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$POCl_3$ mediated one-pot deoxygenative aromatization and electrophilic chlorination of dihydroxy-2-methyl-4-oxo-indeno[1,2-*b*]pyrroles†

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A class of indenopyrroles is presented by the treatment of known dihydroxy-2-methyl-4-oxoindeno[1,2-*b*]pyrroles with phosphorus oxychloride ($POCl_3$). The elimination of vicinal hydroxyl groups at the **3a** and **8b** positions, formation of a π bond, and electrophilic chlorination of the methyl group attached to C^2 resulted in the fused aromatic pyrrole structures. Benzylic substitution of various nucleophiles such as H_2O, EtOH, and NaN_3 with a chlorine atom gave diverse 4-oxoindeno[1,2-*b*]pyrrole derivatives in 58 to 93% yields. The reaction was investigated in different aprotic solvents, and the highest reaction yield was obtained in DMF. The structures of the products were confirmed by spectroscopic methods, elemental analysis, and X-ray crystallography.

Introduction

Deoxygenation–chlorination of oxygen-containing organic compounds is essential in synthesizing a variety of organic and biological materials.[1] Phosphorus oxychloride ($POCl_3$), owing to its outstanding position among the phosphorus-based reagents, plays a prominent role in these transformations. Simultaneous chlorination during deoxygenation using $POCl_3$ could occur by electrophilic or nucleophilic substitution. *N*-oxide and *S*-oxide derivatives of nitrogen or sulfur-bearing heterocycles are typical examples of materials used in these reactions.[2] Furthermore, the great attention paid to $POCl_3$ stems from its diverse applications in chlorination,[3] dehydration,[4] Bischler–Napieralski cyclization,[5] and Vilsmeier–Haack formylation.[6] Dihydroxy-4-oxo-indeno[1,2-*b*]pyrroles possessing two vicinal hydroxyl groups have been deoxygenated by reagents such as triphenylphosphine (route A in Scheme 1),[7] thionyl chloride,[8] and tetraalkylthionylamides ($(NR_2)_2SO$) (route B in Scheme 1).[8,9]

The aromatic 4-oxo-indeno[1,2-*b*]pyrroles have been produced due to the elimination of vicinal hydroxyl groups and the formation of π bond during these reactions. It is noteworthy that other methods have also synthesized 4-oxo-indeno[1,2-*b*]pyrroles as potent human protein kinase CK2 inhibitors;[9] for example, intramolecular cyclization of 5-(*o*-carboxyphenyl) pyrroles *via* trifluoroacetic anhydride (route C in Scheme 1),[10] and copper-catalyzed coupling reaction of 1-(2-iodoaryl)-2-yn-1-ones with isocyanides (route D in Scheme 1).[11]

$POCl_3$ can form phosphate ester through the reaction with alcohols, phenols, and epoxides based on the inherent affinity of phosphorus for oxygen.[12] Meanwhile, vicinal diols can construct cyclic phosphate ester, which is stable as long as there is no stimulating factor to open the ring.[13]

Regard to our recent interest in the study of indenopyrrole structures[14] due to their biological activities,[15] herein, we report an efficient $POCl_3$-mediated deoxygenation–chlorination of dihydroxy-2-methyl-4-oxo-indeno[1,2-*b*]pyrroles *via* a cyclic chlorophosphate ester intermediate to achieve novel derivatives of 2-(chloromethyl)-4-oxo-indeno[1,2-*b*]pyrrole. Nucleophilic substitution of several nucleophiles, such as H_2O, EtOH, and NaN_3, with the chlorine atom, resulted in the related products.

Results and discussion

At the outset, we aimed to formylate the *ortho* position of the hydroxyl group of the phenyl ring in compound **1f** with Vilsmeier–Haack reagent ($POCl_3$/DMF) at 60 °C. Surprisingly, product **3e** was isolated as a major product after hydrolysis instead of formylated product **f*** (Scheme 2). It seems that **3e** with a hydroxymethyl group (OH-product) is a result of the hydrolysis of a chloromethyl derivative (Cl-product) which is primarily formed under the action of $POCl_3$ reagent.

Based on the above results, we proposed a mechanism that has been shown as Scheme 3. First, nucleophilic attack of the two vicinal hydroxyl groups of compound **1** on the phosphorus atom of $POCl_3$ and loss of two moles of HCl leads to the formation of intermediate $\mathbf{Im_1}$ as a cyclic chlorophosphate ester. Enol tautomer of $\mathbf{Im_1}$ shows the nucleophilicity of the methyl group attached to C^2 that can take electrophilic chlorine

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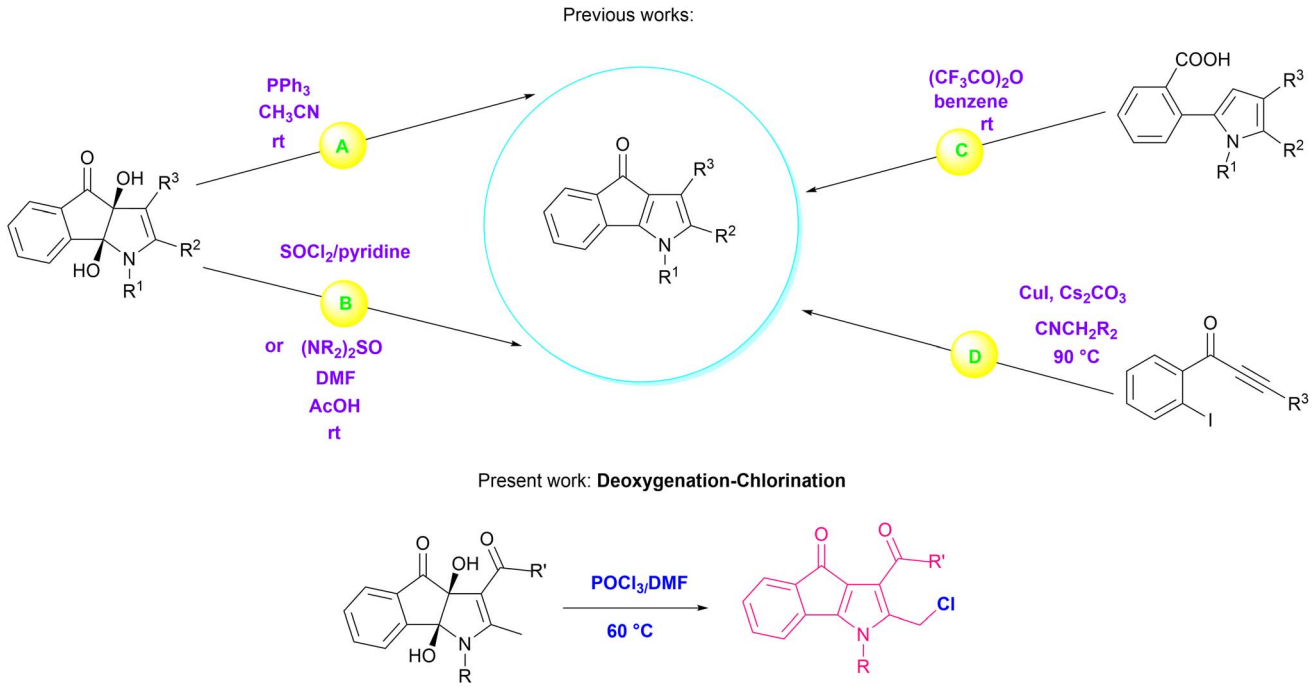
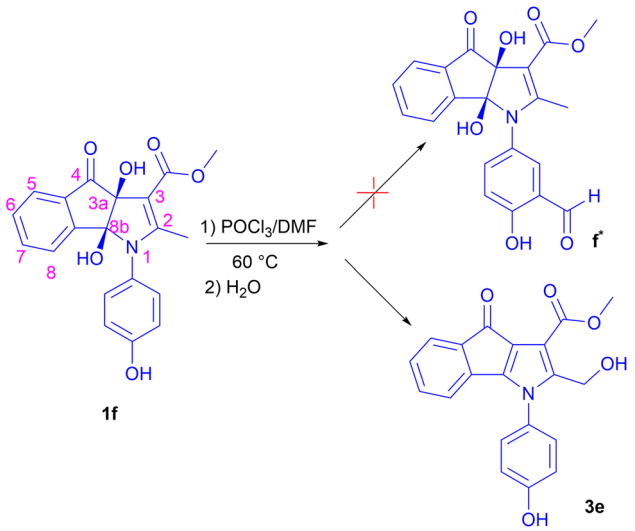


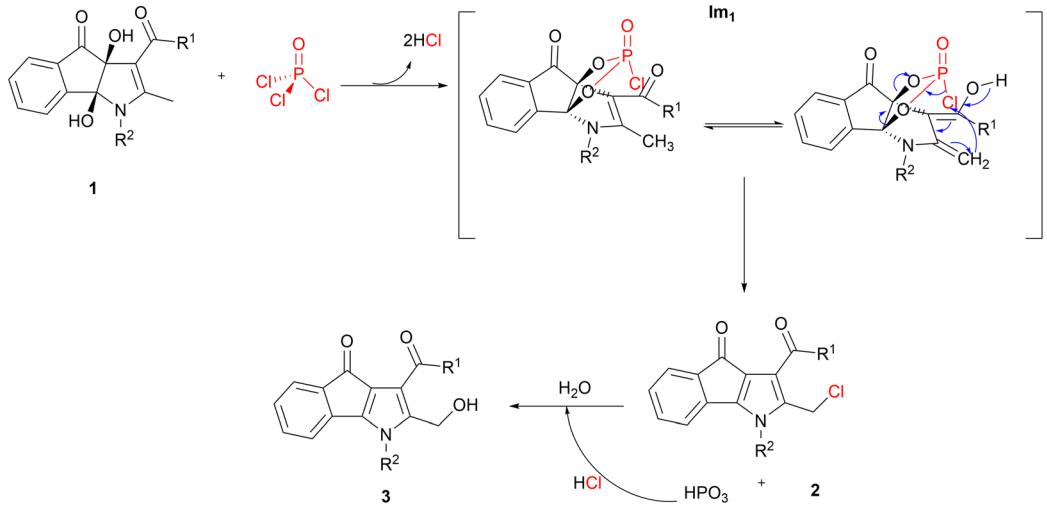
Scheme 1 Known synthesis methods of 4-oxo-indeno[1,2-*b*]pyrroles and our novel synthesis strategy.



Scheme 2 Formation of product **3e** under Vilsmeier–Haack reaction instead of product **f***.

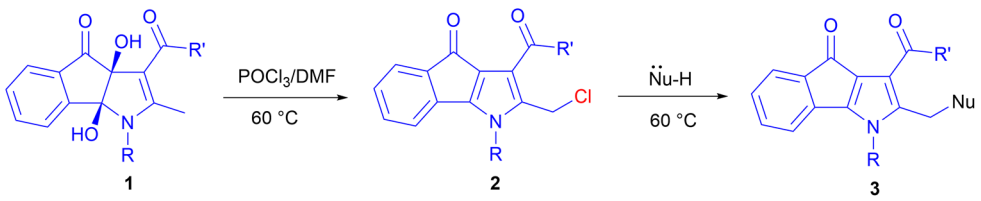
linked to the chlorophosphate ester ring. Chlorination of the benzylic methyl group is accompanied by opening the phosphate ester ring, deoxygenation at **3a** and **8b** positions and the formation of π bond in these positions. Cl-product **2** and metaphosphoric acid (HPO_3) are finally produced (Scheme 3). At last, adding water to the reaction mixture hydrolyses **2**, resulting in the OH-product **3**. Whereas, applying alkaline hydrolysis to accelerate the nucleophilic substitution and neutralize the acidic medium of the reaction caused the decomposition of the product **3**.

To explore the generality of the reaction on substrate scope, a variety of known dihydroxy-2-methyl-4-oxo-indeno [1,2-*b*]pyrroles (**1a–i**,[14] Table 1) were employed in these reactions to the synthesis of diverse 4-oxo-indeno[1,2-*b*]pyrrole derivatives. The related products were obtained with moderate to excellent yields (entries 1–15). We separated the Cl-products in some of the derivatives, which were a precipitate in the reaction mixture (**2a–c**, entries 1–3). Cl-product **2d** was also separated as a major product after the addition of water at room temperature and fast filtration of the formed precipitate (entry 4). Whereas, adding water and stirring the mixture at 60 °C afforded the OH-product **3d** (entry 9). Treatment of **1e** with $POCl_3$ in DMF led to the Cl-product **2e**, which was isolated as the only reaction product after adding water and extraction with chloroform. This indicates that compound **2e** does not tend to hydrolyze (entry 5). To confirm the formation of the primary Cl-products **2**, their nucleophilic substitutions with H_2O, EtOH, and NaN_3 were also examined, and hydroxymethyl (**3a**, **3b** and **3d–h**), ethoxymethyl (**3c** and **3i**), and azidomethyl (**3j**) derivatives were obtained respectively (entries 6–15). Furthermore, the positivity of the NaI in acetone test[16] on all the isolated chlorinated derivatives (**2a–e**) proved the formation of the primary Cl-products. Among the substrates **1**, those containing electron-donating groups attached to the phenyl ring of the N1 position represented higher yield and rate reaction compared to substrates bearing the electron-withdrawing groups, especially the nitro group. It seems that electronic resonance of the phenyl ring containing the electron-donating groups with electrons of the pyrrole ring towards the acetyl or ester group attached to C3 causes more acidity of the methyl hydrogens linked to C2,



Scheme 3 A plausible reaction mechanism.

Table 1 Substrate scope of dihydroxy-2-methyl-4-oxo-indeno[1,2-*b*]pyrroles[a]



Entry	R′	R	Substrate	Nucleophile	Time (h)	Product	Yield[b] %
1	OMe	C_6H_5	**1a**	—	3.5	**2a**	74
2	OEt	4-ClC_6H_4	**1b**	—	3	**2b**	67
3	OMe	4-$O_2NC_6H_4$	**1c**	—	7	**2c**	53
4	O^{t}Bu	*n*-Butyl	**1d**	—	0.25	**2d**	68
5	Me	3-(*N*-Morpholino)propyl	**1e**	—	1.5	**2e**	65
6	OMe	C_6H_5	**1a**	H_2O	3.5	**3a**	81
7	OEt	4-ClC_6H_4	**1b**	H_2O	3	**3b**	81
8	OMe	4-$O_2NC_6H_4$	**1c**	EtOH	24	**3c**	58
9	O^{t}Bu	*n*-Butyl	**1d**	H_2O	0.25	**3d**	76
10	OMe	4-OHC_6H_4	**1f**	H_2O	3	**3e**	93
11	O^{t}Bu	4-$MeOC_6H_4$	**1g**	H_2O	3	**3f**	87
12	O^{t}Bu	4-MeC_6H_4	**1h**	H_2O	3	**3g**	83
13	OMe	2-$OMeC_6H_4$	**1i**	H_2O	1.5	**3h**	80
14	OEt	4-ClC_6H_4	**1b**	EtOH	24	**3i**	75
15	OEt	4-ClC_6H_4	**1b**	NaN_3	3	**3j**	70

[a] Reactions were carried out using 1.0 mmol of substrates and 1.3 mmol of $POCl_3$ in DMF (2 mL) at 60 °C (**2a–e** and **3a–j**). [b] Isolated yield.

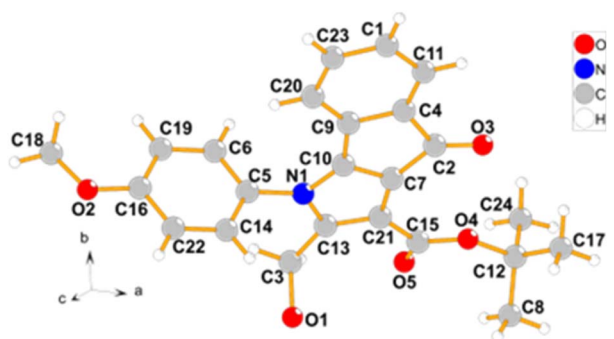
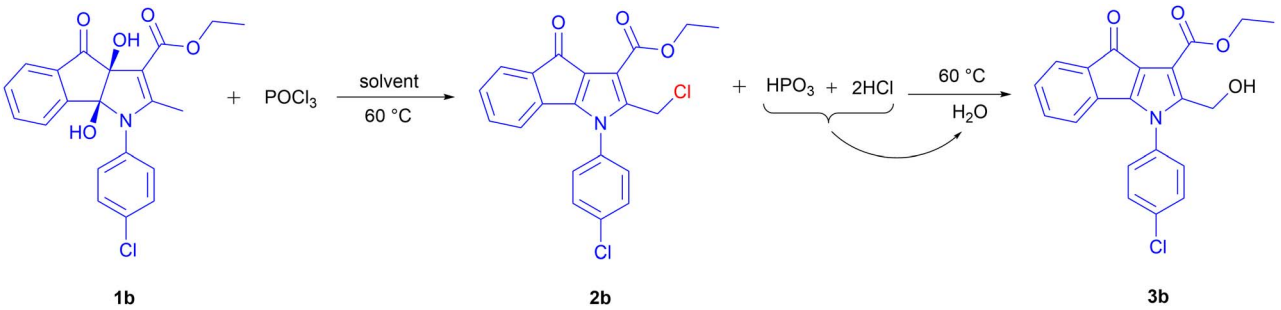


Fig. 1 Molecule of **3f** determined by X-ray crystallographic analysis. Labels of hydrogen atoms were omitted for clarity.

which itself is a driving factor for the fast opening of the phosphate ester ring. The reaction time presented in Table 1 is related to the disappearance of substrate **1**. Moreover, to confirm the assigned structure, a single crystal of **3f** was determined using X-ray crystallography (Fig. 1). Orange crystals of **3f** were formed through slow diffusion of *n*-hexane over a saturated chloroform solution. The compound **3f** crystallizes in the monoclinic crystal system and $P2_1/c$ space group. The X-ray crystallographic study unambiguously elucidated the coplanar indanone–pyrrole–phenyl network. The hydroxyl group bonded to methylene attached to C2 was also verified.

Table 2 Investigation of the solvent effect



1b 2b 3b

Entry	Solvent (dry)	Time (h)	Yield% (**3b**)	Entry	Solvent (dry)	Time (h)	Yield% (**3b**)
1	$CHCl_3$	5	10	3	DMF	3	81
2	CH_3CN	5	15	4	THF	3	70

Finally, to investigate the effect of solvent, substrate **1b** was treated with $POCl_3$ in different dry aprotic solvents such as THF, DMF, $CHCl_3$, and CH_3CN (Table 2). TLC from the reaction mixtures showed the formation of both Cl-product **2b** and OH-product **3b**. Although there was no water in the reaction medium, observation of the OH-product **3b** could be due to water formation during the reaction. According to the mechanism presented in Scheme 2, the generated H_2O in the reaction probably originates from the reaction of HPO_3 and HCl. Eventually, the highest yield and reaction rate was acquired in DMF.

Conclusions

In summary, we have disclosed an exciting deoxygenation–chlorination transformation of known dihydroxy-2-methyl-4-oxo-indeno[1,2-*b*]pyrroles *via* $POCl_3$ reagent in DMF. This reaction caused electrophilic chlorination of the benzylic methyl group attached to C^2 accompanied by dehydroxyalation at **3a** and **8b** positions and the formation of π bond. The cyclic chlorophosphate ester served as a key intermediate in this reaction to achieve 2-(chloromethyl)-4-oxo-indeno[1,2-*b*]pyrroles. Moreover, several nucleophiles such as H_2O, EtOH, and NaN_3 participated in benzylic substitution with a chlorine atom, leading to a variety of 4-oxoindeno[1,2-*b*]pyrroles in moderate to excellent yields. Furthermore, the evaluation of the solvent effect on the yield and reaction rate revealed that the highest reactivity and efficiency were acquired in DMF. We synthesized 15 novel compounds (**2a–e** and **3a–j**) in this work.

Conflicts of interest

There are no conflicts to declare.

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