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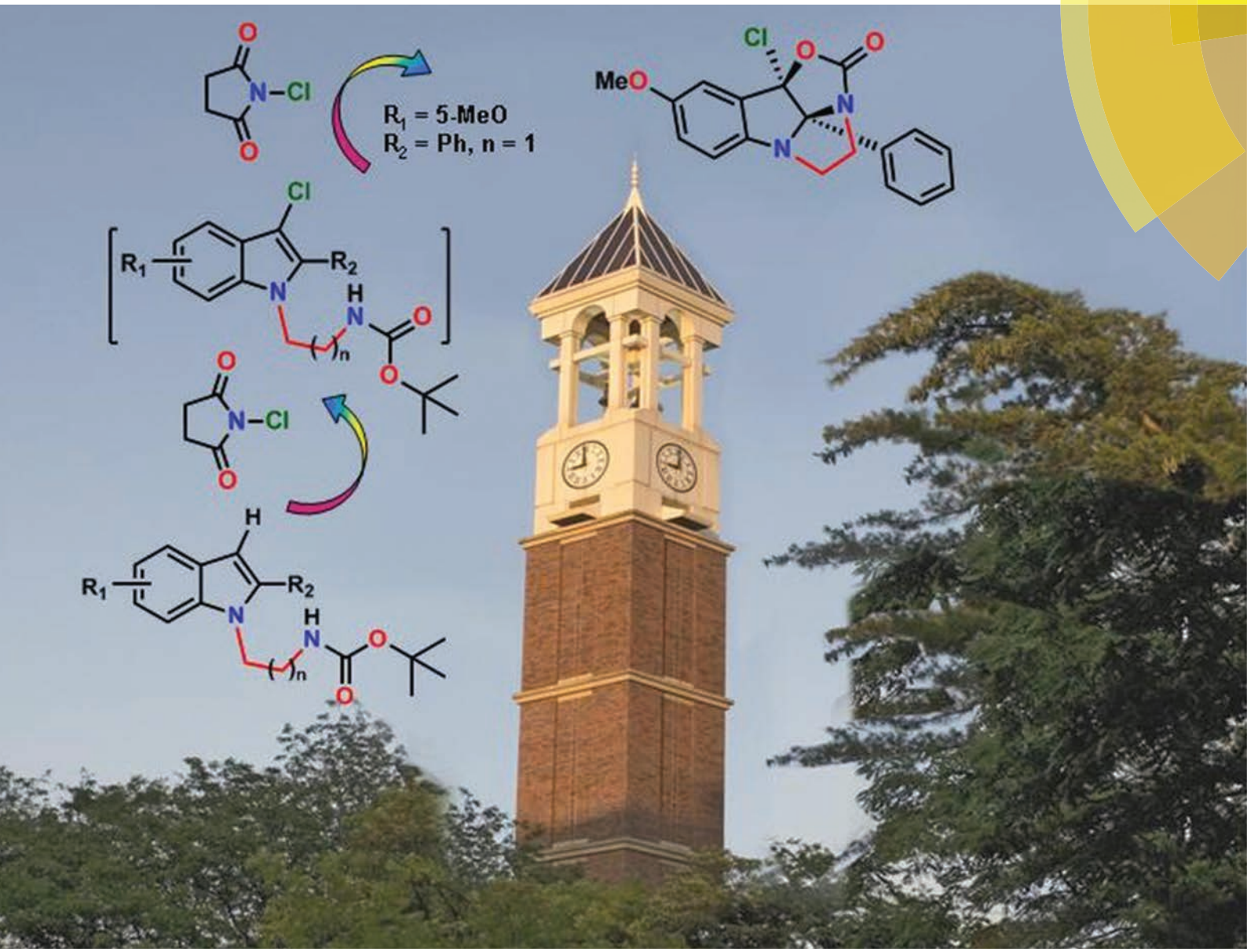

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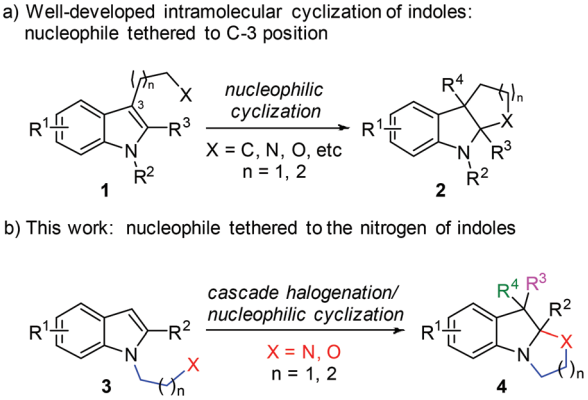
An intramolecular cascade cyclization of 2-aryl indoles: efficient methods for the construction of 2,3-functionalized indolines and 3-indolinones†

Arun K. Ghosh* and Zhi-Hua Chen

Efficient intramolecular *N*/*O*-nucleophilic cyclization of 2-aryl indoles has been developed to afford the corresponding 2-aza-3-oxaindolines and 3-indolinones in 80–95% yield. The methods provided convenient access to fused imidazo[1,2-*c*]oxazolidinone, oxazolidine, or tetrahydro-1,3-oxazine cores under mild conditions.

Functionalized indole rings are one of the most abundant and important heterocycles that occur ubiquitously in bioactive natural products, pharmaceuticals and agrochemicals.[1,2] Consequently, practical and atom-economical modifications of the indole structure have long been a subject of immense interest in organic and medicinal chemistry.[3–5] Among them, intramolecular C2-functionalization of indoles such as *C*-,[6] *N*-,[7] *O*-,[8] and *S*-nucleophilic cyclizations[9] have received much attention since they provide straightforward access to indolines with a fused-ring substructure (Scheme 1a). However, to date, these transformations have mainly focused on indole-based substrates with a pendant nucleophile tethered at the C3 position. Intramolecular cyclization of indole with a nucleophile attached to the nitrogen atom to construct an *N*-fused indoline has rarely been reported.[10] Moreover, *N*-fused indolines exist widely throughout nature and have considerable biological and pharmaceutical importance.[11,12] Therefore, development of efficient synthetic methods toward the formation of *N*-fused indolines is important for their utilization in medicinal and biological chemistry. In connection with our work on the design and synthesis of ligands to probe enzyme active sites, we became interested in functionalized indole derivatives. Herein, we present our studies on the cascade halogenation/intramolecular nucleophilic cyclization of 2-aryl indoles to construct 2-aza-3-oxaindolines and 3-indolinones (Scheme 1b).



Scheme 1 Intramolecular nucleophilic cyclization of indoles.

As indicated in Table 1, our studies commenced with the halogenation/cyclization of **5a**,[13] a model substrate that possesses an NHBoc group as the pendant nucleophile. We envisagated that the potential reactivity of indoles toward electrophilic halogenating reagents, such as *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS), might offer a starting point to identify suitable reaction conditions. Disappointingly, the reactions of **5a** with NBS in CCl_4 at 0 °C or 23 °C under argon both gave complex mixtures (entry 1), and no desired cyclization product was obtained. However, the hypothesized halogenation/cyclization can be carried out employing NCS as an electrophilic reagent, producing an unprecedented polycyclic indoline **6a** in 41% yield. As shown, the indoline derivative contains the expected imidazolidine ring along with an unexpected fused oxazolidinone functionality (entry 2). The structure of **6a** was unambiguously established using ^1H, ^{13}C, and 2D NMR spectra. Optimization of the reaction was next investigated by varying the solvent. The reaction yield increased to 53% when CH_2Cl_2 was used in comparison with CCl_4, toluene, or Et_2O (entries 2–5). Subsequently, reaction temperature, time and the amount of NCS were screened to improve the reaction efficiency (entries 6–9). The best result was obtained (91% yield) when the reaction was performed with 3 equiv. of NCS at

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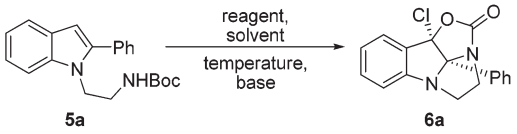
† Electronic supplementary information (ESI) available: Experimental procedure and characterization data of new compounds. See DOI: 10.1039/c4ob00511b

Table 1 Validation and optimization of the *N*-nucleophilic cyclization[a]

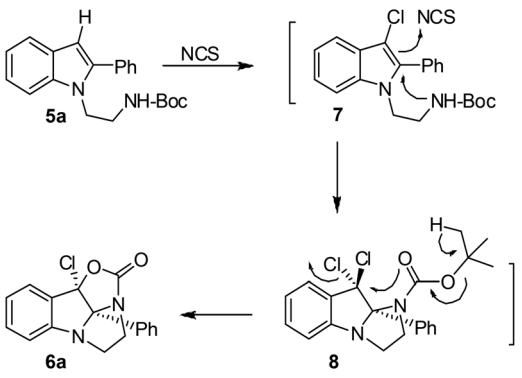


5a 6a

Entry	Halogenating reagent	Solvent	Temp (°C)	Time (h)	Base	Yield[b] (%)
1	NBS (2 eq.)	CCl_4	0/23	1	—	—
2	NCS (2 eq.)	CCl_4	23	2	—	41
3	NCS (2 eq.)	Toluene	23	2	—	46
4	NCS (2 eq.)	CH_2Cl_2	23	2	—	53
5	NCS (2 eq.)	Et_2O	23	24	—	10
6	NCS (2 eq.)	CH_2Cl_2	0	7	—	73
7	NCS (3 eq.)	CH_2Cl_2	0	3.5	—	91
8	NCS (3 eq.)	CH_2Cl_2	−10	24	—	85
9	NCS (4 eq.)	CH_2Cl_2	0	2	—	65
10[c]	NCS (3 eq.)	CH_2Cl_2	0	3.5	$NaHCO_3$	90
11[c,d]	NCS (3 eq.)	CH_2Cl_2	0	3.5	$KHCO_3$	88
12[c]	NCS (3 eq.)	CH_2Cl_2	0	3.5	K_2CO_3	91
13[d]	NCS (3 eq.)	CH_2Cl_2	0	3.5	—	71

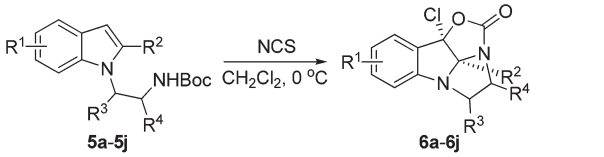
[a] All reactions were performed with 0.2 mmol of **5a** in 2 mL of solvent under argon. [b] Isolated yield. [c] 3 equiv. of base. [d] Reaction performed under air. NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide.

0 °C under argon for 3.5 h (entry 7). It should be noted that only 3-chloroindole was observed upon treatment of **5a** with 1 equiv. of NCS.[14] This observation showed that excess NCS was critical to initiate the cascade cyclization and hydrogen chloride might be generated in this process (pH = 2–3). Accordingly, we attempted to add bases such as $NaHCO_3$, $KHCO_3$, or K_2CO_3 to neutralize the presumed acid. However, no obvious improvement was obtained (entries 10–12), indicating that acidic or basic conditions had no apparent influence on the reaction. Additionally, we found that when the reaction was carried out in the presence of air, the yield of **6a** was substantially reduced (entries 11 and 13). Reactions described above with different conditions all gave polycyclic indoline **6a** as a single *cis* diastereoisomer (entries 2–13), demonstrating the high diastereoselectivity of this cascade reaction. Presumably, the reaction of **5a** with NCS first proceeded with the formation of 3-chloroindole **7**. It then underwent an NCS-promoted intramolecular cyclization as shown in intermediate **8** with the extrusion of isobutene to provide the cyclization product **6a** (Scheme 2).

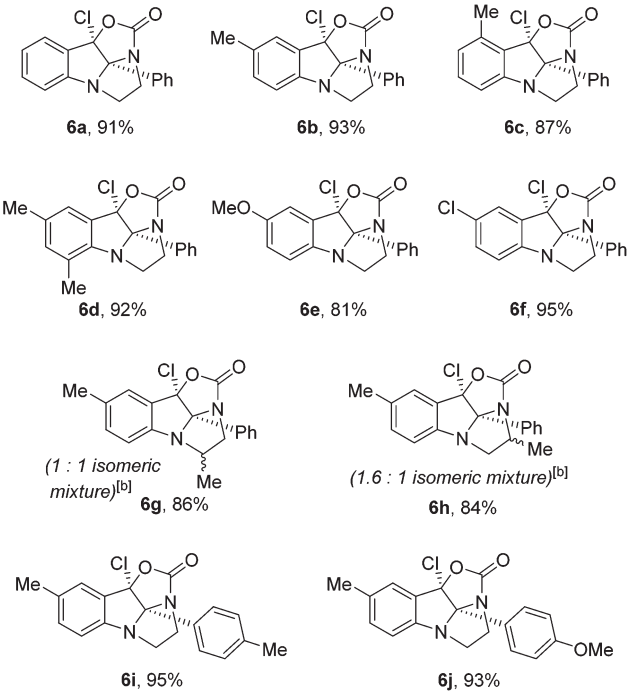


Scheme 2 Intramolecular cascade cyclization of 2-aryl indole **5a**.

Table 2 Substrate scope of the *N*-nucleophilic cyclization[a]



5a-5j 6a-6j



[a] Substrate **5** (0.2 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 mL) at 0 °C under argon followed by addition of NCS (0.6 mmol). [b] The ratio of diastereoisomers was determined by ^1H NMR. NCS = *N*-chlorosuccinimide.

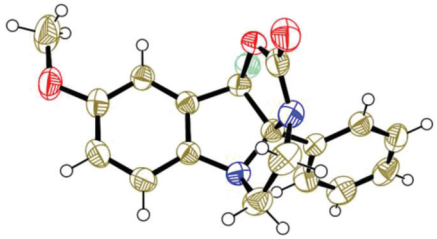


Fig. 1 X-ray structure of **6e**.

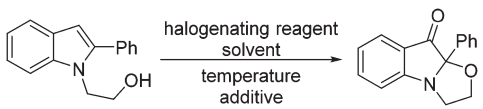
Under the optimized reaction conditions, the scope of this cascade chlorination/cyclization has been explored using different substitutions. As summarized in Table 2, indole scaffolds possessing electron-donating (5-Me, 4-Me, 5,7-dimethyl, and 5-MeO) or halogen (5-Cl) substituents on the benzenoid ring were well-tolerated and excellent yields were obtained (81–95%, **6b–6f**). In contrast, highly deactivated indole bearing a strong electron-withdrawing group (5-NO_2) failed to afford the desired cyclization product. Furthermore, indoles incorporating various methyl-substituted pendant nucleophiles (**5g** and **5h**) underwent the reaction to give products **6g** and **6h** in 86% and 84% yields, respectively. Substitution of the 2-phenyl ring with *p*-methyl or *p*-methoxy substituents (**5i** and **5j**) was also found to give suitable substrates for cyclization, delivering products **6i** and **6j** in 95% and 93% yields, respectively.

A single-crystal X-ray analysis of compound **6e** further confirmed the structure of the halogenation/cyclization product (Fig. 1).[15] Of particular interest, the highly functionalized indoline products **6a–6j**, which possess a new and interesting fused heterocyclic skeleton in common, might have potential applications in biological and material studies.

We have also investigated the development of a parallel halogenation/cyclization of the indole substrates bearing an *O*-nucleophile at the *N*-1 position. Our initial attempt was the reaction of 2-phenylindole **9a**[16] and NCS in CCl_4 at 0 °C under air (Table 3, entry 1). Interestingly, the cyclization proceeded smoothly to afford 3-indolinone **10a** in 50% yield instead of the anticipated C3 monochlorinated indole. The structure of **10a** was confirmed using ^1H, ^{13}C, and 2D NMR spectra. Considering that the oxygen of the newly formed carbonyl group in **10a** might be originating from H_2O in air, we added 3 equiv. of H_2O in the reaction and obtained **10a** in 55% yield (entry 2). We then turned our attention to screening of the solvent and the reaction temperature (entries 3–5). Performing the reaction in CH_2Cl_2 at 23 °C reduced the reaction time and increased the yield to 81% (entry 5). Furthermore, a survey of the base additive along with H_2O was found to accelerate the reaction and improve the yield up to 94% (entries 6–8). This observation is in contrast to the *N*-nucleophilic cyclization described above in which a base additive was not essential.

We further examined a range of indoles with different substitutions. As it turned out, the substrates also underwent the *O*-nucleophilic cyclization under our optimized conditions (Table 4).[17] Indoles bearing electron-donating substituents (5-Me, 4-Me, 7-Me, 5,7-dimethyl, and 5-OMe) on the benzenoid ring worked well, leading to the formation of the cyclization products **10b–10f** in excellent yields (91–95%). When 7-methyl-substituted indole **9d** was used, product **10d** was obtained under standard conditions. Interestingly, chlorination of the indole ring also occurred by increasing the amount of NCS (5 equiv.) and prolonging the reaction time (24 h), affording **10d′** in 93% yield. The electronic nature of the substrate has a slight influence on the reactivity, as indoles **9g** and **9h** with an electron-withdrawing group (5-Cl and 5-NO_2) required longer reaction times and provided relatively lower yields (83% and 80%). The reaction of indoles **9i–9k** with different aryl groups at the C2 position including *p*-MeC_6H_4, *p*-$MeOC_6H_4$, and 1-naphthyl also proceeded effectively to furnish the desired products **10i–10k** in 82–93% yield. Furthermore, formation of a tetrahydro-1,3-oxazine instead of an oxazolidine in this *O*-nucleophilic cyclization was examined. Indole **9l** with an expanded nucleophile was well-tolerated for this reaction,

Table 3 Validation and optimization of the *O*-nucleophilic cyclization[a]

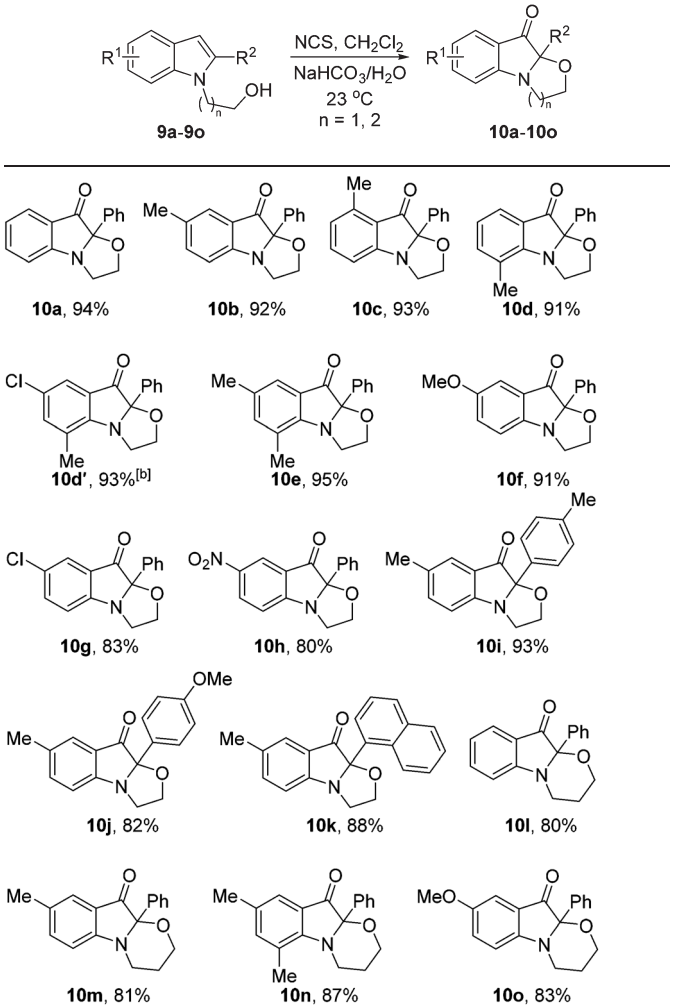


9a **10a**

Entry	Halogenating reagent	Solvent	Temp (°C)	Time (h)	Additive[b]	Yield[c] (%)
1	NCS (2 eq.)	CCl_4	0	15	—	50
2	NCS (2 eq.)	CCl_4	0	15	H_2O	55
3	NCS (2 eq.)	Toluene	0	17	H_2O	48
4	NCS (2 eq.)	CH_2Cl_2	0	12	H_2O	65
5	NCS (2 eq.)	CH_2Cl_2	23	7	H_2O	81
6	NCS (2 eq.)	CH_2Cl_2	23	5	H_2O/K_2CO_3	85
7	NCS (2 eq.)	CH_2Cl_2	23	5	$H_2O/KHCO_3$	90
8	NCS (2 eq.)	CH_2Cl_2	23	5	$H_2O/NaHCO_3$	94

[a] All reactions were performed with 0.2 mmol of **9a** in 2 mL of solvent under air. [b] 3 equiv. of H_2O and base. [c] Isolated yield. NCS = *N*-chlorosuccinimide.

Table 4 Substrate scope of the *O*-nucleophilic cyclization[a]



[a] Substrate **9** (0.2 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 mL) at 23 °C under air followed by addition of $NaHCO_3$ (0.6 mmol), H_2O (0.6 mmol), and NCS (0.4 mmol). [b] Treatment of **9d** (0.2 mmol) with $NaHCO_3$ (1.5 mmol), H_2O (1.5 mmol), and NCS (1.0 mmol) in freshly distilled CH_2Cl_2 (3 mL) at 23 °C under air for 24 h. NCS = *N*-chlorosuccinimide.

producing the expected product **10l** in 80% yield. Other indoles **9m–9o** with different substituents (5-Me, 5,7-dimethyl, and 5-OMe) on the benzenoid ring were also suitable for cyclization. In contrast to the formation of oxazolidine (**10a**, **10b**, **10e**, and **10f**), the cyclization pattern with larger tethers was slightly less favored, as **10l–10o** were obtained in relatively lower yields (80–87%). Single-crystal X-ray analysis of **10e** further confirmed the structure of the *O*-nucleophilic cyclization product (Fig. 2).[15] Overall, the described *O*-nucleophilic cyclization has proved to be efficient and economical in comparison with previous syntheses of 3-indolinone **10a** and its analogs.[9]

In summary, we have developed a new cascade chlorination/cyclization of 2-aryl indoles bearing an *N*-nucleophile. A range of polycyclic indolines were prepared in 81–95% yield

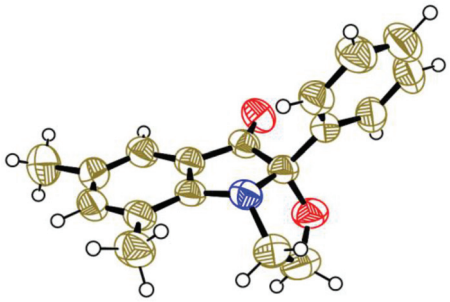


Fig. 2 X-ray structure of **10e**.

by this process that simultaneously generates a fused imidazo-[1,2-*c*]oxazolidinone skeleton and incorporates two adjacent hetero-quaternary stereocenters. Furthermore, we developed an *O*-nucleophilic cyclization in which a number of tricyclic tetrahydrooxazolo[3,2-*a*]indoles and tetrahydro-1,3-oxazino[3,2-*a*]-indoles were effectively assembled in 80–95% yield. The mild conditions and practical convenience of both reactions make these methods valuable synthetic tools. Further studies including mechanistic investigations on the potential bioactivity of these novel compounds are currently ongoing in our laboratory.

Acknowledgements

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