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A mild and efficient synthesis of spiroquinolinones *via* an unexpected rearrangement

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ABSTRACT

A mild and efficient synthesis of spiroquinolinones **6** *via* condensation of chlorooxoindolines **5** and benzene-1,2-diamines **3** is reported. Instead of expected spirooxindole product **4'**, spiroquinolinones **6** were isolated in up to 95% yield. A plausible mechanism involving an interesting ring rearrangement to form spiroquinolinones is proposed.

The spirooxindole motif is a unique architecture found in many natural products and synthetic drugs.[1] After the discovery of NITD609 as a new chemotype with a novel mechanism of action for the treatment of malaria (Figure 1),[2] we recently identified another spirooxindole **1** with promising anti-dengue activity.[3] These interesting findings further enhanced our confidence and interest in the design and synthesis of further novel spirooxindole scaffolds as potential drug lead candidates.[4]

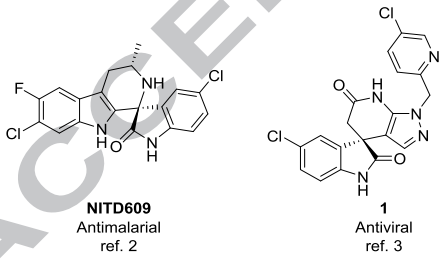
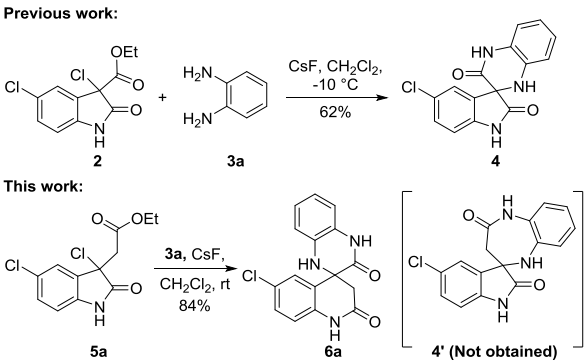


Figure 1. Spriooxindoles identified as possessing antimalarial and antiviral activity.

Previously, we reported a new approach for the synthesis of spriooxindole **4** by condensation of chloroxoindoline **2** with benzene-1,2-diamines **3a** under mild conditions (Scheme 1).[4b] Following a similar approach, we attempted to use compound **5a** with an extended methylene as the substrate for this reaction. However, to our surprise under similar reaction conditions, spiroquinolinone **6a** was formed with excellent yield (84%) instead of the expected spirooxindole **4'** (Scheme 1). The structure of compound **6a** was unambiguously confirmed by single crystal X-ray analysis (Figure 1).[5]



Scheme 1. Synthesis of unexpected spiroquinolinone **6a**.

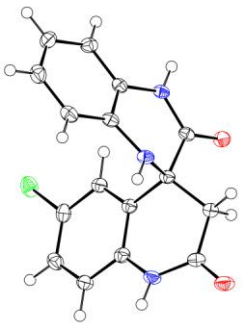


Figure 1. The X-ray crystal structure of compound **6a**.

Following this interesting observation, herein, we report the synthesis of a series of novel spiroquinolinones. We initially

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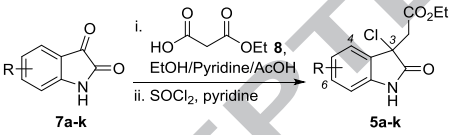
investigated the reaction conditions to study the effect of changing solvent and base (Table 1). When organic bases, Et_3N and DABCO were utilized, the yield of product **6a** was significantly reduced (Entries 2 and 3). Product **6a** was isolated with similar yield to the original experiment (86%) when Cs_2CO_3 was utilized as the base (Entry 4). Further screening of inorganic bases revealed that basicity was critical for the yield (Entries 4-6). For example, only a trace amount of product was isolated when the less reactive base Li_2CO_3 was used (Entry 6). Chlorinated solvents, such as 1,2-dichloroethane, gave a similar yield of **6a** (85%, Entry 7). However, polar solvents, such as THF and DMF, produced relatively low yields (56% and 54%, respectively) of the desired product (Entries 8 and 9).

Table 1 Optimization of the reaction conditions.

Entry	Conditions[a]	Yield (%)[b]
1	CsF, CH_2Cl_2,	84
2	Et_3N, CH_2Cl_2,	11
3	DABCO,[c] CH_2Cl_2	0
4	Cs_2CO_3, CH_2Cl_2	86
5	Na_2CO_3, CH_2Cl_2	61
6	Li_2CO_3, CH_2Cl_2	trace
7	Cs_2CO_3, $ClCH_2CH_2Cl$	85
8	Cs_2CO_3, THF	56
9	Cs_2CO_3, DMF	54

[a]Molar ratio of **5a**/**3a** 0.20/0.40 mmol, base (1 mmol), rt, 16 h; [b]Isolated yield; [c]1,4-diazabicyclo[2.2.2]octane

In order to examine the substrates scope for this reaction, a series of substituted 3-chlorooxoindolines **5a-k** were synthesized *via* condensation of substituted isatins **7a-k** with mono-ethyl malonate **8** followed by chlorination with thionyl chloride (Scheme 2).[6,7]

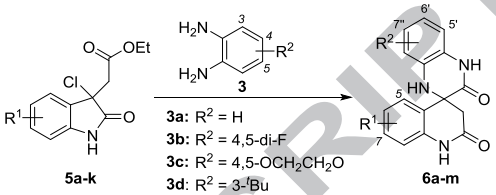


5a: (R = 5-Cl) 76%* **5g:** (R = 5-F) 40%
5b: (R = 4-Cl) 35% **5h:** (R = 5-NO_2) 40%
5c: (R = 6-Cl) 33% **5i:** (R = H) 24%
5d: (R = 7-Cl) 37% **5j:** (R = 5-Me) 14%
5e: (R = 5-OMe) 53% **5k:** (R = 5-^{t}Bu) 12%
5f: (R = 5-OCF_3) 41%
*All yields are over two steps

Scheme 2 Synthesis of 3-chlorooxoindolines **5a-k**.

With a diverse set of 3-chlorooxoindolines **5** in hand, the condensation with diamines **3a-f** was investigated (Table 2).[8] In general, good to excellent yields were observed. For instance, substrates **5a-d** with Cl-substitution at different positions gave compounds **6a-d** in good yields (Table 2, entries 1-4), although the yield of **6c** was somehow lower (61%). As a trend, compounds with electron-donating groups at the 6-position appear more favorable compared to electron-withdrawing groups (Table 2, entries 5-8). For example, product **6e** with 6-OMe substitution was isolated in 88% yield, while compound **6h** with 6-NO_2 substitution was obtained in only 31% yield. A steric effect at the 6-position was not apparent since products **6i-k** were isolated in similar yields (62-65%, Table 2, entries 9-11). These findings were not surprising since 5-substitution of 3-chlorooxoindolines **5i-k** should have only a marginal steric effect on reactivity. 4,5-Di-substiuted diamines **3b-c** gave the corresponding products **6l** and **6m** in 95% and 78% yields, respectively (entries 12-13). In the case of mono-substituted diamines (**3d-f**), the electronic and steric effect of the substituents differentiates the nucleophilicity of the two amino groups, impacting the regioselectivity of the observed products.[4b] Both **3d** (3-^{t}Bu) and **3e** (4-OMe) afforded single regioisomers **6n** and **6o**, respectively (Table 2, entries 14-15). However, in **3f,** the 4-Cl had less impact on the nucleophilicity of the two amino groups, leading to an inseparable 1:1 mixture of **6p** and **6q** (determined by ^{1}H NMR analysis, entry 16).

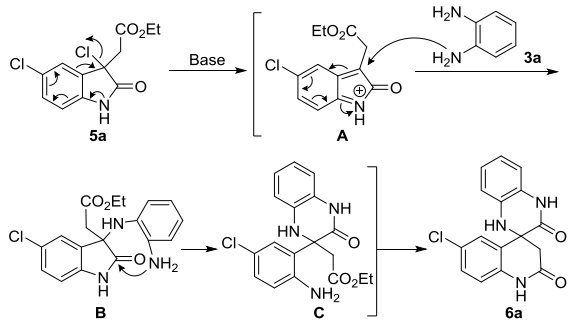
Table 2 Synthesis of spiroquinolinones **6a-m**.[a]



Entry	Compound	R^1	R^2	Yield (%)[b]
1	**6a**	6-Cl	H	86
2	**6b**	5-Cl	H	85
3	**6c**	7-Cl	H	61
4	**6d**	8-Cl	H	81
5	**6e**	6-OMe	H	88
6	**6f**	6-OCF_3	H	79
7	**6g**	6-F	H	70
8	**6h**	6-NO_2	H	31
9	**6i**	H	H	62
10	**6j**	6-Me	H	65
11	**6k**	6-^{t}Bu	H	62
12	**6l**	6-Cl	6',7'-di-F	95
13	**6m**	6-Cl	6',7'-OCH_2CH_2O	78
14	**6n**	6-Cl	5'-^{t}Bu	64
15	**6o**	6-Cl	6'-OMe	78
16	**6p**	6-Cl	6'-Cl	77[c]
	6q	6-Cl	7'-Cl	

[a]Reaction conditions: Molar ratio of **5**:**3** 0.20/0.40 mmol, Cs_2CO_3 (1 mmol), CH_2Cl_2, rt, 16 h; [b]Isolated yield; [c]Total yield of **6p** and **6q**.

A plausible mechanism for this condensation to form the spiroquinolinones is proposed (Scheme 3). Elimination of chloroxoindoline **5a** in the presence of base affords indolone intermediate **A**, which undergoes nucleophilic attack by benzene-1,2-diamine **3a** to give intermediate **B**. The primary amine of intermediate **B** attacks the carbonyl of the oxindoline to give aniline intermediate **C**, which is further transformed to the spiro-6,6-ring system product **6a** by intramolecular lactamization.[9] To the best of our knowledge, this is the first case reported involving an oxindoline rearrangement to form a spiroquinolinone.[10]



Scheme 3. Proposed mechanism of the reaction.

In summary, a mild and efficient synthesis of a novel class of spiroquinolinone compounds *via* a two component condensation reaction has been developed. Evaluation of the biological activities for this new class of spiro-compounds will be reported in due course.

Acknowledgments

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7. General procedure for the synthesis of 3-chlorooxindolines **5a-k**: To the mixture of isatins **7** (5 mmol) in ethanol/pyridine/acetic acid (33 mL, 7.5:2.5:1) was added acid **8** (5.5 mmol) and the resulting mixture was heated at reflux for 16 h. After cooling to rt, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and the resulting solution washed with aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated to give the corresponding 3-hydroxyloxindolines as dark red solids. To the solution of above residue in THF (25 mL) was added pyridine (15 mmol) and $SOCl_2$ (25 mmol) at 0 ℃. After reaction completion as indicated by TLC, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (30 mL) and washed with aqueous sat. $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (0%-50% ethyl acetate in cyclohexane) to give compounds **5a-k**.
8. General procedure for synthesis of spiroquinolinones: A mixture of diamines **3** (0.70 mmol) and Cs_2CO_3 (1.75 mmol) in CH_2Cl_2 (1.5 mL) were stirred at rt for 10 min before a solution of 3-chlorooxindolines **5** (0.35 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise. The resultant mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (0%-50% ethyl acetate in cyclohexane) to give compounds **6** as solids.
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