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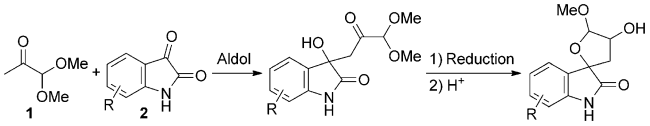
Synthesis of Furanose Spirooxindoles via 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-Catalyzed Aldol Reactions of a Pyruvic Aldehyde Derivative

Dongxin Zhang, Sherida Johnson, Hai-Lei Cui, and Fujie Tanaka*[a]

Abstract: Spirooxindoles are important compounds as they are often found in bioactive molecules. Thus, the development of new spirooxindoles and of synthetic routes to spirooxindoles is a great interest to discover new biofunctional molecules and therapeutic leads. We developed a concise method for the synthesis of spirooxindoles bearing a furanose unit. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used for an aldol reaction of a pyruvic aldehyde derivative with isatin; reduction of the ketone group was followed by treatment with acid to generate the spirofuranose unit. A set of furanose spirooxindoles were obtained in good to high yields.

Spirooxindoles are common in many natural products and bioactive molecules.[1] Thus, to discover therapeutic leads and biofunctional molecules, there is a high demand for new types of spirooxindoles and for the development of efficient, concise synthetic methods to access spirooxindole frameworks.[1,2] Herein, we report a concise, efficient route to furanose spirooxindoles.

As five-membered-ring sugars, furanose units are present in DNA and RNA, hence spirooxindoles with furanose units will likely be biofunctional molecules.[3] To synthesize the furanose-oxindole spirosystem, we designed a synthetic route that begins with an aldol reaction of a pyruvic aldehyde derivative (**1**) with an isatin (**2**), followed by reduction of the ketone carbonyl group and an acidic workup as shown in Scheme 1. When compounds are initially screened in biological assays, racemic mixtures are often sufficient, and compounds of interest are then synthesized in enantiomerically pure forms for further investigation. Thus, as the first stage to explore the furanose spirooxindoles, we sought a rapid and concise reaction method to access the racemic versions of these molecules.



Scheme 1. A route to furanose spirooxindoles.

In our route, the first step is an aldol reaction.[4] Previously reported aldol reactions of pyruvic aldehyde derivative **1** performed under mild conditions are relatively slow. For example, the proline-catalyzed aldol reaction of **1** with α,α-disubstituted alkylaldehydes reported by Enders and Gasperi takes 5–10 days at room temperature or 4 °C to obtain the aldol products in up to 53 % yield in excellent diastereo- and enantioselectivity.[5] Reactions of **1** using primary amine-based catalysis reported by Luo et al. also required up to three days.[6] Kumar and Chimni also reported the reaction of **1** with isatins using cinchona-derived amines with acid additives as catalysts at 25 °C, and the time required for completion of these reactions ranges from 16–30 h.[4i] Here, our goal was to obtain reasonable yields for the aldol reaction within 30 minutes at room temperature.

Catalysts and conditions were evaluated for the aldol reaction of **1** with isatin **2a** to afford aldol product **3a** at room temperature (25 °C) in 30 min (Table 1). When the reaction was performed using pyrrolidine, pyrrolidine/acetic acid (1:1), or pyrrolidine/Et_3N (1:1) as catalyst (20 mol %) in 1,2-dimethoxyethane (DME), isatin **2a** was completely consumed in 30 min, but multiple products were formed including a small amount of desired aldol product **3a** (Table 1, entries 1–3). For these catalysts, neither use of a lower catalyst loading (10 and 5 mol %) nor a shorter reaction time improved the outcome to obtain **3a**. In contrast, the reaction in the presence of pyrrolidine/DBU (1:1, 20 mol %) in DME gave **3a** in good yield (Table 1, entry 4). The reaction using DBU[7] as a sole catalyst in DME also afforded **3a** in similar yield (Table 1, entry 5). A screen of a small set of solvents for the reaction in the presence of DBU revealed that toluene was the optimal solvent of those tested in terms of cleanness of the reaction (less or no byproduct formation) and the yield of **3a** (Table 1, entries 7 and 8). The regioisomer of **3a**, in which a new bond

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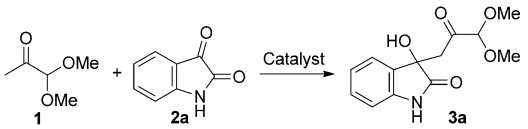
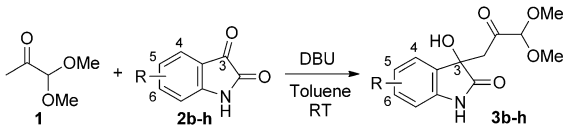
Table 1. Screen of catalysts and conditions for the aldol step.[a]



Entry	Catalyst[b] (loading relative to **2a**)	Solvent	*t*	Yield [%][c]
1	pyrrolidine/Et_3N 1:1 (20 mol%)	DME	30 min	ND
2	pyrrolidine/CH_3COOH 1:1 (20 mol%)	DME	30 min	ND
3	pyrrolidine (20 mol%)	DME	30 min	ND
4	pyrrolidine/DBU 1:1 (20 mol%)	DME	30 min	72
5	DBU (20 mol%)	DME	30 min	74
6	DBU (10 mol%)	1,4-dioxane	30 min	56[d]
7	DBU (20 mol%)	toluene	30 min	79
8	DBU (10 mol%)	toluene	30 min	80
9[e]	DBU (10 mol%)	toluene	30 min	67
10	NaOMe[f] (20 mol%)	toluene	30 min	73
11	DABCO (20 mol%)	toluene	3 h	NR
12	DMAP (20 mol%)	toluene	3 h	NR
13	Et_3N (20 mol%)	toluene	3 h	NR
14[g]	DBU (10 mol%)	toluene	30 min	67

[a] Reaction conditions: **1** (5.0 mmol), **2a** (0.5 mmol), and catalyst (0.10 mmol or 0.05 mmol as indicated; i.e., 20 mol% or 10 mol% relative to **2a**) in solvent (1 mL) at RT (25°C) except where noted. [b] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DABCO = 1,4-diazabicyclo[2.2.2]octane; DMAP = 4-(dimethylamino)pyridine. [c] Isolated yield of **3a**. ND = not determined because of formation of byproducts, see text. NR = no reaction. [d] Yield was determined by ^1H NMR spectroscopy of the crude mixture. [e] Reaction at 0°C for 10 min then RT for 20 min. [f] NaOMe solution (5M) in MeOH was used. [g] **1** (2.5 mmol) was used.

Table 2. Aldol reactions of **1** and **2**.[a]



Entry	R	**3**	DBU [mol%][b]	*t* [min]	Yield [%]
1	4-Cl	**3b**	10	30	70
2	4-Cl	**3b**	20	15	78
3	4-Br	**3c**	10	15	83
4	6-Cl	**3d**	10	15	89
5	5-Br	**3e**	10	30[c]	54
6	5-Br	**3e**	20	15	70
7	5-Me	**3f**	10	30	88
8	5-OMe	**3g**	10	15	45
9[d]	5-OMe	**3g**	10	15	63
10	5-NO_2	**3h**	10	15	47
11[d]	5-NO_2	**3h**	20	15[c]	<10[e]
12[d]	5-NO_2	**3h**	30	15	62

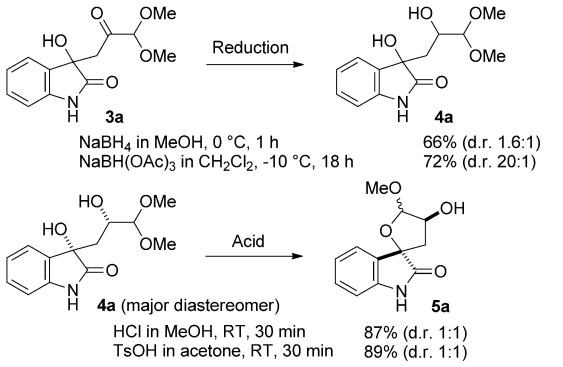
[a] Reaction conditions: **1** (5.0 mmol), **2** (0.50 mmol), and catalyst (0.10 mmol or 0.05 mmol as indicated; i.e., 20 mol% or 10 mol% relative to **2**) in toluene (1 mL) at RT (25°C) except noted. [b] DBU loading amount relative to **2**. [c] Reaction was stopped at the indicated time without complete consumption of **2**. [d] Reaction in DME. [e] Estimated by TLC analysis.

was formed at the acetal carbon atom, was not obtained. We were able to reduce the loading of DBU; the reaction in the presence of DBU (10 mol%) in toluene afforded **3a** in 80% yield (Table 1, entry 8). Further testing of the reaction at 0°C (Table 1, entry 9) and of the use of NaOMe, DABCO, or DMAP as the catalyst (Table 1, entries 10–12) indicated that the reaction with DBU (20 or 10 mol%) in toluene was optimal (Table 1, entries 7 and 8).

Whereas pyrrolidine with or without acetic acid or Et_3N may form an enamine with **1** as nucleophile for the aldol reaction, the reaction using DBU as the catalyst may proceed via an enolate. The enamine and enolate generated by the deprotonation at the dimethoxy substituted carbon atom of **1** may be less reactive than those generated by deprotonation at the methyl group of **1** because of electronic and steric reasons. As a strong base, DBU is an efficient catalyst for the reaction; formation of the dianion[8] of **1** may be involved in the fast reaction.

With the optimal reaction conditions identified to afford **3a**, a series of aldol products were synthesized from substituted isatins (Table 2). Reactions with chloro-, bromo-, and methyl-substituted isatin derivatives afforded the corresponding aldol products **3b**–**3f** in good to high yields (70–89%). The methoxy and the nitro-substituted isatins and their aldol products were less soluble in toluene. Based on this solubility feature, these reactions were performed in DME to increase the yields of the products **3g** and **3h** (62–63% in DME versus 45–47% in toluene; Table 2, entry 8 versus entry 9; entry 10 versus entries 11 and 12).

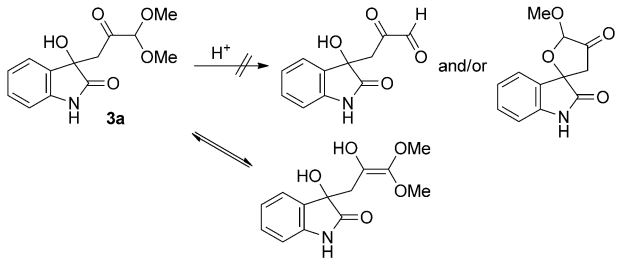
The next step toward the furanose spirooxindoles was the reduction of the ketone carbonyl group (Scheme 2). When **3a** was reduced with $NaBH_4$ in MeOH at 0°C, diol **4a** was obtained as a mixture of the two diastereomers (d.r. 1.6:1). In contrast, reduction of **3a** with $NaBH(OAc)_3$ in CH_2Cl_2 at −10°C afforded mostly a single diastereomer of **4a** (d.r. 20:1) in high yield.[9] This single diastereomer of **4a** was converted into **5a** (d.r. 1:1 at the anomeric center) by an acid treatment. When **4a** (d.r. 1.6:1) was treated under the same acidic conditions, it seemed that all four possible diastereomers of **5a** were formed by TLC analysis. Although an 18 h reaction time for the reduction was significantly



Scheme 2. Reduction of **3a** and transformation of diol **4a** into furanose spirooxindole **5a**.[9]

more time than the aldol reaction step, reduction with $NaBH(OAc)_3$ at −10 °C was chosen to combine with an acidic workup to obtain a set of furanose spirooxindoles.

The acid treatment of **3a** did not afford the corresponding five-membered product (Scheme 3). The acetal group



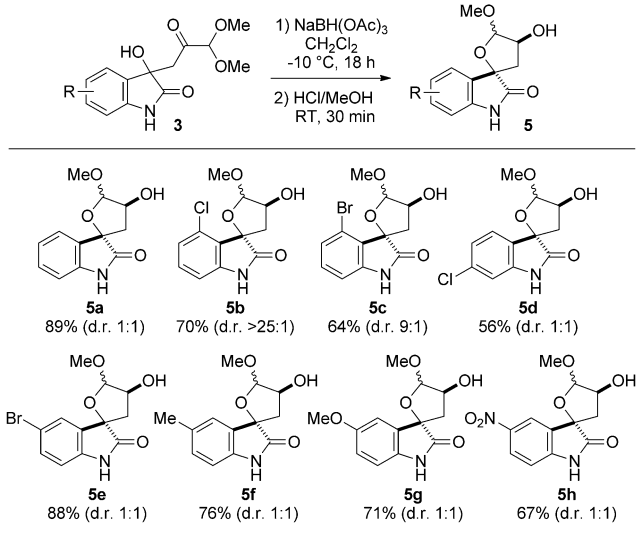
Scheme 3. Reaction of **3a** under acidic conditions.

of **3a**, located next to the carbonyl group, was also not deprotected under typical acidic conditions used for the deprotection of dimethyl acetals. We attribute this to the formation of a stable dimethoxy-substituted enol/enolate. Once the ketone group was reduced, formation of the five-membered ring proceeded smoothly.

The results of the formation of **5** by the reduction of **3** with $NaBH(OAc)_3$ followed by an acidic workup are shown in Table 3. Furanose spirooxindoles **5a–h** were obtained in good to high yields from the corresponding aldol products **3a–h**.

In summary, we have developed a concise method to synthesize furanose spirooxindoles via a DBU-catalyzed aldol reaction of a pyruvic aldehyde derivative with isatins. The aldol step requires only 15–30 min, and the furanose spirooxindoles were obtained in good to high yields from the reaction sequence with the reduction followed by the acidic treatment. The furanose spirooxindoles synthesized by our method will likely be useful to aid the search for biofunctional molecules.

Table 3. Conversion of aldol products **3** into furanose spirooxindoles **5**.[a]



[a] Diastereomers of **5** were generated at the acetal carbon. See ref. [9].

Experimental Section

*DBU-Catalyzed Aldol Reactions of **1** and **2** to Give **3***

DBU (0.05–0.1 mmol) was added to a mixture of **1** (5.0 mmol) and **2** (0.5 mmol) in toluene (1.0 mL) at RT (25 °C). The mixture was stirred at the same temperature until **2** was consumed (monitored by TLC). EtOAc and saturated NH_4Cl solution were added to the mixture and the mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, and purified by silica gel flash column chromatography (hexane/EtOAc = 1:1 or 1:2) to give **3**.

*Transformation of **3** into **5***

$NaBH(OAc)_3$ (0.4 mmol) was added to a solution of aldol product **3** (0.20 mmol) in CH_2Cl_2 (1.0 mL) at −10 °C. The mixture was stirred at the same temperature for 18 h (consumption of **3** was analyzed by TLC). The mixture was added to HCl solution in MeOH (3 M, 1.5 mL) dropwise at 0 °C, stirred at RT (25 °C) for 30 min, and purified by silica gel flash column chromatography (hexane/EtOAc = 1:1 or 1:2) to give **5**.

Acknowledgements

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Keywords: aldol reaction · furanoses · heterocycles · organocatalysis · spiro compounds

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