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Construction of indolenine-substituted spiro[pyrrolidine-2,3′-oxindoles] from 2-alkenylindolenines and isatin-derived azomethine ylides

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ABSTRACT

An organic base-catalyzed 1,3-dipolar cycloaddition between 2-alkenylindolenines and azomethine ylides derived from isatins and benzylamines was successfully developed to assemble indolenine-substituted spiro [pyrrolidine-2,3′-oxindole] ring systems. Generally, good regioselectivities (up to 14:1 *rr*) and high yields (up to 91%) were obtained under mild conditions.

1. Introduction

The construction of functional molecules with potential bioactivities *via* short synthetic pathways is a very important task in synthetic and medicinal chemistry. In this respect, spirooxindoles and indolenines as important synthetic heterocycle frameworks often exhibit various types of bioactivities, such as antimalarial, antibacterial, and CR TH2 receptor antagonistic property (Fig. 1).[1] On the other hand, both spirooxindole and indolenine motifs are also frequently seen in bioactive alkaloid natural products (Fig. 1).[2] To date, although some synthetic methodologies have been developed for the synthesis of spiro [pyrrolidine-2,3′-oxindoles] and indolenines,[2,3] due to the medicinal significance of these structural cores, developing simple and efficient approaches to construct these skeletons is still in urgent demand.

1,3-Dipolar cycloadditions of azomethine ylides with electron-deficient carbon-carbon double bonds represent a powerful approach to access the spirooxindole scaffold.[4] To this end, both organic and metal catalysts performed well in these reactions over the past decades.[5] With respect to isatin-derived azomethine ylides, in 2012 the Sarrafi group developed a 1,3-dipolar cycloaddition of isatins, benzylamines and chalcone derivatives in one pot to construct functionalized spiropyrrolidine oxindoles.[6] After that, several groups reported catalytic asymmetric approaches to synthesize spiro [pyrrolidine-2,3′-oxindoles] through 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from isatin and benzylamine to construct different functional spirooxindole derivatives.[7] Among these commonly applied procedures, changing precursors to the azomethine ylide species was found to have distinct influence on the regio- and stereoselectivities of the [3 + 2] cycloaddition reactions. Specifically, our group recently reported 1,3-dipolar cycloaddition reactions of azomethine ylides derived from 3-amino oxindoles with nitroalkenes,[8] α,β-ynones,[9] chalcones,[10] and methyleneindolinones,[11] affording a diverse array of spiro [pyrrolidine-2,3′-oxindoles].

With respect to indolenine chemistry, utilization of indolenine derivatives to build novel structures in synthetic chemistry has been rarely reported except for a few hydrogenation reactions.[12,13] To the best of our knowledge, 2-alkenylindolenines as 1,3-dipolarophiles in cycloaddition have been exclusively reported by our group, which reacted with 1,3-dipoles *in situ* generated from 3-amino oxindole and benzaldehyde catalyzed by diphenyl

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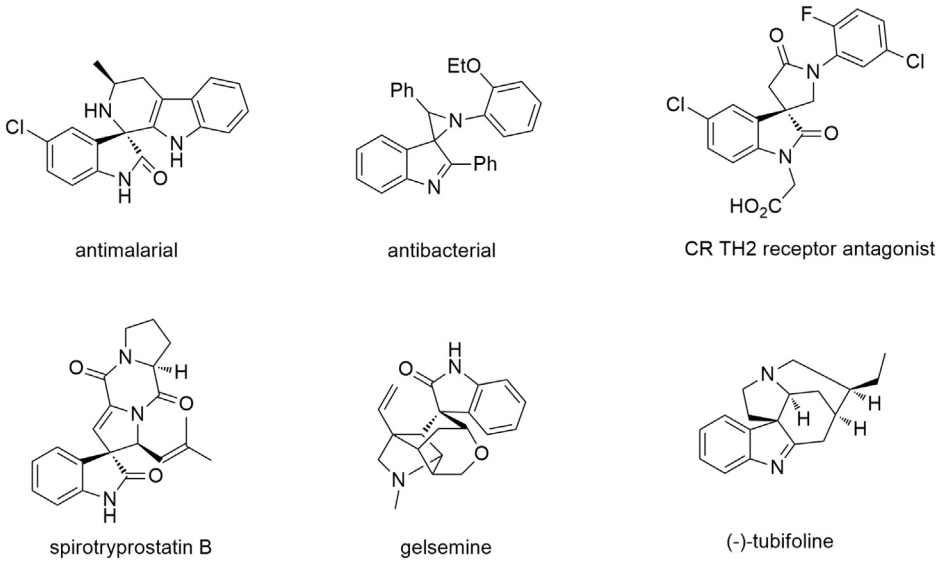
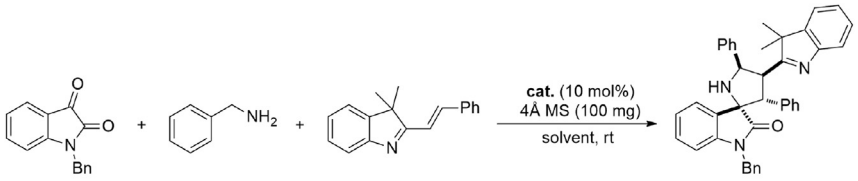


Fig. 1. Bioactive synthetic compounds and alkaloid natural products containing spirooxindole and indolenine nuclei.

Table 1
Screening of the optimal reaction conditions[a].



Entry	Catalyst	Solvent	t [h]	Yield [%][g]	rr[h]
1	DABCO	DCM	48	88	10:1
2	DBU	DCM	72	57	4:1
3	TMG	DCM	72	26	3:1
4	Et_3N	DCM	48	82	8:1
5	AcOH	DCM	48	71	18:1
6	CF_3SO_3H	DCM	36	41	2.5:1
7	TFA	DCM	36	35	4:1
8	DPP	DCM	72	63	10:1
9	BF_3 Et_2O	DCM	24	72	13:1
10	DABCO	$CHCl_3$	48	84	8:1
11	DABCO	DCE	48	80	6:1
12	DABCO	Toluene	24	66	3:1
13	DABCO	Et_2O	36	71	3:1
14	DABCO	THF	36	57	3:1
15	DABCO	CH_3CN	120	38	6:1
16	DABCO	EtOH	120	40	4:1
17[b]	DABCO	DCM	48	75	6:1
18[c]	DABCO	DCM	48	80	7:1
19[d]	DABCO	DCM	24	88	12:1
20[d,e]	DABCO	DCM	96	64	13:1
21[d,f]	DABCO	DCM	20	81	8:1

[a] Unless noted, the reaction was conducted with **1** (0.1 mmol), **2** (0.11 mmol), **3** (0.11 mmol), 4 Å MS (100 mg) and catalyst (0.01 mmol) in solvent (1.0 mL).
[b] 100 mg 3 Å MS.
[c] 100 mg 5 Å MS.
[d] In inert atmosphere, using anhydrous solvent.
[e] Reaction conducted at 0 °C.
[f] Reaction conducted at 40 °C.
[g] Isolated yield.
[h] Detected by ^1H NMR of the crude product.

phosphate and sodium bicarbonate to achieve diastereoselective indolenine-substituted spiro [pyrrolidine-2,3′-oxindole] products in high yields.[14] In order to enhance the ratio of the major cycloaddition product, we conceived the idea of utilizing 1,3-dipoles *in situ* formed from isatin and benzylamine to react with 2-alkenylindolenine *via* [3 + 2] cycloaddition.