigate the effects of the substrate structures on the photoreaction efficiency, other similar substrates 5-chloro-1-(ω-phenylalkynyl)pyrrole-2-carbaldehydes **1b–j** with different substituents on the phenyl group or pyrrole and different tethers were synthesized and examined under the same photoreaction conditions. All of the substrates except **1k** and **1l** could give products **2** in high yields as shown in Table 2. The products were fully identified by ^{1}H, ^{13}C NMR and HRMS, and the structure of **2d** was further confirmed by X-ray crystallography (Fig. 1).

It can be seen in Table 2 that substituents on the phenyl ring or pyrrole and tethers all had some influence on the photoreaction efficiency of the substrates **1**. Electron-withdrawing groups on the phenyl ring (*e.g.*, R^1 = Cl, or R^2 = CO_2CH_3) in **1d** and **1g** (Table 2, entries 4 and 7) retarded the reactions and decreased the yield of the products **2**; comparatively, electron-donating groups on the phenyl ring (*e.g.*, R^1 = CH_3, OCH_3) in **1b–c** (Table 2, entries 2–3) had no great influence on the reactions. On the other hand, the reactions turned slow when the substrates (**1h–j**) contained only one formyl group (R^2 = CHO) and two chlorine atom (R^4 = R^5 = Cl, R^4 = H). The substrates with a short tether (**1c**, and **1d**, *n* = 1) reacted more easily to form five-numbered rings (**2c**, and **2d**) than those with a longer tether (**1e**, and **1f**, *n* = 2) to form six-numbered rings (**2e**, and **2f**). It was noticed that both 3,5-dichloro-2,4-dihydroxymethyl-1-(4-phenylbut-3-ynyl)pyrrole (**1k**) and dimethyl 3,5-dichloro-1-(4-phenylbut-3-ynyl)pyrrole-2,4-dicarboxylate (**1l**), in which the formyl groups were replaced by hydroxymethyl groups or ethoxycarbonyl groups, could not react under the same conditions. Meanwhile, we also examined the photoreaction of a substrate without a 5-chlorine atom, 1-(4-phenylpent-3-ynyl)pyrrole-2-carbaldehyde (**1m**), and also found that no reaction took place after prolonged irradiation (24 h). Thus, it could be deduced that the formyl group and 2- or 5-chlorine atom were necessary for the photocyclization reaction of 5-chloro-1-(ω-phenylalkynyl)pyrrole-2-carbaldehydes.

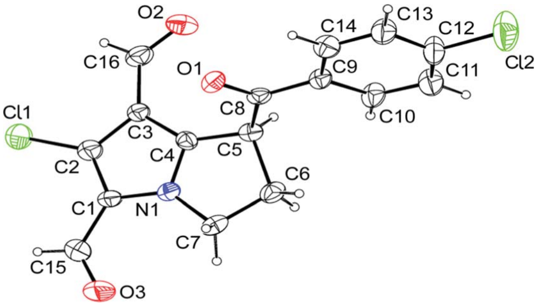
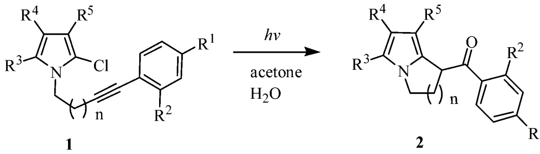


Fig. 1 X-Ray crystal structure of **2d**.

Since the photoreactions of aryl aldehydes were generally derived from long-lived triplets, especially after the acetone sensitization, it could be proposed that the reaction of triplet 3-formyl-2-chloropyrroles or 5-formyl-2-chloropyrroles with alkynes was

Table 2 Photoreaction of 3,5-dichloro-1-(ω-phenylalkynyl)pyrrole-2,4-dicarbaldehydes and 4,5-dichloro-1-(ω-phenylalkynyl)pyrrole-2-carbaldehydes[a]

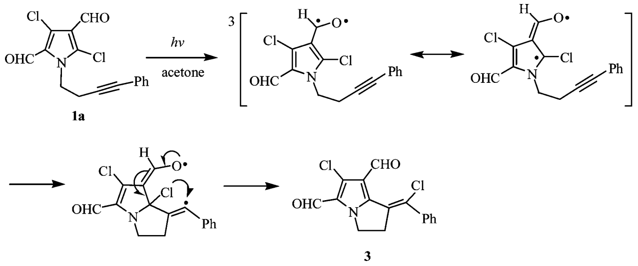


1 **2**

Entry	Substrate	*n*	R^1	R^2	R^3	R^4	R^5	Time [h]	Convn [%][b]	Product	Yield [%][c]
1	**1a**	1	H	H	CHO	Cl	CHO	8	98	**2a**	94
2	**1b**	1	CH_3	H	CHO	Cl	CHO	8	98	**2b**	96
3	**1c**	1	OCH_3	H	CHO	Cl	CHO	8	99	**2c**	98
4	**1d**	1	Cl	H	CHO	Cl	CHO	8	95	**2d**	90
5	**1e**	2	OCH_3	H	CHO	Cl	CHO	8	90	**2e**	88
6	**1f**	2	Cl	H	CHO	Cl	CHO	8	84	**2f**	80
7	**1g**	2	H	CO_2CH_3	CHO	Cl	CHO	8	86	**2g**	84
8	**1h**	1	H	H	CHO	H	Cl	10	96	**2h**	92
9	**1i**	1	CH_3	H	CHO	H	Cl	10	98	**2i**	93
10	**1j**	1	OCH_3	H	CHO	H	Cl	10	99	**2j**	95
11	**1k**	1	H	H	CH_2OH	Cl	CH_2OH	16	0	**2k**	0
12	**1l**	1	H	H	CO_2CH_3	Cl	CO_2CH_3	16	0	**2l**	0

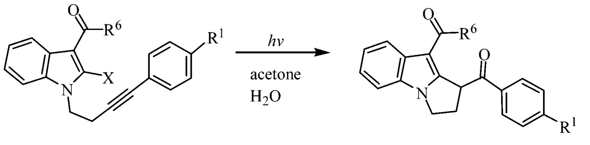
[a] **1a–l** (0.5 mmol) was dissolved in acetone (25 mL) containing H_2O (0.1 mL). The solution was irradiated at $\lambda > 300$ nm with a medium-pressure mercury lamp(500 W) under argon atmosphere at ambient temperature. [b] Conversion was calculated on the basis of substrate. [c] Yield of isolated product based on consumed substrate.

much like that of the photoreaction of triplet α,β-unsaturated enones (a diradical) with alkenes as proposed in Winkler's[8] and our previous papers.[5] The Michael-like coupling of the β-carbon of the diradical in excited 3-formylpyrroles with the triple bonds of the alkyne gave new diradicals; subsequently, the chlorine atom-transfer occurred from the diradicals to afford the cyclization products like **3** before the coupling of diradicals to form cyclobutanes (Scheme 3). Comparatively, it is difficult for 2,4-dihydroxymethylpyrrole (**1k**) and dimethyl pyrrole-2,4-dicarboxylate (**1l**) to become diradicals. Thus, no reaction took place in the irradiation of these two substances under the same conditions.



Scheme 3 Photoinduced chlorine atom-transfer cyclization reactions.

Table 3 Photoreaction of 3-acyl-2-halo-1-(4-phenylbut-3-ynyl)indoles[a]



4 **5**

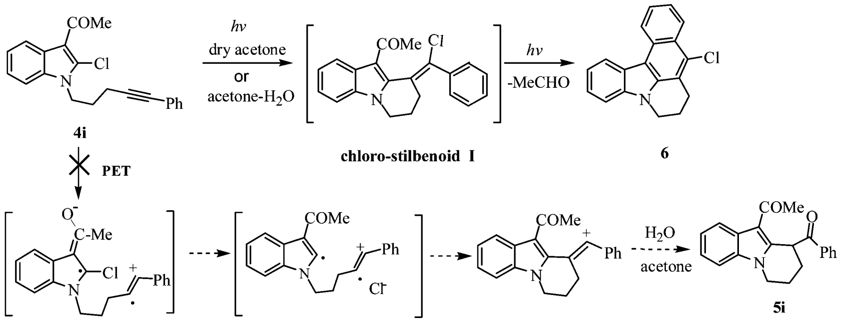
Entry	Substrate	R^1	R^6	X	Time [h]	Convn [%][b]	Product	Yield [%][c]
1	**4a**	H	H	Cl	10	96	**5a**	82
2	**4b**	CH_3	H	Cl	10	96	**5b**	83
3	**4c**	OCH_3	H	Cl	10	98	**5c**	86
4	**4d**	H	CH_3	Cl	12	92	**5d**	78
5	**4e**	CH_3	CH_3	Cl	12	92	**5e**	80
6	**4f**	Cl	CH_3	Cl	12	94	**5f**	83
7	**4g**	H	H	Br	18	82	**5a**	76
8	**4h**	CH_3	H	Br	18	86	**5b**	77

[a] **4a–h** (0.5 mmol) was dissolved in acetone (25 mL) containing H_2O (0.1 mL). The solution was irradiated at $\lambda > 300$ nm with a medium-pressure mercury lamp(500 W) under argon atmosphere at ambient temperature. [b] Conversion was calculated on the basis of substrate. [c] Yield of isolated product based on consumed substrate.

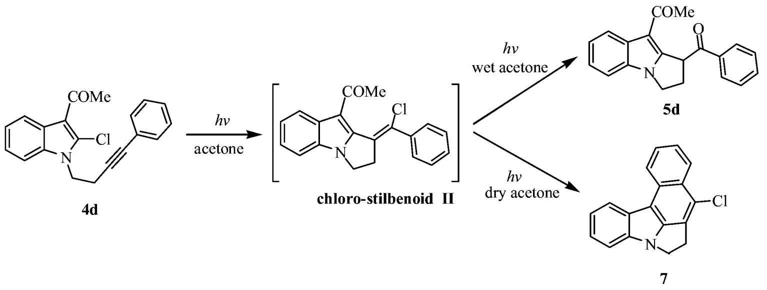
In order to expand the scope of this photoinduced chlorine atom-transfer cyclization/photohydrolysis reaction, we further investigated the photoreactions of 3-acyl-2-halo-1-(4-phenylbut-3-ynyl)indoles (**4a–h**) in wet acetone. As shown in Table 3, the results of these photoreactions were very similar to those of 3,5-dichloro-1-(ω-phenylalkynyl)pyrrole-2,4-dicarbaldehydes (**1a–g**) and 4,5-dichloro-1-(ω-phenylalkynyl)pyrrole-2-carbaldehydes (**1h–j**). Both 3-formyl- and 3-acetyl-2-chloro-1-(4-phenylbut-3-ynyl)indoles afforded the corresponding products in moderate to high yields. Comparatively, 2-chloroindole-3-carbaldehydes (**4a**, and **4b**) reacted more easily with the tethered phenylacetylene to form photocyclization/photohydrolysis products (**5a** and **5b**) than 2-bromoindole-3-carbaldehydes (**4g**, and **4h**). While another substrate **4i** with a longer tether (n = 2) behaved differently, no desired product **5i** was separated instead product **6** was formed (Scheme 4). Obviously, this product was derived from a 6π electrocyclization reaction of the intermediate α-chlorostilbenoid *via* deacylation before photohydrolysis. We then examined the photoreaction of **4b** (n = 1) and **4i** (n = 2) in dry acetone and found both of them could give the deacetylative cyclization product **6** and **7** as main products (Scheme 5). It could be deduced from the formation of these chlorine-retained products **6** and **7** that our proposal of chlorine atom-transfer photocyclization to form the intermediate "chloro-stilbenoids" might be right (Scheme 3). Meanwhile, the photoinduced electron transfer mechanism between 2-chloroindole-3-carbaldehyde and phenylacetylene could be excluded from the formation of **6** in wet acetone because no stilbenoid cation, which could also be generated in the photoinduced electron transfer reaction, was trapped by water to produce **5i** (Scheme 4).

To verify that the ketone was formed from the photohydrolysis of intermediate α-chlorostilbenoid (**3**), we carried the photoreaction of **1a** in dry acetone and found that the intermediate **3** was readily separated as the main product and it could be further converted to **2a** after irradiation in wet acetone (Scheme 6). Thus we are certain that all these benzoyl-substituted bicyclic or tricyclic products (**2a–j** and **5a–f**) were derived from the photolysis of the intermediate α-chlorostilbenoids like **3** *via* photoinduced heterolysis of C–Cl bond and the trapping of the stilbenoid cations by water.

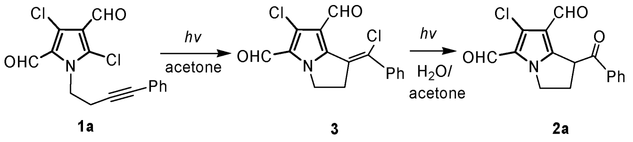
From the above discussion, a plausible mechanistic rationale to account for the formation of **2a** was proposed as shown in Scheme 7. Firstly, the chlorine atom-transfer cyclization occurred from triplet 3,5-dichloro-1-(4-phenylbut-3-ynyl)pyrrole-2,4-dicarbaldehyde (**1a**) to give α-chlorostilbenoid **3**; then a cation



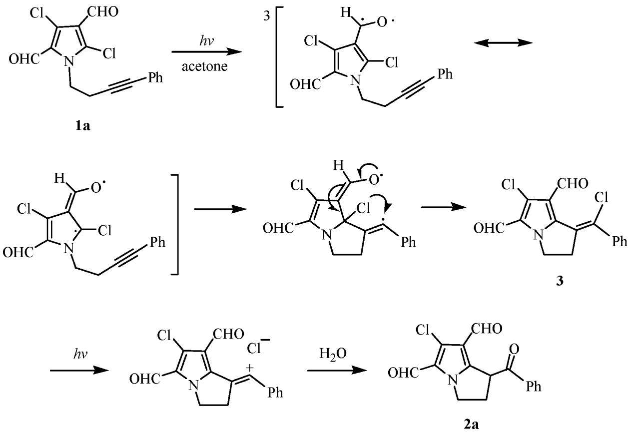
Scheme 4 The photoreaction of 3-acetyl-2-chloro-1-(5-phenylpent-4-ynyl) indole (**4i**) in wet acetone.



Scheme 5 Photoreaction of 3-acetyl-2-chloro-1-(5-phenylbut-4-ynyl) indole (**4b**).



Scheme 6 Photoinduced chlorine atom-transfer cyclization/photohydrolysis reactions.



Scheme 7 A plausible photoreaction mechanism of 2-chloro-*N*-(2-phenylbutynyl)indole-3-carbaldehydes in acetone.

was produced from this intermediate by photoinduced heterolysis of C–Cl and the trapping of the stilbenoid cation by water to afford product **2a**.

In summary, a one-pot synthesis of benzoyl-substituted fused pyrroles and indoles in moderate to high yields has been achieved by the photocyclization/photohydrolysis reactions of *N*-(ω-phenylalkynyl)-5-chloropyrrole-2-carbaldehydes or 3-acyl-2-chloro-*N*-(ω-phenylbutynyl)indoles in wet acetone. The formation of all these products could be inferred by a two-step reaction, namely, photoinduced chlorine atom-transfer cyclization of *N*-(ω-phenylalkynyl)-5-chloropyrrole-2-carbaldehydes or 3-acyl-*N*-(ω-phenylbutynyl)-2-chloroindoles and subsequent photohydrolysis.

We thank the National Natural Science Foundation of China (Grant No. 20872056 and J0730425) and the award "Young Scholar of Distinction of Lanzhou University" for financial support.

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