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One-pot synthesis of benzo[*a*]phenanthridin-5-ones by photoinduced cycloaddition of 3-chloroisoquinolin-1-ones with styrenes

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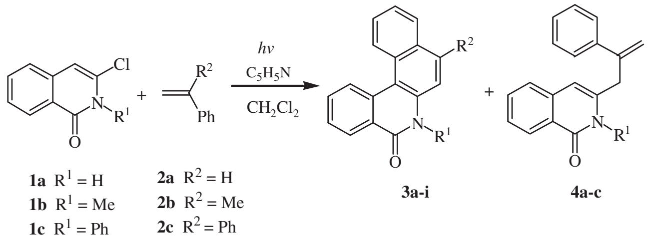
ABSTRACT

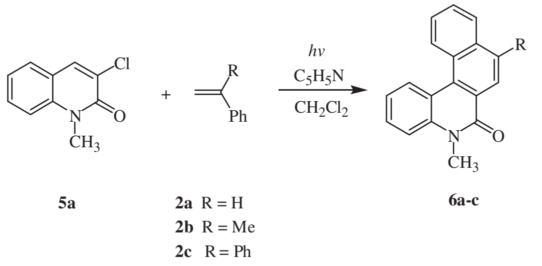
One-pot synthesis of benzo[*a*]phenanthridin-5-ones and benzo[*k*]phenanthridin-6-ones in fairly good yields was achieved by the photocycloaddition reactions of 3-chloroisoquinolin-1-ones and 3-chloroquinolin-2-ones with styrenes. The reactions were proceeded via photoinduced dechlorinative coupling of 3-chloroisoquinolin-1-ones and 3-chloroquinolin-2-ones with styrenes and subsequent photocyclization, oxidative aromatization.

The photochemistry of aryl halides has long received great attention due to their values in the organic synthesis and the reaction mechanistic investigation.[1] Photoinduced addition reactions of aryl halogens to alkenes and arenes have become useful tools for the synthesis of aryl-substituted alkylamines, alkanols, ketones, and biaryls.[2] In this strategy, photochemistry could offer a convenient access to the formation of aryl-C bonds under mild conditions, via fragmentation of an Ar–X bond in aromatic derivatives to give a trappable intermediate (e.g., an aryl radical or cation). Recently, Albini and co-workers were engaged in the extensive research on the inter- and intramolecular photoaddition reactions of amino- and alkoxy-substituted aryl halogens to electron-rich alkenes, alkynes, and arenes.[2a–e] We have focused on inter- or intramolecular reactions of halogenated heterocycles with alkenes as they hold promise for a tin-free route to polycyclic heterocycles.[3] Although the photoreactions of halogenated heterocycles such as 5-halofurfural and 5-halothaphene with styrenes were investigated by others,[4] only stilbene-like coupling products were produced. We found that high yields of polycyclic aromatic heterocycles benzo[*a*]phenanthridin-5-ones and benzo[*k*]phenanthridin-6-ones could be obtained in the photoreactions of 3-chloroisoquinolin-1-ones and 3-chloroquinolin-2-ones with styrenes (Schemes 1 and 2).

Procedures for the synthesis of benzo[*a*]phenanthridines and benzo[*k*]phenanthridines are of interest since these compounds have similar skeletons to the benzophenanthridine alkaloids and have many pharmacological properties[5a–c] and some applications in material sciences.[5d,e] A variety of methods was reported for the synthesis of benzo[*a*]phenanthridines and benzo[*k*]phenanthridines, such as photocyclization of *N*-(2-iodiophenyl)-2-naph-



Scheme 1. Reactions of 3-chloroisoquinolin-1-ones with styrenes.



Scheme 2. Reactions of 3-chloro-1-methylquinolin-2-one with styrenes.

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Table 1
Photoreaction of 3-chloroisoquinolin-1-one (**1a**) and styrene (**2a**) under different conditions

Entry	Solvent	λ >300 nm			λ >200 nm		
		Time (h)	Convn[a] (%)	Yield [b] (%)	Time (h)	Convn[a] (%)	Yield [b] (%)
1	CH_2Cl_2	32	77	52	25	88	65
2	CH_2Cl_2/C_5H_5N	30	86	61	25	95	69
3	CH_3COCH_3	30	84	28	25	93	35
4	CH_3OH	—	—	—	25	92	30
5	C_6H_6	—	—	—	25	95	28

[a] Conversion was calculated on the basis of **1a**.
[b] Yield of isolated product based on consumed **1a**.

thalenecarboxamide ions via SRN1 reactions;[6a] Bu_3SnH-mediated radical cyclization of 3-(2-iodiophenylethenyl)quinoline;[6b] SmI_2-mediated radical cyclization of *N*-(2-iodiophenyl)-2-naphthalenecarboxamide;[6c] cyclocondensation of lithiated *N*,*N*-diethyl-2-toluamides with benzaldimines and subsequent bromination and $AgBF_4$-catalyzed rearrangements of spirodihydroisoquinolones[6d] and photocyclization of 3-(2-phenylethenyl)quinolin-2-ones.[6e] Despite of these developments, to the best of our knowledge, there has been no procedure for a direct synthesis of benzo[*a*]phenanthridines and benzo[*k*]phenanthridines by the photocycloaddition of isoquinolin-1-one and quinolin-2-one with olefins. Herein we report the first one-pot synthesis of benzo[*a*]phenanthridin-5-ones and benzo[*k*]phenanthridin-6-ones by the photochemical annulation of readily available 3-chloroisoquinolin-1-one and 3-chloroquinolin-2-one with styrenes (Schemes 1 and 2).

We surveyed the effects of reaction conditions on the photoreaction of 3-chloroisoquinolin-1-one (**1a**) with styrene (**2a**). No great difference was found for the photoreaction of **1a** and **2a** under oxygen or air in solutions, but the photoreaction was greatly affected by the solvents as shown in Table 1. Mixtures were produced in all selected solvents in short time, but the yield of **3a** in dichloromethane was increased after the irradiation was continued for a longer time. Solvent-mediated reaction products were detected in methanol and benzene, which resulted in the decrease of the yield of **3a**. The conversion of **1a** and the yield of **3a** were increased a little with the addition of base such as pyridine. Moreover the conversion of **1a** and the yield of **3a** were also influenced by the reaction vessels as indicated in Table 1. A mixture was produced in dichloromethane in Pyrex tubes under irradiation of a medium-pressure mercury lamp (500 W), but **3a** was obtained as a main product when quartz tubes were used. Thus irradiation in dichloromethane in quartz tubes with the addition of pyridine was selected as the standard condition for the photoreactions of all substrates.

A spectrum of 3-chloroisoquinolin-1-ones (**1a**–**c**) and styrenes (**2a**–**c**) was first examined to explore the generality of this new one-pot photochemical cycloaddition reaction. The photoreactions were conducted under above-mentioned reaction conditions for 18–40 h and the expected benzo[*a*]phenanthridin-5-ones **3a**–**i** were obtained as major products in all cases (Table 2). The products were fully identified by ^{1}H NMR, ^{13}C NMR, and MS,[7] and the structure of **3h** was further confirmed by the X-ray analysis as depicted in Figure 1.[8] It was noticed that the conversion of **1a**–**c** and the yields of **3a**–**i** were increased when the time of irradiation was prolonged. Intermediates were produced during the reactions of **1a**–**c** with **2a**–**c** and these intermediates could be converted to **3a**–**i** after prolonged irradiation except the intermediates **4a**–**c** which were produced in the reactions of **1a**–**c** with **2b** and led to the great decrease of the yields of **3b**, **3e**, and **3h**. The presence of substituents (R^1 = Me, Ph) in **1b** and **1c** retarded the photoreactions, but substituents (R^2 = Me, Ph) in **2b** and **2c** favored the conversion of **1a**–**c**.

Table 2
Photoreaction of 3-chloroisoquinolin-1-ones (**1a**–**c**) and styrenes (**2a**–**c**)

Entry	Reactant				Product	Time (h)	Convn[a] (%)	Yield[b] (%)
		R^1		R^2				
1	**1a**	H	**2a**	H	**3a**	25	95	69
2	**1a**	H	**2b**	Me	**3b + 4a**	18	93	25 + 50
3	**1a**	H	**2c**	Ph	**3c**	25	96	71
4	**1b**	Me	**2a**	H	**3d**	25	85	60
5	**1b**	Me	**2b**	Me	**3e + 4b**	28	90	23 + 46
6	**1b**	Me	**2c**	Ph	**3f**	36	96	82
7	**1c**	Ph	**2a**	H	**3g**	40	80	50
8	**1c**	Ph	**2b**	Me	**3h + 4c**	35	85	22 + 44
9	**1c**	Ph	**2c**	Ph	**3i**	35	90	63

[a] Conversion was calculated on the basis of **1a**–**c**.
[b] Yield of isolated product based on consumed **1a**–**c**.

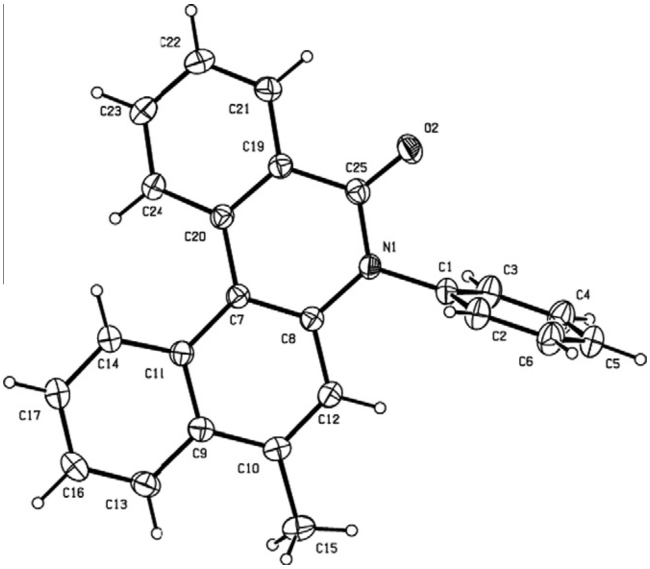


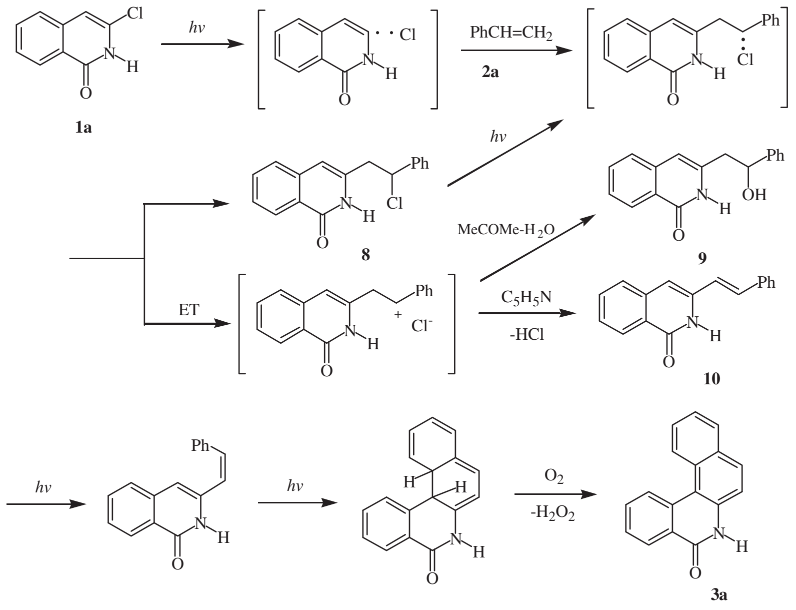
Figure 1. X-ray crystal structure of **3h**.

Table 3
Photoreaction of 3-chloroquinolin-2-one (**5a**) and styrenes (**2a**–**c**)

Entry	Reactant				Product	Time (h)	Convn[a] (%)	Yield[b] (%)
		R^1		R^2				
1	**5a**	Me	**2a**	H	**6a**	18	98	57
2	**5a**	Me	**2b**	Me	**6b**	20	97	65
3	**5a**	Me	**2c**	Ph	**6c**	20	97	68

[a] Conversion was calculated on the basis of **5a**.
[b] Yield of isolated product based on consumed **5a**.

To expand the scope of this one-pot photochemical synthesis of polycyclic compounds, we next examined the reactions of another reactant 3-chloroquinolin-2-one (**5a**) with **2a**–**c** under similar conditions (Scheme 2). As shown in Table 3, the results were very sim-



Scheme 3. Proposal mechanism for the photoreaction 3-chloroisoquinolin-1-one with styrene.

ilar to those obtained from 3-chloroisoquinolin-1-one (**1a**–**c**) that the photoreactions of **5** with **2a**–**c** afforded benzo[*k*]phenanthridin-6-ones (**6a**–**c)** as the main products from dechlorinative coupling, cyclization, and oxidative aromatization. All products were fully identified by ^{1}H NMR, ^{13}C NMR, and MS.

A plausible mechanism for the formation of benzo[*a*]phenanthridin-5-one (**3a**) via the photoreaction of **1a** with **2a** is shown in Scheme 3. The coupling of **1a** with **2a** was initiated by the photoinduced C–Cl bond cleavage in **1a** and subsequent addition of the produced 3-isoquinolinyl radical to double bond of styrene (**2a**). The homolysis of C–Cl bond to produce 3-isoquinolinyl radical could be confirmed from the formation of the coupling product 3-phenylisoquinolin-1-one while the photoreaction of **1a** with **2a** was conducted in benzene. The adduct 3-(2-chloro-2-phenylethyl)isoquinolin-1-one (**8**) could be converted to coupling product 3-(2-phenylethenyl)isoquinolin-1-one (**10**) upon prolonged irradiation via homolysis of C–Cl bond and subsequent electron transfer and deprotonation. Photoisomerization, photocyclization, and oxidation aromatization of **10** afforded the product **3a**. It was supposed that the light of λ <300 nm would be helpful to the homolysis of **8** because the yield of **3a** was higher in quartz tube than that in Pyrex tube. In fact benzyl cation could be easily produced from photolysis of benzyl chloride under 254 nm irradiation in polar solvents and transformed to stilbene as observed by Sket[9] and the cation-trapping product **9** was also separable when the photoreaction of **1a** and **2a** was conducted in acetone–water.

In summary, an efficient one-pot synthesis of benzo[*a*]phenanthridin-5-one and benzo[*k*]phenanthridin-6-one derivatives by the photoreactions of 3-chloroisoquinolin-1-ones and 3-chloroquinolin-2-ones with styrenes has been developed. To the best of our knowledge, this is the first report on the synthesis of these compounds via photoinduced dechlorinative annulation of 3-chloroisoquinolin-1-ones and 3-chloroquinolin-2-ones with styrenes.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.037.

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7. *General procedure for the photochemical reactions*: To 100 mL dry dichloromethane were added 2.0 mmol **1a**, 2.5 mmol **2a**, and a drop of dry pyridine. The solution was distributed in five 25 mL quartz tubes and irradiated with a medium-pressure mercury lamp (500 W) at ambient temperature for appropriate time. The progress of the reaction was monitored by TLC at regular intervals. After **1a** and other intermediates were disappeared, the solvent was washed with water, dried on anhydrous sodium sulfate, and removed in vacuo. The residual was separated by silica gel column chromatography eluted with hexane/acetone 10:1(v/v) to afford **3a**. The solid was further purified by recrystallization from ethanol to give pure **3a**.
Benzo[a]phenanthridin-8-one (**3a**): white solid; mp: 240–244 °C. ^{1}H NMR (DMSO-d_6) δ 7.51–7.57 (m, 2H), 7.67–7.71 (m, 2H), 7.92 (dt, *J* = 7.6, 1.6 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 8.45 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.80 (t, *J* = 8.4 Hz, 2H), 12.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 110.3, 116.5, 123.9, 124.3, 126.2, 126.3, 126.6, 127.1, 127.2, 128.7, 128.9, .129.8, 130.2, 131.9, 134.1,135.2, 160.3. MS *m/e* (relative intensity) 245 (M^+, 100), 217 (151), 216 (16), 189 (15); ESI-HRMS: *m/z* calcd for $C_{17}H_{11}NO + H^+$: 246.0915, found 246.0921.

6,8-Diphenylbenzo[a]phenanthridin-5-one (**3i**): Pale yellow solid; mp: 222–224 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.90$ (d, 1H, $J = 8.4$ Hz, ArH), 8.76 (d, 1H, $J = 8.4$ Hz, ArH), 8.65 (dd, 1H, $J = 8.0$ Hz, 1.6 Hz, ArH), 7.91–7.84 (m, 2H, ArH), 7.67–7.63 (m, 2H, ArH), 7.60 (d, 2H, $J = 7.2$ Hz, ArH), 7.52–7.50 (m, 1H, ArH), 7.44–7.39 (m, 4H, ArH), 7.37–7.34 (m, 4H, ArH), 6.68 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.9$, 141.6, 139.7, 138.2, 136.7, 134.2, 132.0, 130.3, 130.2, 129.2, 129.1, 128.9, 128.8, 128.3, 127.7, 127.3, 127.2, 127.1, 127.0, 126.9, 126.3, 124.9, 117.4, 113.2; MS (EI-*m/z*): 397 (M^+, 34), 320 (12), 290 (6), 259 (21), 237 (4), 165 (12), 77 (100), 51 (53); ESI-HRMS: *m/z* calcd for $C_{29}H_{19}NO + H^+$: 398.1539, found 398.1535.

5-Methyl-8-phenylbenzo[k]phenanthridin-6-one (**6c**): Pale yellow solid; mp 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.91$ (d, 1H, $J = 8.4$ Hz, ArH), 8.63 (d, 1H, $J = 8.4$ Hz, ArH), 8.46 (s, 1H, CH), 8.07 (d, 1H, $J = 8.0$ Hz, ArH), 7.65 (t, 1H, $J = 7.2$ Hz, ArH), 7.61–7.50 (m, 7H, ArH), 7.47 (d, 1H, $J = 7.2$ Hz, ArH), 7.37 (t, 1H, $J = 7.6$ Hz, ArH), 3.86 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.8$, 140.4, 139.9, 138.5, 134.7, 132.0, 130.0, 130.0, 129.0, 128.8, 128.4, 128.4, 128.2, 128.0, 127.8, 127.6, 126.9, 126.4, 124.4, 123.8, 121.9, 119.3, 114.8, 30.40; MS (EI-*m/z*): 335 (M^+, 89), 319 (2), 307 (3), 291 (10), 276 (7), 167 (100), 152 (20), 144 (10); ESI-HRMS: *m/z* calcd for $C_{24}H_{17}NO + H^+$: 336.1383, found 336.1378.

8. Crystal data for compound **3h** (recrystallized from acetone–hexane). $C_{24}H_{17}NO$, $M_r = 335.39$. Monoclinic, $a = 11.7093(19)$ Å, $b = 17.477(3)$ Å, $c = 9.2337(15)$ Å, $\beta = 109.781(2)$, $V = 1778.1(5)$ Å^3, colorless plates, $\rho = 1.253$ g cm^{-3}, $T = 296(2)$ K, space group $P2\ (1)/c$, $Z = 4$, μ (Mo Kα) = 0.71073 mm^{-1}, $2\theta_{max} = 51.0°$, 3298 reflections measured, 2223 unique ($R_{int} = 0.0729$) which were used in all calculation. the final $wR(F^2)$ was 0.1191 (for all data), $R_1 = 0.0431$. CCDC file No. 763203.
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