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Highly Stereoselective Construction of Novel Dispirooxindole-imidazolidines via Self-1,3-dipolar Cyclization of Ketimine

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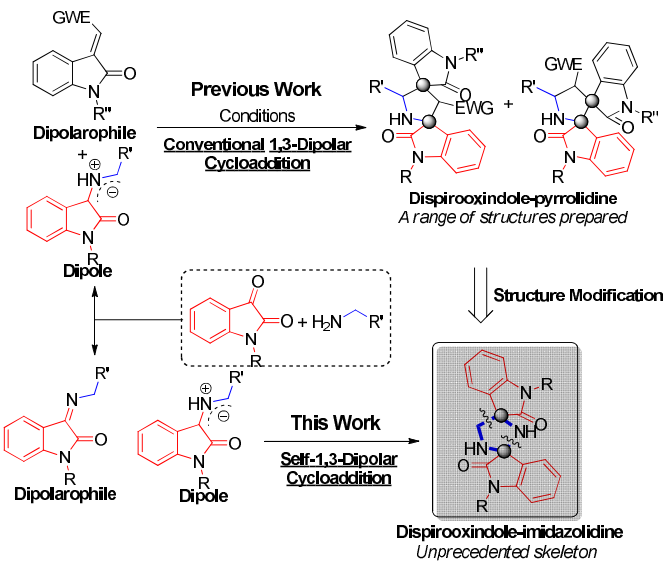
An acid-promoted self-1,3-dipolar cycloaddition of ketimines derived from isatins and benzylamines was successfully developed to assemble unprecedented dispirooxindole-imidazolidine ring systems. Generally, excellent diastereoselectivities (only single stereoisomer formed) and good yields (up to 94%) were obtained. Consequently, this self-1,3-dipolar cycloaddition protocol offers a facile access to novel dispiroheterocycle skeleton.

In the last decades, spirooxindoles have received extensive attention due to their interesting biological activities and versatile synthetic utilities.[1-6] Among all the developed synthetic methodologies, 1,3-dipolar cycloaddition (1,3-DC) of azomethine ylide drived from isatin has been found to be one of the most efficient and straightforward pathways, leading to rapid assembly of spirooxindole-pyrrolidine skeletons.[7-15] In recent years, dispirooxindole-pyrrolidines, prepared from 1,3-DC between dipoles and dipolarophiles bearing oxindole moieties simultaneously, have attracted the increasing interests due to their potentially pronounced biological activities. As a consequence, a variety of dispirooxindole-pyrrolidines have been prepared for medicinal studies (Scheme 1).[16-26] In this context, much more attention is being focused on the development of novel dispirooxindoles to meet the increasing requirement for medicinal research.

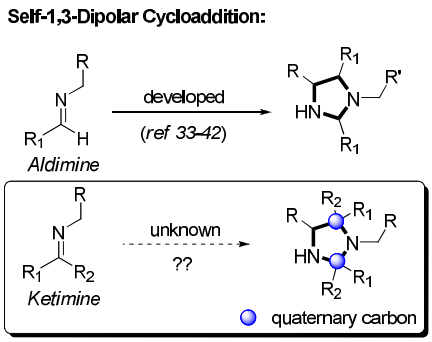
In our previous work, we reported a highly diastereoselective preparation of dispirooxindole-pyrrolidines *via* 1,3-DC of azomethine ylide.[27] Driven by extensive investigation on dispiroheterocycles, we questioned that the structural modification of dispirooxindole-pyrrolidines by introducing imidazolidine, one of the privileged structural motifs in medicinal chemistry, might offer this class of spiroheterocycles interesting biological profiles. Unfortunately, the literature survey disclosed that the synthesis of dispirooxindole-imidazolidines has never been tackled, which severely hampered their synthetic application as well as medicinal investigation. Obviously, it can be envisaged that the strategy employing self-1,3-DC of imines, in which the corresponding imines served as dipole and dipolarophile simultaneously, should provide a concise and direct access to dispirooxindole-imidazolidine skeleton.



Scheme 1. 1,3-Dipolar cycloaddition to construct various dispirooxindole heterocycles

On the other hand, it is well known that electron-deficient alkenes are amenable for 1,3-dipolar cycloaddition by behaving as effective dipolarophiles.[28-32] The imines derived from isatins and amines without direct attachment of electron-withdrawing group usually exhibited relatively low reactivity toward 1,3-DC. Consequently, it can be rationalized that the conflicting electronic requirements for dipoles and dipolarophiles in self-1,3-DC essentially posed intrinsic hurdle for harnessing this class of reaction to serve as an effective

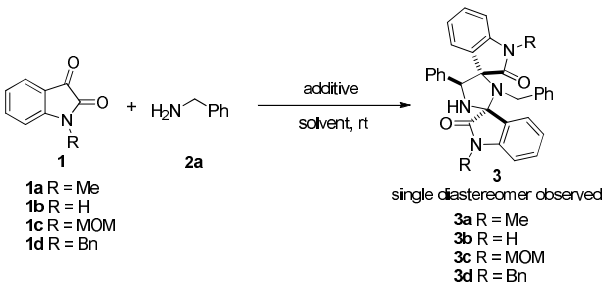
synthetic pathway. The early series reports by Grigg and coworkers contributed the fundamental advance for the access to imidazolidine through self-1,3-dipolar cycloaddition of aldimines.[33-36] However, limited progress has been made in this area ever since.[37-42] In 2002, Pearson and coworkers observed that the deprotonation of aldimine using LDA afforded self-1,3-dipolar cycloadducts in unsatisfactory yield and regioselectivity.[39] Thereafter, Cossío reported an unusual [3+2] autocyclization of aldimine derived from aromatic aldehyde and glycine methyl ester in the presence of $AgClO_4$, providing the corresponding imidazolidine in poor to moderate yields, albeit with high diastereoselectivity.[40] Very recently, a catalytic asymmetric self-1,3-DC of aldimine was reported by Shi and coworkers to synthesize the corresponding imidazolidines.[42] Unfortunately, to date, all the studies on self-1,3-DC were limited on aldimine (Scheme 2). Apparently, the employment of ketimine in self-1,3-DC would be more challenging due to the formation of two quaternary carbon centers on the resulting imidazolidine ring, which still remains undeveloped at the present stage. Undoubtedly, further investigation on self-1,3-DC, especially using ketimines, is a highly demanding task to be fulfilled in the synthetic chemistry, which surely will enrich the chemistry of 1,3-DC and provide a facile pathway to construct novel heterocyclic systems. Herein, we disclose an acid-promoted and highly diastereoselective self-1,3-DC of ketimines using isatins and benzylamines to construct the unprecedented dispirooxindole-imidazolidines. To our knowledge, this is the first time to achieve self-1,3-DC reaction of ketimines under mild conditions.



Scheme 2. Self-1,3-dipolar cycloaddition of imines to assemble imidazolidines

We initiated our studies by using *N*-methylisatin **1a** and benzylamine **2a** to optimize reaction parameters (Table 1). Not surprisingly, without adding any additive, mixing *N*-methylisatin **1a** and benzylamine **2a** in THF did not afford the corresponding cycloadduct. Basic additive was tested to promote this reaction and no cycloadduct was observed by adding triethylamine. To our delight, addition of acids including PTSA (p*K*a = -0.43) or *p*-nitrobenzoic acid (*p*-NBA, p*K*a = 3.42) in the reaction system successfully furnished the desired dispirooxindole-imidazolidine in excellent diastereoselectivity (single stereoisomer obtained), albeit with low to moderate chemical yields (26% and 44% respectively). And the employment of acetic acid with less acidity (p*K*a = 4.76) provided only trace amount of the desired product (Table 1, entries 1-5). It can be rationalized that the appropriate acidity would play a vital role in the chemical yield for this reaction. Presumably, this reaction could be dramatically facilitated by finely tuning the acidity of additive to a specific range between that of PTSA and *p*-nitrobenzoic acid. Gratifyingly, when using 3,5-dinitrobenzoic acid (3,5-DNBA, p*K*a = 2.77) as the additive, the yield was significantly improved to 79% (entry 6). Next, effects of the substituting groups on N-H of isatin were investigated. Surprisingly, using straight isatin led to an extremely sluggish reaction and only trace amount of product was obtained in even longer reaction duration. However, both *N*-MOM- and *N*-benzylisatins afforded only moderate yields (entries 7-9). Clearly, *N*-methylisatin showed the superior reactivity and was employed for the following tests. Subsequently, solvent effects were also evaluated, and it turned out that polar solvent generally gave better yield than nonpolar solvent due to poor solubilities of *N*-methylisatin or 3,5-DNBA in nonpolar solvents. THF was still the most suitable solvent for this reaction (entries 10-12). Interestingly, the amount of 3,5-DNBA severely affected the chemical yield. Lower (0.2 equiv) or large amount (5 equiv) of 3,5-DNBA dramatically decreased chemical yields (entries 13-15). It is worth noting that a slow decomposition of cycloadduct on silica gel column was observed and a slightly higher yield was achieved *via* purification on neutral aluminum oxide column (comparison of entry 14 and entry 16). Therefore, neutral aluminum oxide chromatography was employed to purify the corresponding cycloadduct. Ultimately, effect of water in the reaction system was examined. The chemical yield was slightly increased in the presence of 4Å MS and the addition of 1.0 equiv of water severely eroded the chemical yield (entries 17 & 18).

Table 1. Optimization of self-1,3-dipolar cycloaddition reaction[a]



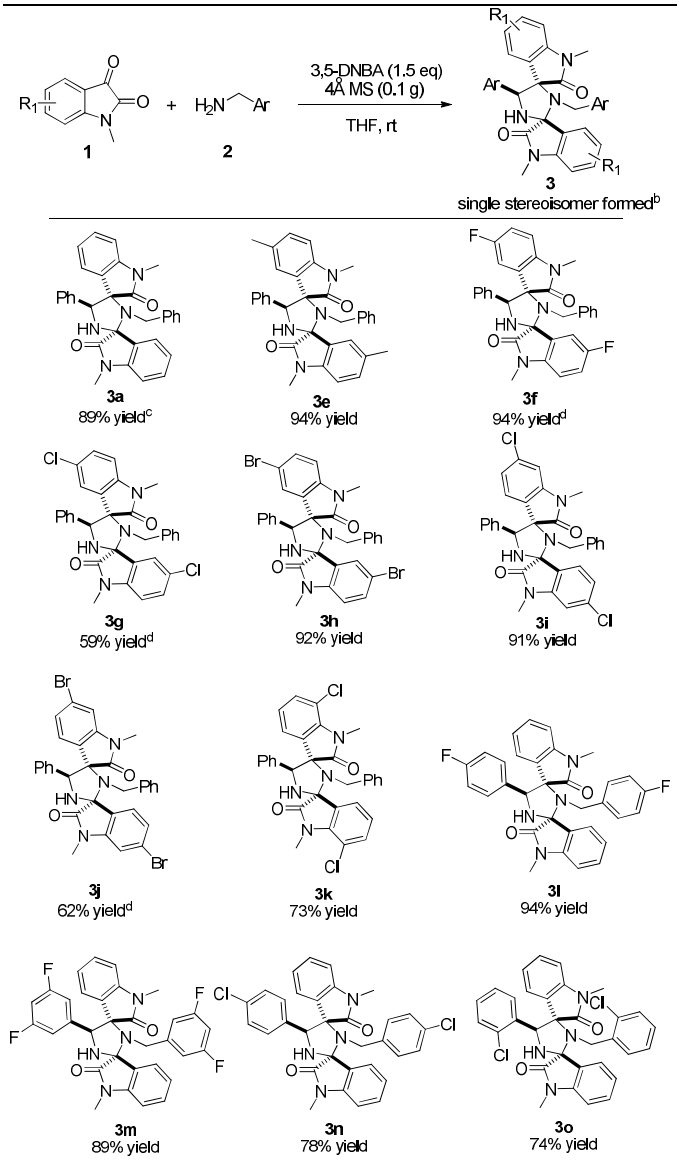
Entry	Solvent	1	Additive (mol%)	Time (h)	Yield (%)[b]
1	THF	**1a**	---	12	---
2	THF	**1a**	Et_3N	12	---
3	THF	**1a**	PTSA (2.0)	12	26
4	THF	**1a**	AcOH (2.0)	72	trace

5	THF	**1a**	*p*-NBA (2.0)	12	44
6	THF	**1a**	3,5-DNBA(2.0)	12	79
7	THF	**1b**	3,5-DNBA (2.0)	72	trace
8	THF	**1c**	3,5-DNBA (2.0)	12	50
9	THF	**1d**	3,5-DNBA (2.0)	12	48
10	DCM	**1a**	3,5-DNBA (2.0)	12	59
11	Toluene	**1a**	3,5-DNBA (2.0)	72	trace
12	MeOH	**1a**	3,5-DNBA (2.0)	12	74
13	THF	**1a**	3,5-DNBA (0.2)	12	55
14	THF	**1a**	3,5-DNBA (1.5)	12	79
15	THF	**1a**	3,5-DNBA (5.0)	12	54
16[c]	THF	**1a**	3,5-DNBA (1.5)	12	86
17[c]	**THF**	**1a**	**3,5-DNBA (1.5)[d]**	**12**	**89**
18[c]	THF	**1a**	3,5-DNBA (1.5)[e]	12	58

[a]Unless otherwise noted, all reactions were carried out at 0.2 mmol scale in THF (4 mL) at RT with a molar ratio of **1a**/**2a**=1:1.2. [b]Isolated yield. [c]Purification through neutral aluminum oxide column. [d]0.1 g of 4Å MS added. [e]1.0 Equiv H_2O added.

Having established the optimal conditions, the scope of this protocol was then studied (as shown in Table 2). As for 5-substituted *N*-methylisatins, excellent chemical yields (>90%) and diastereoselectivities were achieved (**3e**, **3f** & **3h**), except a relatively lower yield for 5-chloroisatin (59%, **3g**). The employment of 6-chloro-*N*-methylisatin also afforded a satisfactory chemical yield and diastereoselectivity (**3i**). Surprisingly, only moderate chemical yields were obtained by using 6-bromo and 7-chloro-*N*-methylisatin (**3j** & **3k**). Furthermore, substituted benzyl amines were also evaluated to proceed this cycloaddition. Pleasingly, using 4-fluoro- and 3,5-difluorobenzylamine consistently afforded the corresponding cycloadducts in good yields and excellent *dr* (**3l** & **3m**), in which fluorine substituents were readily introduced to facilitate their further medicinal studies. However, only moderate yields were obtained when 4-chloro- and 2-chlorobenzylamines were employed in this reaction (**3n** & **3o**). Finally, the relative configuration of **3a** was unequivocally established by X-ray crystallographic analysis of a single crystal (Figure 1).[43]

Table 2. Scope of self-1,3-dipolar cycloaddition of isatins and benzylamines[a]



[a]Unless otherwise noted, all reactions were carried out at 0.2 mmol scale in THF (4 mL) at RT in 12h with a molar ratio of **1a**/**2a**=1:1.2. [b]Determined by ^{1}HNMR. [c]Isolated yield. [d]Without 4 Å MS.

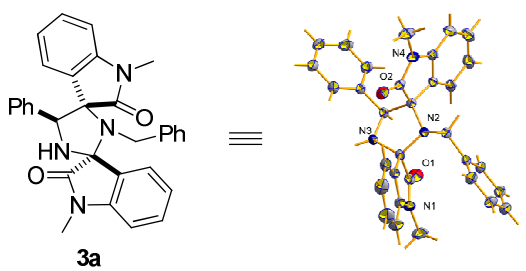
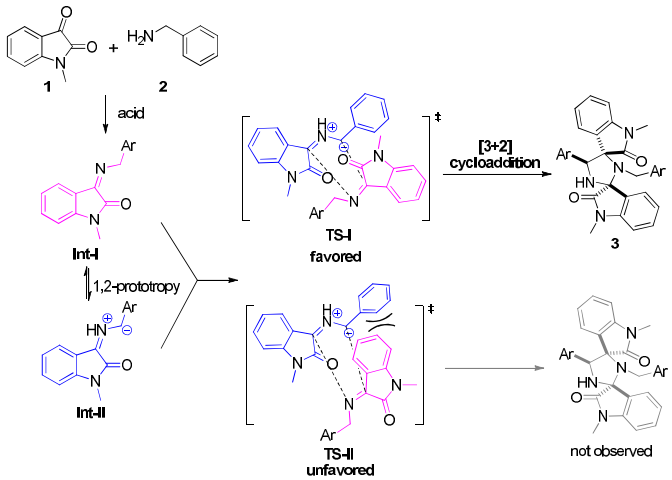


Figure 1. ORTEP diagram of **3a**

Based on the experimental results and X-ray analysis, plausible reaction pathways are proposed and illustrated in Scheme 3. Imine (**Int-I**) was firstly generated from the condensation between isatin and amine in the presence of acid. A subsequent 1,2-prototropy of **Int-I** led to the formation of azomethine ylide (**Int-II**). When these two reaction partners approaching each other, two possible transitions states (**TS-I** and **TS-II**) could be generated. Presumably, **TS-I** would be favored since **TS-II** suffered from the severe steric repulsion between the phenyl moiety in **Int-I** and phenyl group of **Int-II**. The subsequent cycloaddition of **Int-I** resulted in the formation of dispirooxindole-imidazolidine **3**.



Scheme 3. Proposed reaction pathways

In summary, a novel self-1,3-dipolar [3+2]-cycloaddition of ketimine prepared from isatin and benzylamine was developed, which was effectively promoted by 3,5-dinitrobenzoic acid. Consequently, a variety of novel dispirooxindole-imidazolidines bearing two quaternary carbons and three stereogenic centers were prepared for the first time in high yields and excellent stereoselectivities (only single stereoisomer formed). More importantly, these findings demonstrated the synthetic utilities of self-1,3-DC in the assembly of polyheterocycles, which would offer a beneficial complement to the classical 1,3-DC in the construction of heterocycles.

Acknowledgments

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Notes and references

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[§] These authors contributed equally to this work.

† Electronic Supplementary Information (ESI) available: [^{1}H NMR and ^{13}C NMR spectra for compounds **3a**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **3n** and **3o**]. See DOI: 10.1039/c000000x/

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43 CCDC 1021636 (3a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.