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A Highly Efficient DBU-Catalyzed Green Synthesis of Spirooxindoles

Cite this: DOI: 10.1039/x0xx00000x

Liqun Wang,[a] Daming Zhang,[a] Jian Li,[a] Guangyang Xu,[a] and Jiangtao Sun[a]

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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A DBU-catalyzed atom economy and green synthesis of spirooxindoles has been developed under environmentally benign conditions. This highly efficient transformation could be explained by its superior carbon basicity combined with nucleophilicity of DBU comparable to other bases.

The spirooxindole nucleus is an important motif found in many natural products, synthetic pharmaceuticals and leading compounds with significantly biological and pharmaceutical activities (Figure 1).[1] Thus, the construction of spirooxindole frameworks has always attracted much attention and many approaches have been developed toward diverse synthesis of spirooxindole skeletons with different functionality in the past decades.[1,2] Among various naturally occurring as well as synthetic scaffolds, the 3,3'-pyrrolidonyl spirooxindole is an important family with widely biological activities.[3] Recently, several elegant methodologies have been reported to achieve this nucleus either in an enantioselective or stereoselective way.[4] In 2011, Wang and co-workers described a chiral bifunctional thiourea catalyzed highly efficiently enantioselective synthesis of 3,3'-pyrrolidonyl spirooxindoles.[5] In that case, the spirooxindoles were obtained with three contiguous stereocenters in excellent yields and *trans*-selectivity was observed for the two carboxylate groups (Scheme 1).

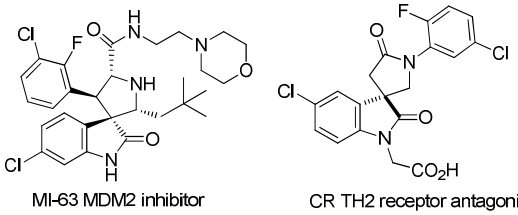
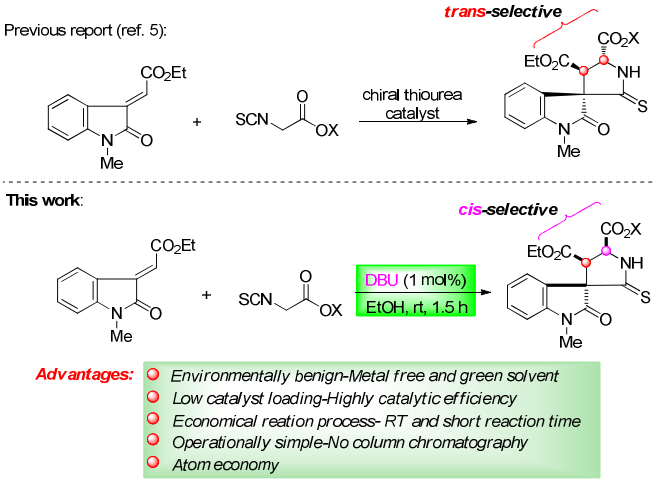


Fig. 1 Leading compounds containing spirooxindole cores.

Despite those advances, generally the presence of transition metal complexes or thiourea catalysts (> 5 mol%) was essential to realize this transformation, which inevitably limited their applications in practicability and large amount synthesis. Moreover, the relatively expensive and toxic solvents, such as dichloromethane and toluene were often used. Clearly, the development of novel protocols with environmentally benign and transition-metal free, lower catalyst loading, shorter reaction time and the use of lower toxic solvent for the construction of spirooxindole skeletons are highly desirable especially in a green way as well as large scale synthesis.[6] Herein, we report the highly efficient and green synthesis of 3,3'-pyrrolidonyl spirooxindoles in the presence of a catalytic amount of DBU (low to 0.5 mol%) in ethanol under mild conditions. Furthermore, different with the former *trans*-selective transformation reported by Wang and co-workers, this DBU-catalyzed protocol featured *cis*-selective for the two carboxylate groups.

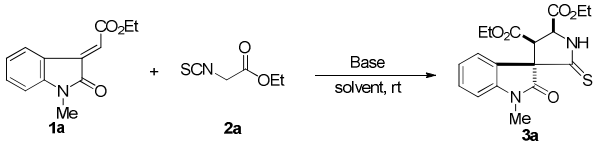


Scheme 1. Previous report and our approach toward 3,3'-pyrrolidonyl spirooxindoles

Initially, several bases (20 mol%) were screened to evaluate their catalytic activity to promote the cyclization of methyleneindolinone (**1a**) and isothiocyanato ester (**2a**) at room temperature in dichloromethane. Among the bases examined, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided **3a** in the highest yield although in poor selectivity within 8 h. However, the attempts to use other organic bases such as triethylamine, diisopropyl

ethylamine (DIPEA), 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded **3a** in very low yields (Table 1, entries 1, 3 and 4.). The use of KO^{t}Bu gave low yield too (Table 1, entry 5). Next, solvents screening showed that the relatively low polar solvents such as dichloroethane (DCE), tetrahydrofuran (THF), chloroform, methyl *tert*-butyl ether (MTBE) gave **3a** in moderate to high yields but with very low stereoselectivities in the presence of DBU (Table 1, entries 6 to 9). In contrast, the use of more polar solvents such as *N*,*N*-dimethyl-formamide (DMF) and ethanol gave **3a** almost in quantitive yields and better stereoselectivities (Table 1, entries 10 and 11). Notably, the reaction was completed immediately when 5 mol% of DBU was added to the DMF solution (Table 1, entry 12). Furthermore, even in the presence of 1 mol% of DBU, the reaction could be finished in 10 seconds in DMF (Table 1, entry 13). By contrast, the use of DABCO (1 mol%) in DMF still gave very low yield (Table 1, entry 14). More gratifyingly, the use of cheaper and greener ethanol as solvent also gave the product in quantitive yield and 84:16 d.r. value in the presence of 1 mol% of DBU although within longer reaction time (Table 1, entry 15). Moreover, when 0.5 mol% of DBU was used, the reaction can be finished in 3 minutes for DMF (Table 1, entry 16) and 8 h for ethanol (Table 1, entry 17). Based on the above results, we used ethanol as the ideal solvent and DBU as the catalyst (1 mol%) for further studies.

Table 1 Optimization of the reaction conditions[a]

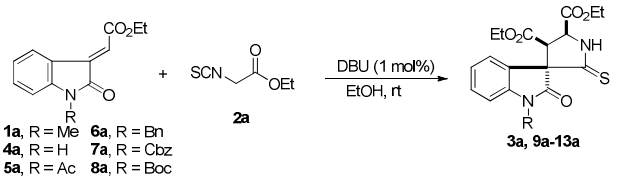


Entry	Base (mol%)	Solvent	Time	Yield (%)[b]	d.r.[c]
1	Et_3N (20)	DCM	8 h	10%	60:40
2	DIPEA (20)	DCM	8 h	7%	-
3	DABCO (20)	DCM	8 h	8%	-
4	DBU (20)	DCM	8 h	86%	60:40
5	KO^{t}Bu(20)	DCM	8 h	7%	-
6	DBU (20)	DCE	1.5 h	77%	60:40
7	DBU (20)	THF	1.5 h	84%	65:35
8	DBU (20)	$CHCl_3$	1.5 h	70%	60:40
9	DBU (20)	MTBE	1.5 h	66%	56:44
10	DBU (20)	DMF	< 5 sec	97%	80:20
11	DBU (20)	EtOH	3 min	97%	84:16
12	DBU (5)	DMF	< 5 sec	97%	80:20
13	DBU (1)	DMF	10 sec	97%	80:20
14	DABCO (1)	DMF	5 h	10%	-
15	DBU (1)	EtOH	1.5 h	96%	84:16
16	DBU (0.5)	DMF	3 min	96%	80:20
17	DBU (0.5)	EtOH	8 h	96%	84:16

[a] All reactions were carried out with **1a** (1 mmol), **2a** (1.1 mmol), solvent (3 mL) at rt under air unless otherwise noted. [b] Isolated yields of **3a** for two diastereomers. [c] D.r. values were determined by ^{1}H-NMR analysis of crude products.

Under the above optimized conditions, various N-protecting groups of the methyleneindolinone bearing different electronic and steric parameters were examined (Table 2). As observed, the protecting groups did not affect the yield distinctly and all of the corresponding products were obtained almost in quantitive yield, however in lower stereoselectivities compared with **1a** (Table 2, entries 2 to 6).

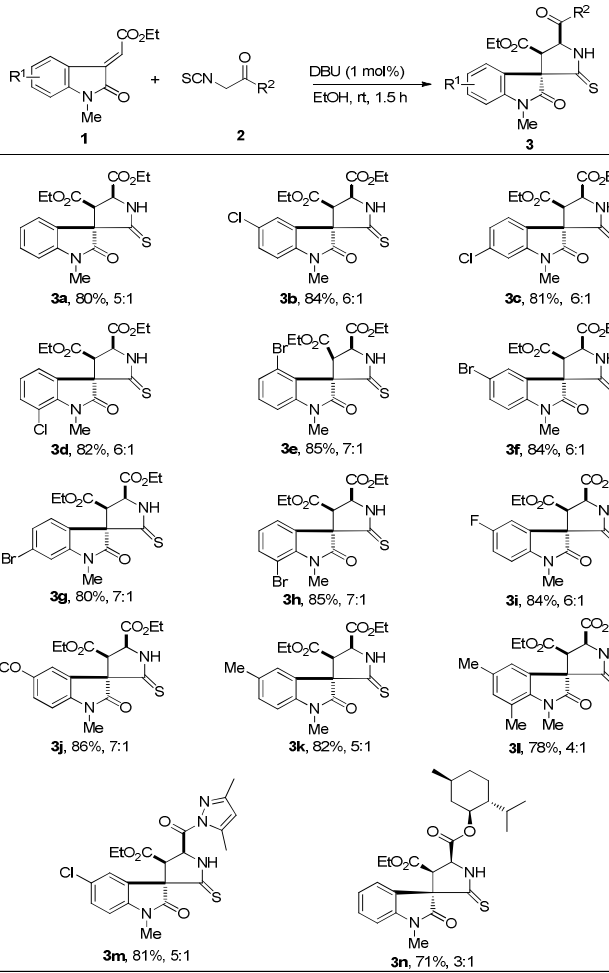
Table 2 Screening of N-protecting groups for methyleneindolinone[a]



Entry	R (methyleneindolinone)	Yield (%)[b]	d.r.[c]
1	Me (**1a**)	96% (**3a**)	84:16
2	H (**4a**)	95% (**9a**)	65:35
3	Ac (**5a**)	97% (**10a**)	70:30
4	Bn (**6a**)	96% (**11a**)	65:35
5	Cbz (**7a**)	96% (**12a**)	60:40
6	Boc (**8a**)	96% (**13a**)	65:35

[a] All reactions were carried out with **1a-8a** (1 mmol), **2a** (1.1 mmol), DBU (0.01 mmol), ethanol (3 mL) at rt under air for 1.5 h. [b] Isolated yields for two diastereomers. [c] D.r. values were determined by ^{1}H-NMR analysis of crude products.

Table 3 Substrate scope[a, b, c]



[a] All reactions were carried out with **1** (1.0 mmol), **2** (1.1 mmol), DBU (0.01 mmol), in ethanol (3 mL) at rt for 1.5 hours. [b] Isolated yields for one single isomer. [c] D.r. values were determined by ^{1}H-NMR analysis of crude products.

With the optimal reaction condition in hand, we further investigated the substrate scope. A variety of methyleneindolinones (**1**) and isothiocyanato carbonyl compounds (**2**) were subjected to the reaction (Table 3). Both electron-donating and electron-withdrawing substituents at different positions on the aromatic ring of methyleneindolinones gave the corresponding products in excellent yields and good stereoselectivities. The major isomer for each reaction can be isolated in pure form with good yields (71% to 85%). The introduction of bromo group on the phenyl ring afforded the products in higher yields and better selectivities (Table 3, **3e** to **3h**). An increase of the steric hindrance introduced by a bulkier ester group decreased the d.r. value of the corresponding product (Table 3, **3n**). Moreover, isothiocyanato imide (**2b**) was also tolerated in this reaction and gave one isomer in 81% isolated yield and 5:1 d.r. value (Table 3, **3m**).

The relative configurations of the 3,3'-pyrrolidonyl spirooxindoles were unambiguously determined by X-ray crystallography of **3b** (Figure 2).[7] The relative configuration of **3b** disclosed that the two carboxylate groups of the newly formed five-membered ring located on the same side, which is different with the former report developed by Wang and co-workers.[5a]

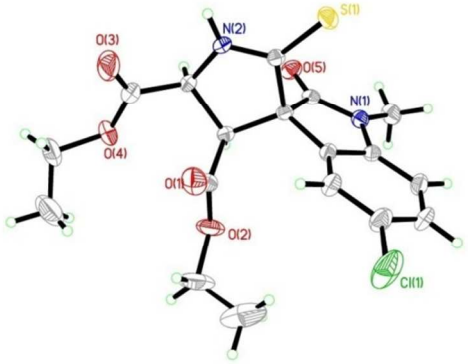
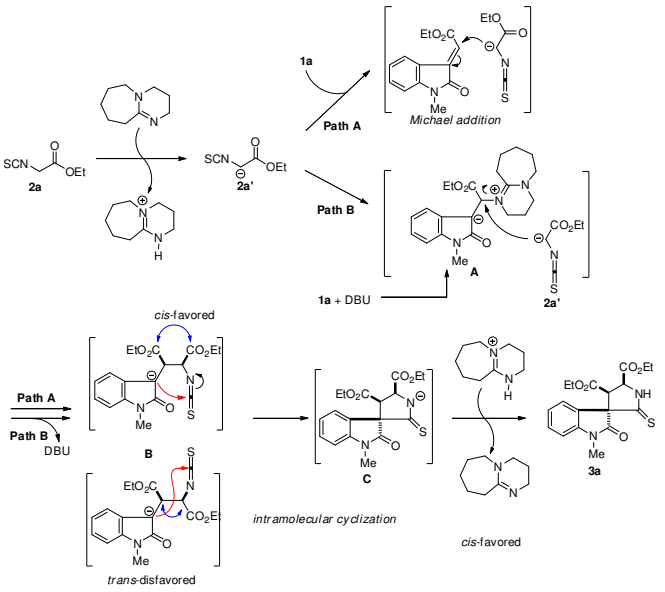


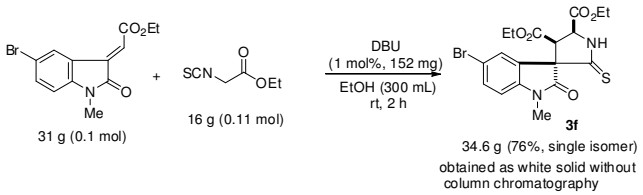
Fig. 2 X-ray crystal structure of compound **3b**.

The plausible reaction mechanism was proposed in Scheme 2. One possible explanation is that DBU acted only as a base (path A). The α-carbon atom of the α-isothiocyanatoacetate (**2a**) is deprotonated by DBU to afford the carbon anion intermediate. The carbon anion undergoes Michael addition to the electron-deficient methyleneindolinone (**1a**) to produce *cis*-dicarboxylates intermediate (**B**). Subsequently, **B** undergoes rapidly intramolecular cyclization leading to the nitrogen anion intermediate (**C**), which abstracts one hydrogen ion from the $DBUH^+$ to produce the spirooxindile (**3a**) and regenerate the DBU to complete the catalytic cycle. However, the fact that a smaller amount of DBU (0.5 to 1 mol%) displayed significantly enhanced rate compared with other bases indicated that DBU acted not only as a base but also as a nucleophilic trigger.[8] First, the addition of DBU to **1a** generates active intermediate **A** (Scheme 2, path B). Secondly, the protonated anion (**2a'**) attacks the zwitterionic intermediate **A** to produce intermediate **B** and regenerate DBU. Clearly, the *cis*-selective addition is preferred over the *trans*-addition according to the possible transition state (Scheme 2). Finally, intramolecular cyclization affords **3a** and recovers DBU. The significant acceleration of the reaction by DBU compared to DABCO and other bases made us believe that path B probably was the superior reaction way.



Scheme 2 Plausible reaction mechanism

To test the feasibility of this approach, we further conducted the large scale synthesis of **3f** in 0.1 mol scale (Scheme 3). The reaction was finished in 2 h and delivered 34.6 g of **3f** in single isomer without column chromatography. Moreover, most of ethanol can be recovered by simple distillation.



Scheme 3 Large scale synthesis of spirooxindole **3f**

Conclusions

In conclusion, we have developed a highly efficient and green synthesis of 3,3'-pyrrolidonyl spirooxindoles in the presence of catalytic amount of DBU and ethanol was used as "greener" solvent. Also, the reaction was very fast and clean. Moreover, the large scale synthesis could be finished in 2 hours at room temperature without column chromatography. We believed DBU acted not only as a base but also as a nucleophilic trigger in this highly efficient transformation.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (No. 21172023), A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110) for their financial supports.

Notes and references

[a] School of Pharmaceutical Engineering & Life Science, Changzhou University, Changzhou 213164, P. R. China. E-mail: jtsun08@gmail.com; Fax: +86 519 86334598; Tel: +86 519 86334597.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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