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Interaction of β-Lactam Carbenes with Aryl Isonitriles: An Unprecedented Rearrangement of 2-Azetidinonylidene Indoles to δ-Carbolinones

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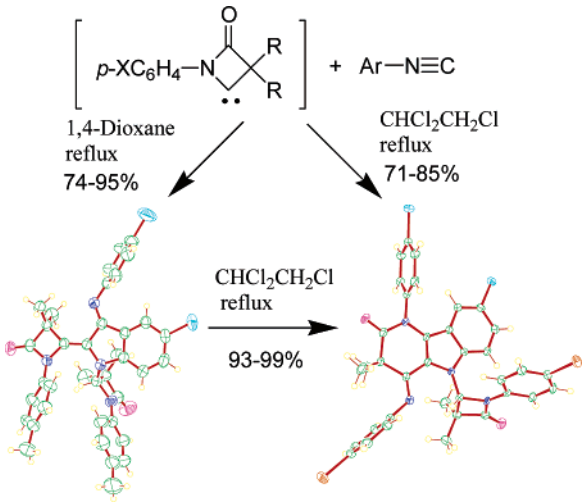

The reaction of β-lactam carbenes with aryl isonitriles proceeded in a novel [2 + 2] fashion to give high yields of 2-azetidinonylidene indoles **4**, which underwent an unprecedented rearrangement to furnish 4-arylimino-δ-carbolin-2-ones **5** in almost quantitative yields. Acid catalyzed rearrangement and the subsequent hydrolysis of 2-azetidinonylidene indoles **4** produced two types of δ-carbolin-2,4-diones **10** and **11**, respectively, in good to excellent yields. The photophysical study showed that both δ-carbolin-2,4-diones **10** and **11** are highly fluorescent with the fluorescent quantum yields being up to 0.43.

Introduction

Nucleophilic and ambiphilic carbenes are emerging in active research fields not only because these divalent species are powerful ligands in the formation of metal complexes[1] but also because they are useful organocatalysts[2] and versatile intermediates in organic synthesis.[3] We have been interested in the chemistry of nucleophilic and ambiphilic carbenes for some years[3a,4] and showed previously that nucleophilic and ambiphilic carbenes such as amino(chloro)carbene,[4a] chloro(oxy)carbine,[4b] and diaminocarbene[4c] served as unique building blocks in the construction of a variety of novel heterocycles. Our recent interest in amino substituted carbenes led us to focus on 2-azetidinone-4-ylidenes, a type of β-lactam carbene pioneered by Warkentin and Zoghbi in the 1990s.[5] The cyclopropanation reactivity toward both electron-rich and -deficient alkenes labeled β-lactam carbenes as the ambiphilic carbenes.[6] Very recently, however, we have shown that these β-lactam ambi-

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philic carbenes behaved actually as good nucleophiles and classical nucleophilic carbenes, such as diaminocarbene and aminooxycarbene species, to react with aryl isocyanates to produce spiro[azetidine-2-one-4,3′-indole-2′-ones].[4d]

Isonitriles constitute the other formal divalent species, and they are able to react with various functional groups.[7] Although alkyl isonitriles have been reported to react with carbenes to form ketenimines[8] that were utilized to trap carbenes and measure the electrophilicity of a variety of carbenes, the study on the reaction of free carbenes with isonitriles, especially aromatic ones,[9] is very limited. The synthetic application of the reaction between carbenes and isonitriles has been largely unexplored. To explore the synthetic utility and to obtain deep insight into the unique reactivity of β-lactam carbenes, we undertook the current study to investigate their reaction with aryl isonitriles. We were delighted to discover that the reaction of β-lactam carbenes with aryl isonitriles proceeded in a novel pathway, which comprised an unprecedented rearrangement of 2-azetidinonylidene indoles to δ-carbolinones.

Results and Discussion

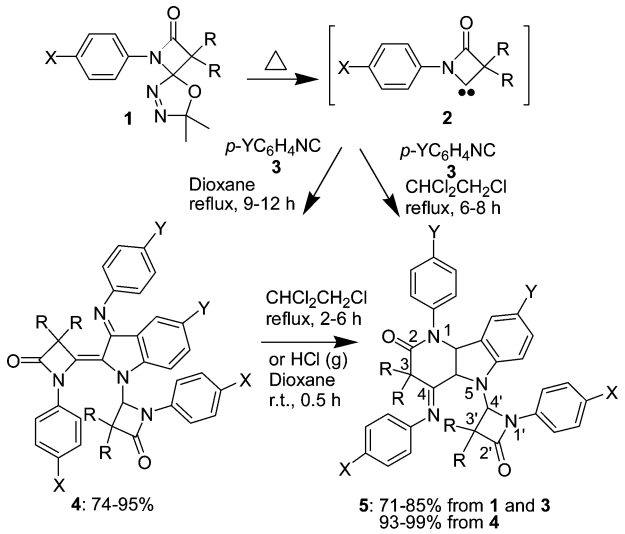
In practice, all β-lactam carbenes **2** are generated in situ by thermolysis of spiro[β-lactam-4,2′-oxadiazolines] **1** following Warkentin and Zoghbi's method.[5] Since the optimal temperature for the generation of carbene **2** was around 100−110 °C,[4d] the reaction of **2a** with *p*-chlorophenyl isonitrile **3c** was initially carried out in refluxing 1,1,2-trichloroethane (bp 110−115 °C) for 6 h. Surprisingly, the reaction gave a totally unexpected product, 4-arylimino-δ-carbolin-2-one **5a**, in 80% yield. Compound **5a** was apparently derived from a [2 + 2] addition reaction between **2a** and **3c**, although the construction of a δ-carboline ring from β-lactam species and aryl isonitriles remained a mystery. During the process of the reaction, it was noted that an orange compound was initially formed and then disappeared later. To isolate the intermediate, the reaction of **2a** with **3c** in trichloroethane was repeated but at a lower temperature (100 °C). After 12 h, an orange product, 2-azetidinonylidene indole **4a**, was isolated in addition to the yellow δ-carbolin-2-one **5a** (Table 1). The reaction was then optimized using different solvents. Interestingly, in all reactions carried out in toluene, 1,4-dioxane, and propionitrile, indole **4a** was obtained as the sole product. However, in refluxing 1,1,2-trichloroethane, **4a** was converted completely into **5a** (Scheme 1 and Table 1). As indicated in Table 1, both solvent and reaction temperatures governed the transformation of **4** to **5**. For example, although toluene and 1,1,2-trichloroethane have very similar boiling points, almost no product (**5a**) was observed in refluxing toluene, while **4a** was efficiently converted into **5a** in refluxing trichloroethane. On the other hand, in trichloroethane, the complete transformation of **4a** finished in 6 h at 110−115 °C, while only half the amount of **4a** was transformed into **5a** within 12 h at 100 °C. It is worth noting that although arenes were not good solvents for the formation of product **5**, **4a** could also be converted into **5a** in xylene at elevated temperatures (140 °C) and in a prolonged reaction time (40 h), indicating that high reaction temperatures can promote the conversion of **4** to **5**. The smooth and ready transformation of **4** into **5** in refluxing trichloroethane led us to propose that a trace amount of hydrochloride released from the solvent might accelerate the reaction. To validate our hypothesis, dry HCl gas was bubbled into the solution of 2-azetidinonylidene indole **4a** in 1,4-dioxane. Compound **4a** was forced to undergo transformation into δ-carbolinone **5a** in 93% yield in 30 min at room temperature (Table 2, entry 23). Taking all results aforementioned into consideration, it was concluded that the transformation of **4** to **5** was an acid catalyzed thermal rearrangement.

TABLE 1. Reaction of β-Lactam Carbene 2a with *p*-Chlorophenyl Isonitrile 3c under Different Conditions

entry	starting materials R, X, Y	reaction conditions	yield (%) 4a	5a
1	**1a**, **3c** Me, H, Cl	dioxane 100−110 °C, 11 h	81	
2	**1a**, **3c** Me, H, Cl	toluene 110−120 °C, 11 h	64	
3	**1a**, **3c** Me, H, Cl	propionitrile 100−110 °C, 12 h	77	
4	**1a**, **3c** Me, H, Cl	TCE[a] 110−120 °C, 6 h		80
5	**1a**, **3c** Me, H, Cl	TCE[a] 100 °C, 12 h	30	28
6	**1a**, **3c** Me, H, Cl	xylene 140−150 °C, 40 h		47

[a] TCE = 1,1,2-trichloroethane.

SCHEME 1. Reaction of β-Lactam Carbenes with Aryl Isonitriles



To examine the scope of the reaction, β-lactam carbenes **2** bearing different substituents were employed to react with different aryl isonitriles **3** (Scheme 1). As summarized in Table 2, in refluxing 1,4-dioxane, all reactions produced indole **4** in 74−95% yields, while 71−85% yields of δ-carbolinone **5** were obtained from the reaction in refluxing trichloroethane. The substituents on both starting materials have a negligible effect on the outcome of the reaction. δ-Carbolinone **5** were also prepared in almost a quantitative yield by refluxing indole **4** in trichloroethane.

The structures of all products were fully characterized by spectroscopic data and microanalysis, which indicated **4** and **5**

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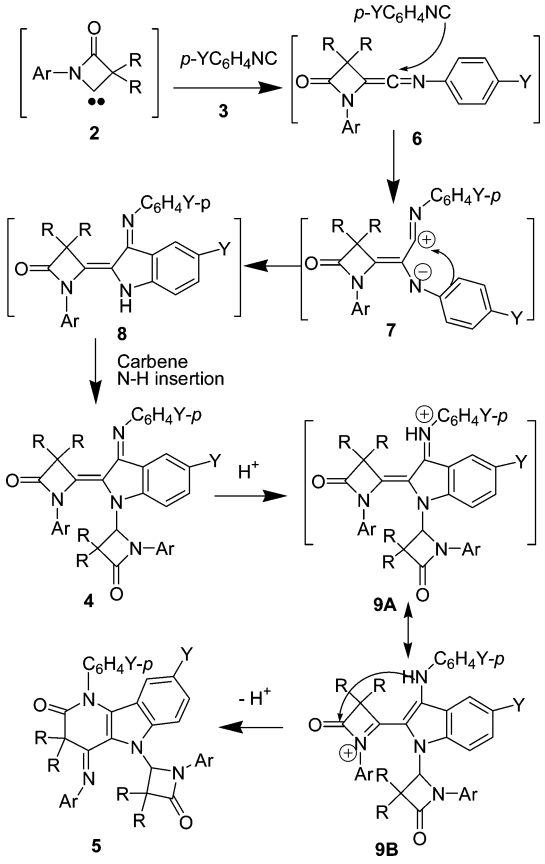
TABLE 2. Preparation of 2-Azetidinonylidene Indoles 4 and δ-Carbolin-2-ones 5

entry	**1** and **3**	R, X, Y	reaction conditions	**4**	yield (%)	**5**	yield (%)
1	**1a**, **3c**	Me, H, Cl	dioxane, reflux, 11 h	**4a**	81		
2	**1b**, **3a**	Me, Me, Me	dioxane, reflux, 9 h	**4b**	78		
3	**1b**, **3b**	Me, Me, OMe	dioxane, reflux, 12 h	**4c**	83		
4	**1b**, **3c**	Me, Me, Cl	dioxane, reflux, 9 h	**4d**	84		
5	**1b**, **3d**	Me, Me, Br	dioxane, reflux, 11 h	**4e**	85		
6	**1b**, **3e**	Me, Me, F	dioxane, reflux, 11 h	**4f**	74		
7	**1c**, **3c**	Me, OMe, Cl	dioxane, reflux, 10 h	**4**g	82		
8	**1d**, **3c**	Me, Cl, Cl	dioxane, reflux, 12 h	**4h**	77		
9	**1e**, **3c**	Me, Br, Cl	dioxane, reflux, 10 h	**4i**	81		
10	**1f**, **3c**	Et, OMe, Cl	dioxane, reflux, 10 h	**4j**	82		
11	**1g**, **3c**	Et, Cl, Cl	dioxane, reflux, 11 h	**4k**	80		
12	**1h**, **3c**	Et, Br, Cl	dioxane, reflux, 11 h	**4l**	83		
13	**1i**, **3c**	Ph, Me, Cl	dioxane, reflux, 11 h	**4**m	95		
14	**1j**, **3c**	Ph, Cl, Cl	dioxane, reflux, 11 h	**4n**	94		
15	**1k**, **3c**	Ph, Br, Cl	dioxane, reflux, 11 h	**4o**	95		
16	**1a**, **3c**	Me, H, Cl	TCE, reflux, 6 h			**5a**	80
17	**1b**, **3d**	Me, Me, Br	TCE, reflux, 8 h			**5e**	85
18	**1e**, **3c**	Me, Br, Cl	TCE, reflux, 4 h			**5i**	77
19	**1f**, **3c**	Et, OMe, Cl	TCE, reflux, 8 h			**5j**	78
20	**1g**, **3c**	Et, Cl, Cl	TCE, reflux, 8 h			**5k**	71
21	**1h**, **3c**	Et, Br, Cl	TCE, reflux, 8 h			**5l**	82
22	**4a**	Me, H, Cl	TCE, reflux, 3 h			**5a**	98
23	**4a**	Me, H, Cl	dry HCl, dioxane r.t., 0.5 h			**5a**	93
24	**4e**	Me, Me, Br	TCE, reflux, 3 h			**5e**	99
25	**4k**	Et, Cl, Cl	TCE, reflux, 6 h			**5k**	97
26	**4**m	Ph, Me, Cl	dry HCl, dioxane r.t., 1 h			**5**m	94

to be two isomeric products. To identify the isomers beyond doubt, the structures of **4d** and **5i** were determined unambiguously by single-crystal X-ray diffraction analysis (see Figure S1 in the Supporting Information). It is worth addressing the characteristics of the ^{1}H NMR spectra of δ-carbolinones **5**. For compounds **5a**, **5e**, and **5i** that were derived from 3,3-dimethyl-2-azetidinone-4-ylidenes, when the spectra were recorded at room temperature (298 K), the signals of partial methyl protons, the β-lactam proton, and some aromatic protons appeared as broad peaks. On the other hand, however, the ^{1}H NMR spectra of compounds **5j**, **5k**, and **5l** that were yielded from 3,3-diethyl substituted carbene species exhibited sharpened proton signals with good resolution. We rationalized that in the case of geminally dimethylated compounds **5a**, **5e**, and **5i**, the β-lactam moiety might slowly rotate along the N5−C4′ single bond, yielding a number of rotamers on the NMR time scale, whereas with **5j**, **5k**, and **5l**, the same rotation was prohibited due to the steric bulkiness of a pair of the geminally substituted ethyl groups. The rotamers were frozen when the temperature decreased, as the variant temperature ^{1}H NMR showed that all broad signals observed at room temperature became very well-resolved, and three sets of the β-lactam proton were observed at 248 K (see Figure S2 in the Supporting Information).

The formation of 2-azetidinonylidene indole **4** can be best explained by a reaction pathway depicted in Scheme 2. The reaction was initiated by coupling of the carbene with isonitrile to form a ketenimine intermediate **6**. Nucleophilic addition of a second isonitrile to **6** followed by intramolecular aromatic electrophilic cyclization led to the indole derivative **8**. Finally, N−H insertion of β-lactam carbene to **8** afforded product **4**. The rearrangement of indole **4** to δ-carbolinone **5** proceeded most probably through a novel acid catalytic N-to-N′ [1,5]-acyl migration. In the presence of an acid catalyst, indole **4** was protonated into **9A**, which rearranged its π system, giving rise to resonance form **9B**. Intramolecular nucleophilic attack led to [1,5]-acyl migration of **9B** to form δ-carbolinone **5** (Scheme 2). Theoretically, nucleophilic attack of isonitrile to ketenimine **6** might take place at either face of the imine carbon

SCHEME 2. Proposed Mechanism for Formation of 2-Azetidinonylidene Indole 4 and δ-Carbolinone 5



and lead to the formation of both *Z*- and *E*-isomers of **4**. However, only the *Z*-isomer was detected. The structure of ketenimine intermediate **6a** (Figure 1) optimized with the B3LYP/6-31G method (Gaussian 98)[10] clearly shows that

(10) See Supporting Information.

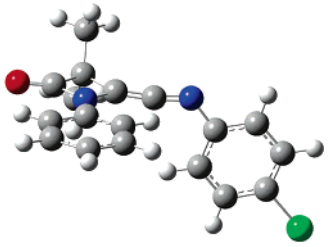
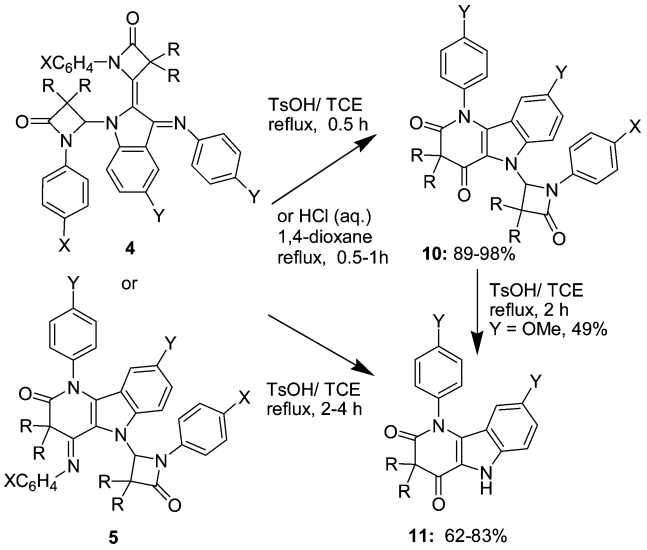


FIGURE 1. Gaussian 98 optimized structure of ketenimine intermediate **6a**.

isonitrile can only attack on one face of the imine double bond of **6** and form the *Z*-configuration of the carbon−carbon double bond since the other face of the imine is hindered by the *N*-aryl group of the carbene moiety.

Carbolines and their derivatives comprise an important family of heterocyclic compounds owing to their unique biological properties. Some δ-carboline derivatives, for example, have shown antiplasmodial,[11a] antitrypanosomal,[11b] antimalarial,[11b] and antineoplastic[11c] activities. In addition, a few δ-carboline derivatives exhibit interesting photophysical behaviors. The fluorescence and phosphorescence spectra of δ-carbolines are influenced by the polarity, hydrogen-bonding property, and acidity of the solvents.[12] The advantage of their fluorescent property has been applied to localize a δ-carboline derivative inside the human cell.[11a] In the literature, studies on the construction of a δ-carboline unit were very limited. All of the known syntheses were based on either the intramolecular coupling of phenylpyridine or anilinopyridine compounds[13] or cyclic condensation of 2 or 3 substituted indole derivatives.[14] Having considered the easy rearrangement of indole **4** to δ-carbolin-2-one **5** and the possible hydrolysis of the imine group of compound **5,** we envisioned that our β-lactam carbene approach would provide a very simple and efficient method for the preparation of δ-carbolin-2-one and δ-carbolin-2,4-dione derivatives. Thus, upon the treatment of indole **4** with different acids including *p*-toluenesulfonic acid monohydrate, boron trifluoride, and aqueous hydrochloride, two types of novel δ-carbolin-2,4-diones were obtained, respectively, under different reaction conditions. When compound **4** was warmed with hydrated *p*-toluenesulfonic acid, boron trifluoride, or aqueous hydrochloride in trichloroethane or in dioxane for 0.5−1 h, *N*-β-lactam-δ-carbolin-2,4-dione **10** was obtained in excellent yield. On the other hand, in the presence of 10 equiv of hydrated

SCHEME 3. Preparation of δ-Carbolin-2,4-dione Derivatives 10 and 11 from 2-Azetidinonylidene Indoles 4 and 4-Arylimino-δ-carbolinones 5



p-toluenesulfonic acid, the N-unsubstituted δ-carbolin-2,4-dione **11** was obtained generally in good yield in a prolonged time (2−4 h) (Scheme 3 and Table 3, see the Supporting Information for X-ray data of **10a** and **11a**). Hydrochloric acid was not an efficient catalyst for the preparation of δ-carbolin-2,4-dione **11** because compound **10** did not undergo further hydrolysis to **11**, even in the presence of a large excess of hydrochloric acid (about 100 equiv) for 6 h. Transformation of indole **4** to δ-carbolin-2,4-diones **10** and **11** can be easily explained by isomerization of **4** to δ-carbolinone **5** followed by hydrolysis of **5** into **10** and then to **11**. This mechanism was further supported by the hydrolysis of **5** to **10** or **11** using hydrated *p*-toluenesulfonic acid (Table 3, entries 11 and 17).

Both δ-carbolin-2,4-diones **10** and **11** were found to be fluorescent. To study the photophysical properties of compounds **10** and **11**, their fluorescent quantum yields were measured. To examine the solvent effects on the fluorescent property, the fluorescent spectra of **10a** and **11a** were first measured in different solvents. As indicated in Table 4, the solvents have a larger effect on the emission maximum (λ_{em}max) and quantum yield (Φ_F) of **11a** than that of **10a**. Since δ-carbolin-2,4-dione **11** can form intramolecular and intermolecular hydrogen bonds, the influence of the solvents on the fluorescence of **11** was most probably due to the formation of a hydrogen bond between **11** and solvents. The fluorescence spectra of other δ-carbolin-2,4-diones **10** and **11** were then recorded in the optimal solvent (Table 5). It was noted that the substituents bearing the carboline ring and lactam moiety have a significant influence on the fluorescence of compounds **10** and **11**. The *N* substituted carbolin-2,4-dione **10** generally has stronger fluorescence than its *N*-unsubstituted analogue **11**. For example, the Φ_F value of **10a** was 0.35 measured in ethyl acetate, while that of **11a** was only 0.25 in the same solvent (Table 4, entries 2 and 7). The halogen substituted carbolin-2,4-diones **10** (Φ_F = 0.32−0.43) and **11** (Φ_F = 0.23−0.25) have higher fluorescent quantum yields than the electron-donating methoxy and methyl substituted analogues (see Table 5).

In summary, we have shown that the reaction of β-lactam carbenes with aryl isonitriles proceeded in a [2 + 2] fashion to give high yields of functionalized 2-azetidinonylidene indoles.

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TABLE 3. Preparation of δ-Carbolin-2,4-dione Derivatives 10 and 11

entry	4 or 5	reaction conditions	10: R, X, Y	yield (%)	11: R, Y	yield (%)
1	**4a**	3 × TsOH·H_2O, TCE reflux, 0.5 h	**10a**: Me, H, Cl	91		
2	**4a**	2 × BF3·Et_2O, TCE, reflux, 1 h	**10a**: Me, H, Cl	87		
3	**4b**	10 × HCl (aq), dioxane, reflux, 0.5 h	**10b**: Me, Me, Me	98		
4	**4c**	10 × HCl (aq), dioxane, reflux, 0.5 h	**10c**: Me, Me, OMe	89		
5	**4d**	3 × TsOH·H_2O, TCE, reflux, 0.5 h	**10d**: Me, Me, Cl	94		
6	**4e**	10 × HCl (aq), dioxane, reflux, 0.5 h	**10e**: Me, Me, Br	97		
7	**4f**	10 × HCl (aq), dioxane, reflux, 0.5 h	**10f**: Me, Me, F	98		
8	**4g**	3 × TsOH·H_2O, TCE, reflux, 0.5 h	**10g**: Me, OMe, Cl	94		
9	**4h**	3 TsOH·H_2O, TCE, reflux, 0.5 h	**10h**: Me, Cl, Cl	97		
10	**4i**	3 × TsOH·H_2O, TCE, reflux, 0.5 h	**10i**: Me, Br, Cl	90		
11	**5**g	3 × TsOH·H_2O, TCE, reflux, 0.5 h	**10g**: Me, OMe, Cl	95		
12	**4a**	10 × TsOH·H_2O, TCE, reflux, 3 h			**11a**: Me, Cl	83
13	**4b**	10 × TsOH·H_2O, TCE, reflux, 3 h			**11b**: Me, Me	62
14	**4e**	10 × TsOH·H_2O, TCE, reflux, 3 h			**11e**: Me, Br	75
15	**4f**	10 × TsOH·H_2O, TCE, reflux, 4 h			**11f**: Me, F	83
16	**4j**	10 × TsOH·H_2O, TCE, reflux, 4 h			**11j**: Et, Cl	77
17	**5a**	10 × TsOH·H_2O, TCE, reflux, 2 h			**11a**: Me, Cl	82
18	**10c**	6 × TsOH·H_2O, TCE, reflux, 2 h			**11c**: Me, OMe	49

TABLE 4. Emission Maxima and Fluorescent Quantum Yields of δ-Carbolin-2,4-diones 10a and 11a Measured in Different Solvents

entry	compound	solvent	λ_{em}max (nm)	Φ_F[a]
1	**10a**	CH_3CN	452	0.32
2	**10a**	$CH_3CO_2C_2H_5$	448	0.35
3	**10a**	THF	449	0.35
4	**10a**	CH_2Cl_2	454	0.36
5	**10a**	$PhCH_3$	449	0.31
6	**11a**	CH_3CN	447	0.11
7	**11a**	$CH_3CO_2C_2H_5$	441	0.25
8	**11a**	THF	444	0.21
9	**11a**	CH_2Cl_2	448	0.16
10	11a	$PhCH_3$	437	0.18

[a] The quantum yields (Φ_F) were determined with reference to perylene (1.2×10^{-6} M in toluene) excited at 395 nm for **10** and 376 nm for **11**.

TABLE 5. Selected Fluorescent Properties of δ-Carbolin-2,4-diones 10 and 11

entry	10: R, X, Y or 11: R, Y	solvent	λ_{em}max (nm)	Φ_F
1	**10a**: Me, H, Cl	CH_2Cl_2	454	0.36
2	**10b**: Me, Me, Me	CH_2Cl_2	466	0.28
3	**10c**: Me, Me, OMe	CH_2Cl_2	470	0.14
4	**10d**: Me, Me, Cl	CH_2Cl_2	456	0.32
5	**10e**: Me, Me, Br	CH_2Cl_2	458	0.41
6	**10f**: Me, Me, F	CH_2Cl_2	458	0.43
7	**10g**: Me, OMe, Cl	CH_2Cl_2	456	0.13
8	**10h**: Me, Cl, Cl	CH_2Cl_2	454	0.37
9	**10i**: Me, Br, Cl	CH_2Cl_2	453	0.37
10	**11b**: Me, Me	$CH_3CO_2C_2H_5$	449	0.13
11	**11c**: Me, OMe	$CH_3CO_2C_2H_5$	452	0.11
12	**11a**: Me, Cl	$CH_3CO_2C_2H_5$	441	0.25
13	**11e**: Me, Br	$CH_3CO_2C_2H_5$	441	0.23
14	**11f**: Me, F	$CH_3CO_2C_2H_5$	443	0.23

The resulting azetidinonylidene indoles underwent a novel N-to-N′ [1,5]-acyl migration in an enamino imine system to furnish δ-carbolinones in almost quantitative yields. Acid catalyzed rearrangement and the subsequent hydrolysis of 2-azetidinonylidene indoles **4** produced two types of novel δ-carbolin-2,4-diones **10** and **11**, respectively, in good to excellent yields. 2-Azetidinonylidene indoles, δ-carbolin-2-ones, and δ-carbolin-2,4-diones obtained from the current study are new chemical entities of potential biological properties. They are also valuable intermediates subject to further elaborations owing to their multifunctional structures. The high fluorescence emission efficiencies of δ-carbolin-2,4-diones suggest their potential applications in advanced functional organic materials and medicinal chemistry.

Experimental Section

General Procedure for the Reaction of β-Lactam Carbenes with Aryl Isonitriles. Under nitrogen atmosphere, a mixture of spiro[β-lactam-4,2′-oxadiazoline] **1** (1.5 mmol) and aryl isonitrile **3** (1.5 mmol) was refluxed in 1,4-dioxane (30 mL) for 9−12 h or in 1,1,2-trichloroethane (30 mL) for about 6−8 h. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether (30−60 °C) and ethyl acetate (petroleum ether/ethyl acetate from 12:1 to 6:1). The product 2-azetidinonylidene indole **4** was obtained in 74−95% yield from the reaction in 1,4-dioxane, while 4-arylimino-δ-carbolin-2-one **5** was obtained in 71−85% yield from reaction in 1,1,2-trichloroethane. The δ-carbolin-2-one **5** could also be prepared in 93−99% yield by refluxing the indole **4** in 1,1,2-trichloroethane for 3−6 h or by bubbling the dry HCl gas into the solution of indole **4** in 1,4-dioxane for 0.5−1 h at room temperature.

(*Z*)-5-Chloro-1-(3,3-dimethyl-1-phenylazetidin-2-one-4-yl)-2-(3,3-dimethyl-1-phenylazetidin-2-one-4-ylidene)-3-(*p*-chlorophenyl)imino-2,3-dihydroindole (4a). 81%, mp 229−230 °C; IR υ (cm^{-1}) 1800, 1772, 1677, 1615; ^{1}H NMR (500 MHz, C_6D_6) δ (ppm): 7.46 (d, J = 7.9 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.10 (brs, 4H), 6.91−6.96 (m, 4H), 6.64 (d, J = 8.3 Hz, 2H), 6.57 (d, J = 8.8 Hz, 1H), 5.11 (s, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.06 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ (ppm): 174.1, 170.2, 157.7, 149.8, 149.6, 138.2, 136.2, 135.1, 132.7, 130.0, 129.8, 129.2, 127.4, 127.2, 126.8, 125.9, 124.4, 124.3, 122.1, 121.4, 119.8, 117.6, 117.1, 76.0, 61.2, 57.5, 22.1, 18.3, 18.2, 16.0. MS (APCI): 621 (M + 1)/623. Anal. Calcd for $C_{36}H_{30}Cl_2N_4O_2$: C 69.57, H 4.87, N 9.01. Found: C 69.68, H 4.90, N 8.87.

8-Chloro-1-(*p*-chlorophenyl)-3,3-dimethyl-4-phenylimino-5-(3,3-dimethyl-1-phenylazetidin-2-one-4-yl)-δ-carbolin-2-one (5a). 80% from **1a** and **3c**, 98% from **4a**, mp 241−242 °C; IR υ (cm^{-1}) 1764, 1693, 1626. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.58 (d, J = 8.1 Hz, 2H), 7.35−7.40 (m, 6H), 7.28 (brs, 4H), 7.08−7.10 (m, 2H), 7.02 (d, J = 9.1 Hz, 1H), 6.84 (brs, 2H), 6.06 (brs, 1H), 1.70 (s, 3H), 1.54 (brs, 3H), 1.49 (brs, 3H), 1.15 (brs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 173.8, 170.8, 158.3, 149.5, 137.6, 136.2, 135.1, 130.1, 130.0, 129.5, 129.0, 126.9, 126.4, 125.4, 124.7, 122.9, 120.7, 120.1, 117.4, 116.3, 115.1, 115.0, 73.8, 58.1, 53.2, 27.5, 25.9, 22.1, 16.2. MS (MALDI-TOF): 621 (M + 1). Anal. Calcd for $C_{36}H_{30}Cl_2N_4O_2$: C 69.57, H 4.86, N 9.01. Found: C 69.35, H 4.60, N 8.88.

General Procedure for the Preparation of 5-(Azetidin-2-one-4-yl)-δ-carbolin-2,4-dione 10. The mixture of 2-azetidinonylidene

indole **4** (0.5 mmol) with hydrated *p*-toluenesulfonic acid (1.5 mmol) in trichloroethane (40 mL), or with aqueous HCl (36% w/v, 10 mmol) in 1,4-dioxane (40 mL), refluxed for 0.5 h. After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether (30−60 °C) and ethyl acetate (petroleum ether/ethyl acetate 6:1) to give 5-(azetidin-2-one-4-yl)-δ-carbolin-2,4-dione **10** in 87−98% yield.

8-Chloro-1-(*p*-chlorophenyl)-3,3-dimethyl-5-(3,3-dimethyl-1-phenylazetidin-2-one-4-yl)-δ-carbolin-2,4-dione (10a). 91%, mp 187−188 °C; IR υ (cm^{-1}) 1777, 1701, 1650; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 (t, J = 6.4 Hz, 2H), 7.41 (d, J = 9.3 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.30−7.33 (m, 4H), 7.19 (s, 1H), 7.10−7.13 (m, 2H), 6.03 (d, J = 1.5 Hz, 1H), 1.74 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 189.9, 175.4, 170.5, 137.4, 137.2, 135.8, 135.6, 132.2, 130.4, 130.3, 129.6, 129.5, 126.8, 124.9, 121.5, 118.1, 117.6, 116.3, 115.2, 73.2, 58.2, 54.6, 25.2, 24.4, 21.9, 16.0. MS (ESI): 546 (M + 1), 568 (M + Na^+). Anal. Calcd for $C_{30}H_{25}Cl_2N_3O_3$: C 65.94, H 4.61, N 7.69. Found: C 65.91, H 4.51, N 7.52.

General Procedures for the Preparation of δ-Carbolin-2,4-diones 11. The mixture of 2-azetidinonylidene indole **4** (0.5 mmol) with hydrated *p*-toluenesulfonic acid (5 mmol) in trichloroethane (50 mL) refluxed for 2−4 h. After removal of the solvent and *p*-toluenesulfonic acid, the residue was chromatographed on silica gel eluting with a mixture of petroleum ether (30−60 °C) and ethyl acetate (petroleum ether/ethyl acetate 4:1) to give δ-carbolin-2,4-dione **11** in 62−83% yield.

8-Chloro-1-(*p*-chlorophenyl)-3,3-dimethyl-δ-carbolin-2,4-dione (11a). 83%, mp 282−283 °C; IR υ (cm^{-1}) 3216, 1699, 1688, 1625; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.01 (s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.31 (dd, J = 8.9, 1.7 Hz, 1H), 6.13 (s, 1H), 1.70 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 189.7, 175.9, 137.3, 135.8, 135.5, 131.2, 130.3, 130.2, 129.0, 126.2, 121.0, 118.7, 116.9, 114.4, 53.7, 25.1. MS (EI): 84 (100)/86 (60), 372 (25%, M^+)/374 (15). Anal. Calcd for $C_{19}H_{14}Cl_2N_2O_2$: C 61.14, H 3.78, N 7.51. Found: C 61.46, H 3.83, N 7.49.

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Supporting Information Available: Experimental procedures for the preparation of 2-azetidinonylidene indoles **4**, δ-carbolinones **5**, δ-carbolin-2,4-diones **10** and **11**; full characterization for compounds **4**, **5**, **10**, and **11**; copies of ^1H NMR and ^{13}C NMR spectra of products **4**, **5**, **10**, and **11**; single-crystal data of **4d**, **5i**, **10a**, and **11a** (CIF); as well as the computational calculated data for intermediate **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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