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Facile Synthesis of Acridine Derivatives by $ZnCl_2$-Promoted Intramolecular Cyclization of *o*-Arylaminophenyl Schiff Bases

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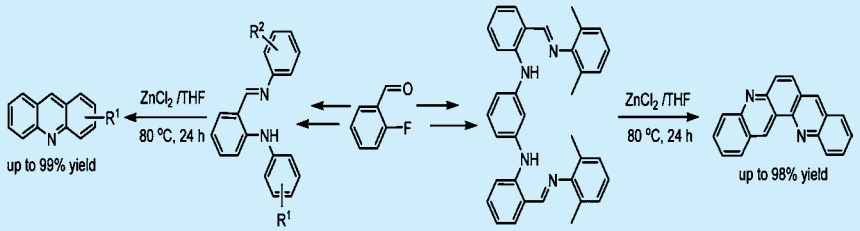
Supporting Information



ABSTRACT: A concise and efficient method for the synthesis of a wide range of acridine derivatives and polycyclic aza-aromatic compounds from a $ZnCl_2$-promoted cyclization reaction of readily available *o*-arylaminophenyl Schiff base compounds under convenient conditions was developed. Reaction conditions and scope of the new method were examined in detail.

Acridines as an important class of heteroaromatic compounds have attracted considerable interest because of their novel hetreocycle chemistry, broad range of properties, and industrial applications.[1] It has been well-known that acridine derivatives possess versatile biological activities[2] such as antibacterial, antimalarial, and anticancer. Some acridine compounds have been studied as DNA and RNA intercalating agents.[3] Acridine derivatives and related compounds have been applied in industry as pigments and dyes for long time.[4] Recently, acridine derivatives with extended conjugated systems were reported to exhibit unusual electronic and photophysical properties, which are expected to be promising candidates for organic semiconductor materials.[5] Therefore, many efforts have been focused on the development of synthetic methods for the construction of a variety of acridine derivatives. The Brenthsen reaction is one of the earliest used methods for the preparation of acridines, which is achieved by heating a diphenylamine and a carboxylic acid together with $ZnCl_2$ under 200−270 °C.[6] The most common method for preparing acridines is by the reduction of 9-acridanones and 9-chloroacridines, which are readily available from the cyclization of diphenylamine-2-carboxylic acids.[7] The synthetic methods for acridine derivatives by cyclization of diphenylamine-2-aldehydes or diphenylamine-2-ketones were also reported, but the starting aldehydes and ketones are difficult to prepare.[8] A small number of acridines were also synthesized by dehydrogenation,[9] C−H functionalization,[10] or other reactions.[11] Most of these known synthetic methods require either harsh reaction conditions, such as high temperature, strongly basic or acidic media, or difficultly obtained starting materials. Therefore, it is highly desirable to develop new synthetic methods for acridine derivatives under relatively mild conditions. Herein, we report an efficient method to synthesize acridine derivatives and related polycyclic aza-aromatic compounds, such as benzo[*j*]-[1,7]phenanthroline, dibenzo[*b*,*j*][4,7]phenanthroline, dibenzo[*b*,*j*][1,7]phenanthroline, and acridino[4,3-*c*]acridine, from a $ZnCl_2$-promoted cyclization reaction of *o*-arylaminophenyl Schiff base compounds.

In an attempt to synthesize new Zn complexes chelated by anilido-imine ligands from reactions of $ZnCl_2$ with *o*-arylaminophenyl Schiff base compounds, acridine derivatives were obtained instead of the expected Zn complexes. We therefore began to investigate the cyclization reaction of the *o*-arylaminophenyl Schiff base compounds in the presence of $ZnCl_2$ in detail. Treatment of *o*-$C_6H_4(CH{=}NC_6H_5)(NC_6H_5)$ **1** with 0.5−2 equiv of $ZnCl_2$ in THF at 50−80 °C for 24 h resulted in acridine **1a** in 35−99% yields (Table S1, Supporting Information). Relatively low yields were obtained when the reaction was carried out in other common organic solvents, such as toluene, benzene, CH_2Cl_2, or $CHCl_3$. $(PhNH_2)_2{\cdot}ZnCl_2$ adduct was also obtained from the reaction by concentrating the reaction solution, and its crystal structure was determined (Table S2, Supporting Information). High $ZnCl_2$ loadings (100−200 mol %) were found to accelerate the cyclization reaction probably because $ZnCl_2$ could be coordinated by both the amine and imine groups in the starting material and by the produced acridine and aniline in the reaction system. After the reaction conditions were briefly optimized, this new synthetic method has been applied to prepare a range of acridines with different substituents by varying the *o*-arylaminophenyl Schiff base substrates, and the results are listed in Table 1.

The cyclization reactions of the substrates *o*-$C_6H_4(CH{=}NC_6H_4\text{-Me-}p)(NC_6H_4\text{-Me-}p)$ (**2**) and *o*-$C_6H_4(CH{=}NC_6H_3$-

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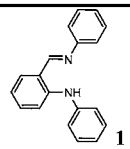
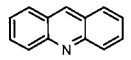
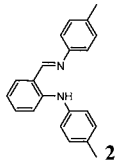
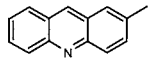
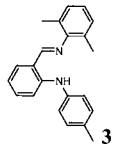
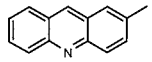
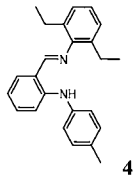
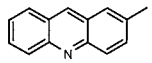
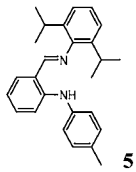
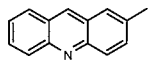
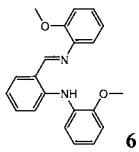
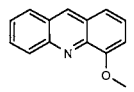
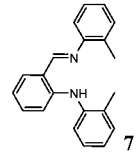
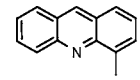
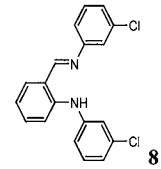
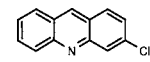
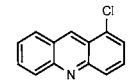
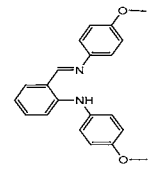
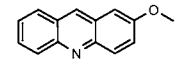
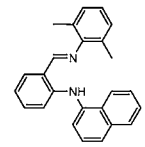
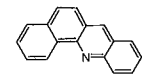
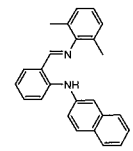
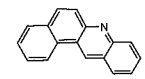
Table 1. Results of the $ZnCl_2$-Promoted Cyclization Reactions of *o*-Arylaminophenyl Schiff Base Compounds[a]

entry	start material	product	yield[b]
1	 **1**	 **1a**	70% 99%[c]
2	 **2**	 **2a**	76%
3	 **3**	 **2a**	73%
4	 **4**	 **2a**	70%
5	 **5**	 **2a**	0%
6	 **6**	 **6a**	95%
7	 **7**	 **7a**	73%
8	 **8**	 **8a**[d]  **8b**[d]	50%[c] 36%[c]
9	 **9**	 **9a**	97%[c]
10	 **10**	 **10a**	49%
11	 **11**	 **11a**	61%

[a]Reactions were performed at 80 °C for 24 h on a 0.20 mmol scale in 2 mL of solvent with 1.0 equiv of $ZnCl_2$. [b]Isolated yield. [c]With 2.0 equiv of $ZnCl_2$. [d]Determined by NMR analysis.

R_2-2,6)(NC_6H_4-Me-*p*) (R = Me, **3**; R = Et, **4**) with less sterically demanding substituents on their imine N atoms proceeded smoothly to give 2-methylacridine **2a** with similar yields (70−76%, entries 2−4). However, the substrate **5** with a bulky 2,6-^{i}Pr$_2$Ph on the imine N atom was found to be unsuitable for the cyclization reaction (entry 5). When the *o*-methoxy-substituted substrate **6** was employed, 4-methoxyacridine **6a** was obtained in a high yield of 95% (entry 6). The cyclization reaction of the *o*-methyl-substituted substrate **7** proceeded efficiently to produce 4-methylacridine **7a** in similar yields (entry 7) to those for the reactions of substrates **3** and **4**. Notably, the cyclization of the *m*-chloro-substituted substrate **8** produced a 3:2 mixture of acridines **8a** and **8b** in a total yield of 86% (entry 8). Similar to the reaction of **6**, the cyclization reaction of the *p*-methoxy-substituted substrate **9** produced 2-methoxyacridine **9a** in a high yield of 97% (entry 9). With these results, it is evident that the reactivity of the *o*-arylaminophenyl Schiff base substrates and the regioselectivity of their products are sensitive to the electronic and steric effects of the aryl substituents at both the amine and imine N atoms. In comparison, the steric effect of the aryl substituent at the imine N atom and the electronic effect of the aryl substituent at the amine N atom on the reactivity of these substrates seem to be more remarkable.

Two naphthalene-based substrates **10** and **11** were also examined for the intramolecular cyclization reaction. As expected, a tetracyclic acridine derivative benz[*c*]acridine **10a** was obtained from the reaction of **10** in a yield of 49% (entry 10). In the case of the substrate **11**, the cyclization reaction regioselectively proceeded at the 1-position of the 2-naphthylamine moiety, producing benz[*a*]acridine **11a** in a yield of 62% (entry 11). In a previously reported example, fluorobenz[*c*]-acridines were synthesized by thermolysis of arylenaminoimine hydrochlorides and subsequent aromatization of the intermediates with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-chlorobenzene systems.[12]

In our further studies, two 7-quinoline-substituted derivatives **12** and **13** were synthesized and used as the substrates of the cyclization reaction. 2,4-Dimethylbenzo[*j*][1,7]phenanthroline **12a** was obtained in high yields of 96% and 95%, respectively, from the reactions of **12** and **13** in the presence of 1 equiv of $ZnCl_2$ in THF (eq 1). The molecular structure of **12a** was confirmed by X-ray diffraction analysis as shown in Figure 1. The fact that compound **12a** was formed as only product in the reactions indicates that, in comparison to the 6-position, the 8-position of the 2,4-dimethylquinoline moiety is much more easily attacked by the electrophilic group. From a structural point of view, it seems abnormal for the quinoline-containing substrates **12** and **13** showing higher reactivities than the

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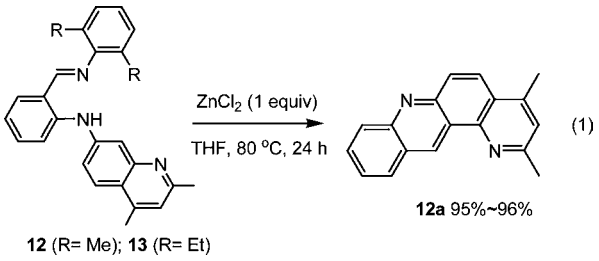


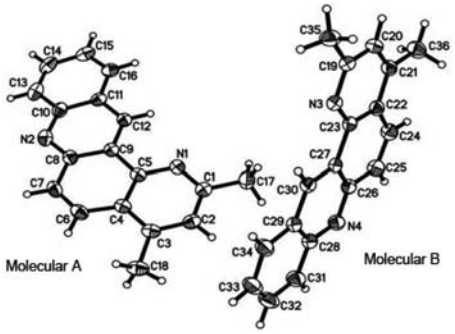


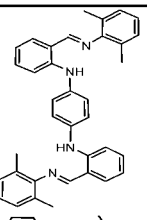
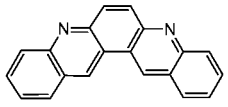
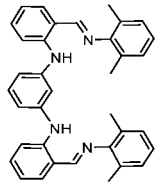
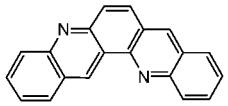
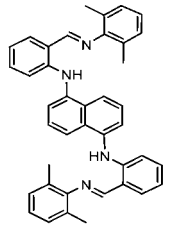
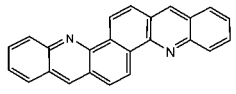
Figure 1. Molecular structure of **12a**.

naphthalene-based substrates **10** and **11**. The two electron-donating methyl groups on the quinoline moiety in **12** and **13** are apparently responsible for the high reactivities of the two compounds. In addition, the two methyl substituents in product **12a** would provide opportunities for further structural modification such as halogenation, acylation, and carboxylation.[7d,13]

In order to further screen the scope of this new $ZnCl_2$-promoted cyclization reaction of *o*-arylaminophenyl Schiff base compounds, we have synthesized three new bis(*o*-arylaminophenyl Schiff base) substrates **14**–**16** as shown in Table 2 and investigated their intramolecular cyclization reactions under different conditions. For the reactions of **14**, a polycyclic heteroaromatic compound dibenzo[*b*,*j*][4,7]phenanthrolin **14a** was isolated as the only product in all cases. It is not very clear why the expected linear product quino[2,3-*b*]acridine was not formed in the reactions. When the reactions were carried out at 80 °C for 24 h in the presence of 2 or 4 equiv of $ZnCl_2$ (entries 1 and 2, Table 2), **14a** was obtained in a yield of 28% or 50%, respectively. The reaction was found to be quite sensitive to temperature. When the reaction was run at 60 °C for 48 h in the presence of 2 equiv of $ZnCl_2$, **14a** was obtained in a yield of only 10%. As in the case of **14**, a bent polycyclic heteroaromatic compound dibenzo[*b*,*j*][1,7]phenanthroline **15a** was obtained as the only product from the reactions of substrate **15**. No linear product was obtained. By comparing the yields of **14a** and **15a** obtained under similar conditions, it can be seen that the reactivity of **15** is abviously higher than the one of **14**.

The observed regioselectivity for the reactions of **14** and **15** suggests that the double-cyclization reactions in these systems happen sequentially, and the electrophilic attack for both cyclization reactions takes place at the most active *ortho*-position or one of the equally active *ortho*-positions of an amine group in the substrates or intermediates. Attempts to observe the intermediates by following the reactions with ^1H NMR were not successful. Similar regioselectivity has been observed previously for the acid-catalyzed cyclization of (phenylendiamino)bisbenzophenone and (phenylendiamino)bisacetophenone.[14] The expected polycyclic heteroaromatic product

Table 2. Synthesis of Dibenzo[*b*,*j*][4,7]phenanthrolin, Dibenzo[*b*,*j*][1,7]phenanthrolin, and Acridino[4,3-*c*]acridine by the Cyclization Reaction[a]

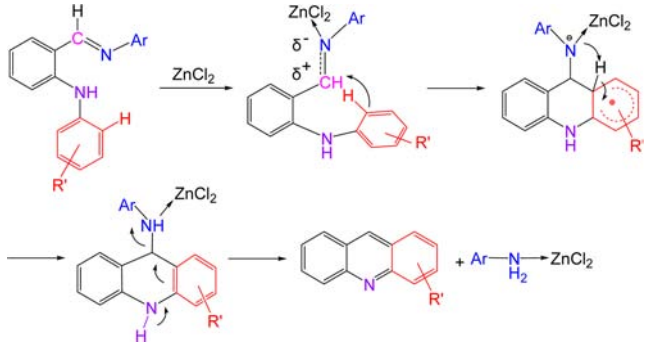
entry	start material	product	yield[b]
1	 **14**	 **14a**	28%
2			50%[c]
3	 **15**	 **15a**	95%
4			98%[c]
5	 **16**	 **16a**	35%[c]

[a]Reactions were performed on a 0.10 mmol scale in 2 mL of solvent at 80 °C for 24 h using 2.0 equiv of $ZnCl_2$. [b]Isolated yield. [c]Using 4.0 equiv of $ZnCl_2$.

acridino[4,3-*c*]acridine **16a** was obtained from the double cyclization reaction of the naphthalene-1,5-diamine-derived substrate **16**. The isolated yield of **16a** is lower than those of **14a** and **15a**, indicating that the reactivity of **16** is relatively low in comparison to the ones of **14** and **15**. Above results demonstrates that the new cyclization reaction can been applied to the synthesis of complex polycyclic heteroaromatic compounds.

On the basis of our investigations and reported similar results,[8a] a plausible mechanism for the cyclization reaction of *o*-arylaminophenyl Schiff base compounds is shown in Scheme 1. The imine N atom in the *o*-arylaminophenyl Schiff base coordinates to $ZnCl_2$ to form a $ZnCl_2$ complex, in which the Zn atom induces a polarization of the imine C═N bond to make the C atom positively charged. The cyclization reaction then takes place by an intramolecular electrophilic attack of the C

Scheme 1. Plausible Mechanism for the Cyclization Reaction of *ortho*-Arylaminophenyl Schiff Base Compounds



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atom on the aromatic ring at an *ortho*-position of the amine group in the substrate to generate a zwitterionic intermediate. The allylic carbocation is deprotonated by transferring the proton to the nitrogen anion to form a substituted 9,10-dihydroacridine which is unstable and aromatization reaction happens by splitting off an aniline molecule. Similar aromatization reactions of 1,4-dihydropyridine derivatives to form pyrazolo[3,4-*b*]quinoline, acridine, and pyrimido[4,5-*b*]quinoline derivatives have been reported in the literature.[15]

In summary, we have developed a concise and efficient method for the synthesis of acridine derivatives by a $ZnCl_2$-promoted cyclization reaction of readily available *o*-arylaminophenyl Schiff base compounds. This new cyclization reaction can also be applied to the synthesis of complex polycyclic aza-aromatic compounds by double cyclization reactions of bis(*o*-arylaminophenyl Schiff base) substrates.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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