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Highly efficient and diastereoselective construction of bispirooxindoles through a cascade Michael-cyclization reaction

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ABSTRACT

A series of bispirooxindole derivatives have been synthesized via a cascade Michael-Cyclization reaction between isothiocyanato oxindoles and methyleneindolinones with high yields (up to 98%) and excellent diastereoselectivities (up to >95:5 dr) under mild conditions. The structure and effect on the reaction of less studied 4-substituted methyleneindolinones have also been investigated.

1. Introduction

Spirocyclic oxindoles are structural motifs frequently found in many natural and unnatural compounds with diverse biological activities.[1] Among various spirocyclic oxindoles, bispirooxindole has also been found to possess many important biological properties (Fig. 1).[2] Consequently, many diverse methods to access structurally diverse bispirooxindoles have been developed and significant achievements have been obtained.[2–6] Most studies have focused on 1,3-dipolar cycloaddition of azomethine ylides.[3–6] However, this approach usually requires heating, ultrasonic or microwave irradiation. Therefore, recent effort has been devoted to developing other some simple and efficient strategies to construct bispirooxindole skeletons.[7] For example, the Overman group described the formation of bispirocyclic oxindoles by Heck reaction.[7a,b] Barbas and co-workers explored an organocatalytic domino Michael-aldol reaction between 3-substituted oxindoles and methyleneindolinones.[7c] More recently, a cascade Michael-alkylation strategy[7d] and a cycloaddition reaction of cyclic imino ester[7e] have been reported by Wang's group. Despite these remarkable advances, the significant bioactivities and diverse structural scaffolds of bispirooxindoles have been attracting the interest of chemists. In 2011, Yuan and co-workers firstly demonstrated that 3-isothiocyanato oxindoles could be used as efficient substrates to synthesize spirooxindoles by aldol-cyclization sequence.[8] Subsequently, this kind of compounds is proved to be robust and versatile synthons in the construction of complex spirooxindoles.[9] Inspired by these results and the studies on the application of α-isothiocyanato imides and esters,[10] Herein, we wish to describe a facile and efficient strategy for accessing 3,2′-pyrrolidinyl bispirooxindole compounds by Michael addition–cyclization cascade reaction of 3-isothiocyanato oxindoles **1** with methyleneindolinones **2** in the presence of tetramethylguanidine (TMG).[11]

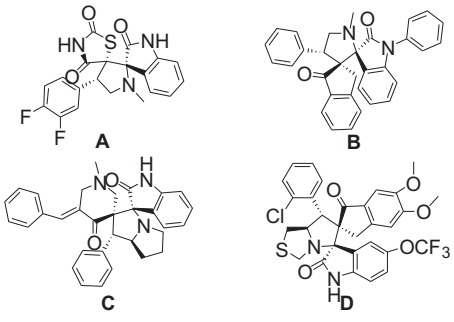

Fig. 1. Some biologically active compounds with bispirooxindole skeletons.

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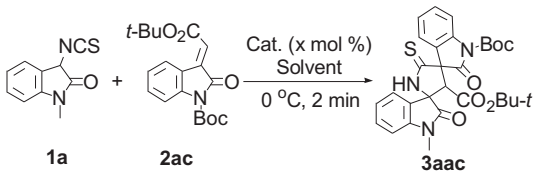
2. Results and discussion

Initially, 3-isothiocyanato oxindole **1a** and (*E*)-methyleneindolinone **2ac** were chosen as model substrates for surveying the reaction parameters, and the results are summarized in Table 1. We were particularly pleased to find that all reactions could proceed to completion within 2 min by TLC analysis. Firstly, the reaction was performed in the presence of 10 mol % TEA and the desired product **3aac** could be obtained in 93% yield with 91:9 dr (Table 1, entry 1). And then, other several organic base catalysts, such as DABCO, DMAP, and DIPEA, were also investigated, and slightly improved diastereoselectivities could be observed (Table 1, entries 2–4). To our delight, when TMG was used as catalyst, excellent yield (98%) and dr (>95:5) could be attained (Table 1, entry 5). A further study showed that inorganic base catalyst K_2CO_3 did not provide better result (Table 1, entry 6). Subsequently, several solvents were also screened. However, no better results were obtained compared with DCM, in terms of yields and diastereoselectivities (Table 1, entries 7–10). Gratifyingly, the survey of catalyst loading indicated that the amount of catalyst could be decreased to 5 mol % even 1 mol %, without compromising yields and diastereoselectivities (Table 1, entries 11 and 12).

Table 1
Optimization of reaction conditions[a]



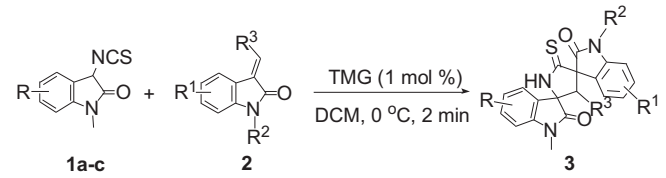
1a **2ac** **3aac**

Entry	Cat[b]	*x*	Solvent	Yield[c] (%)	dr[d]
1	TEA	10	DCM	93	91:9
2	DABCO	10	DCM	93	92:8
3	DMAP	10	DCM	90	92:8
4	DIPEA	10	DCM	97	92:8
5	TMG	10	DCM	98	>95:5
6	K_2CO_3	10	DCM	90	92:8
7	TMG	10	Toluene	93	93:7
8	TMG	10	THF	95	93:7
9	TMG	10	Et_2O	95	89:11
10	TMG	10	$CHCl_3$	96	>95:5
11	TMG	5	DCM	98	>95:5
12	TMG	1	DCM	98	>95:5

[a] The reactions were carried out with **1a** (0.1 mmol) and **2ac** (0.11 mmol) with specified catalyst loading in solvent (1.0 mL) at 0 °C for 2 min.
[b] TEA (triethylamine), DABCO (1,4-Diazabicyclo[2.2.2]octane), DMAP (4-dimethylaminopyridine), DIPEA (diisopropylethylamine), TMG (tetramethylguanidine).
[c] Isolated yield.
[d] Determined by ^{1}H NMR analysis of the crude reaction mixture.

With the optimized reaction conditions in hand, we then screened a series of 3-isothiocyanato oxindoles **1** and methyleneindolinones **2** to establish the general utility of this transformation. Firstly, various methyleneindolinones **2** were investigated. As seen from Table 2, the structure of the substituent on aromatic ring of methyleneindolinone seems to show important influence on the diastereoselectivity of the reaction. For example, when 5-Me-substituted **2ba**–**bc**, 5-OMe-substituted **2ca**–**cc** and 5-halogen substituted **2da**–**fa** were employed, Michael-cyclization reactions could smoothly occur with excellent yields and dr values (Table 2, entries 4–12). Nevertheless, when 5-NO_2-substituted **2ga**–**gc** were applied, only moderate diastereoselectivities could be obtained albeit with excellent yields (Table 2, entries 13–15). In addition, the position of the substituent on aromatic ring of methyleneindolinone has also been found to have a major impact

Table 2
Substrate scope studies of Michael addition–cyclization sequence[a]



1a-c **2** **3**

1a: R = H **1b**: R = 5-Me
1c: R = 6-F

Entry	1	**2**,R^1,R^2,R^3	3	Yield[b] (%)	dr[c]
1	**1a**	**2aa**,H,Boc,CO_2Me	**3aaa**	98	>95:5
2	**1a**	**2ab**,H,Boc,CO_2Et	**3aab**	98	>95:5
3	**1a**	**2ac**,H,Boc,CO_2Bu-*t*	**3aac**	98	>95:5
4	**1a**	**2ba**,5-Me,Boc,CO_2Me	**3aba**	97	>95:5
5	**1a**	**2bb**,5-Me,Boc,CO_2Et	**3abb**	98	>95:5
6	**1a**	**2bc**,5-Me,Boc,CO_2Bu-*t*	**3abc**	98	>95:5
7	**1a**	**2ca**,5-OMe,Boc,CO_2Me	**3aca**	97	>95:5
8	**1a**	**2cb**,5-OMe,Boc,CO_2Et	**3acb**	98	>95:5
9	**1a**	**2cc**,5-OMe,Boc,CO_2Bu-*t*	**3acc**	98	95:5
10	**1a**	**2da**,5-F,Boc,CO_2Me	**3ada**	96	95:5
11	**1a**	**2ea**,5-Cl,Boc,CO_2Me	**3aea**	97	94:6
12	**1a**	**2fa**,5-Br,Boc,CO_2Me	**3afa**	97	93:7
13	**1a**	**2ga**,5-NO_2,Boc,CO_2Me	**3aga**	95	80:20
14	**1a**	**2gb**,5-NO_2,Boc,CO_2Et	**3agb**	96	83:17
15	**1a**	**2gc**,5-NO_2,Boc,CO_2Bu-*t*	**3agc**	96	74:26
16	**1a**	**2ha**,6-F,Boc,CO_2Me	**3aha**	95	>95:5
17	**1a**	**2hb**,6-F,Boc,CO_2Et	**3ahb**	98	>95:5
18	**1a**	**2hc**,6-F,Boc,CO_2Bu-*t*	**3ahc**	96	>95:5
19	**1a**	**2ia**,6-Cl,Boc,CO_2Me	**3aia**	98	>95:5
20	**1a**	**2ib**,6-Cl,Boc,CO_2Et	**3aib**	97	>95:5
21	**1a**	**2ic**,6-Cl,Boc,CO_2Bu-*t*	**3aic**	97	92:8
22	**1a**	**2ja**,6-Br,Boc,CO_2Me	**3aja**	97	>95:5
23	**1a**	**2jb**,6-Br,Boc,CO_2Et	**3ajb**	93	>95:5
24	**1a**	**2jc**,6-Br,Boc,CO_2Bu-*t*	**3ajc**	95	92:8
25	**1a**	**2ka**,4-Cl,Boc,CO_2Me	**3aka**	96	71:29
26	**1a**	**2kb**,4-Cl,Boc,CO_2Et	**3akb**	96	70:30
27	**1a**	**2kc**,4-Cl,Boc,CO_2Bu-*t*	**3akc**	96	57:43
28	**1a**	**2la**,4-Br,Boc,CO_2Me	**3ala**	93	75:25
29	**1a**	**2ma**,H,Me,CO_2Me	**3ama**	93	92:8
30	**1a**	**2nd**,H,Boc,COPh	**3and**	98	>95:5
31	**1b**	**2ba**,5-Me,Boc,CO_2Me	**3bba**	98	>95:5
32	**1b**	**2bb**,5-Me,Boc,CO_2Et	**3bbb**	98	>95:5
33	**1b**	**2bc**,5-Me,Boc,CO_2Bu-*t*	**3bbc**	98	>95:5
34	**1b**	**2ha**,6-F,Boc,CO_2Me	**3bha**	98	94:6
35	**1b**	**2hb**,6-F,Boc,CO_2Et	**3bhb**	98	93:7
36	**1b**	**2hc**,6-F,Boc,CO_2Bu-*t*	**3bhc**	97	94:6
37	**1c**	**2ba**,5-Me,Boc,CO_2Me	**3cba**	98	>95:5
38	**1c**	**2bb**,5-Me,Boc,CO_2Et	**3cbb**	98	>95:5
39	**1c**	**2bc**,5-Me,Boc,CO_2Bu-*t*	**3cbc**	97	92:8

[a] All reactions were carried out with **1** (0.1 mmol), **2** (0.11 mmol), and TMG (0.001 mmol) in DCM (1.0 mL) at 0 °C for 2 min.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.

on the reaction. When less studied 4-substituted methyleneindolinones **2ka**–**la** were reacted with **1a**, only poor diastereoselectivities were observed, albeit with excellent yields (Table 2, entries 25–28). This may be attributed to the steric hindrance of 4-substituted methyleneindolinones. Fortunately, the crystal structure of 4-chloro-substituted **2ka** was obtained by recrystallization from ethyl acetate/petroleum ether, and the *Z*-configuration of double bond and nearly vertical orientation between double bond and ester group were unambiguously determined by X-ray crystallography (Fig. 2),[12] which is completely different from previously reported *E*-configuration and almost coplanar arrangement of methyl (3-indolylidene)acetate,[13a] ethyl (3-indolylidene) acetate,[13b] and methyl (1-benzyl-3-indolylidene)acetate.[13c] These results perhaps imply that steric hindrance is crucial for the structure of 4-substituted methyleneindolinones. Further study reveals that nitrogen protecting group R^2 in **2** has little influence on