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One-pot Double Annulations to Confer Diastereoselective Spirooxindole-pyrrolothiazoles

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Abstract

A novel four-component reaction with pot, atom, step and economic process to synthesize diastereoselective spirooxindole-pyrrolothiazoles through sequential N, S-acetalation of aldehydes with cysteine and decarboxylative [3+2] cycloaddition with olefinic oxindoles. High synthetic efficiency, operational simplification and reaction process economy using EtOH as solvent, and only releasing CO_2 and H_2O as side products confer this approach favorable in green chemistry metrics analysis.

Keywords

Double Annulations; N, S-acetalation; cascade; azomethine ylides; pyrrolothiazoles; spirooxindole

Introduction

The nitrogen-containing heterocycles play a dominant role as a structural fragment of therapeutic agents in medicinal chemistry and drug discovery [1-9]. The nitrogen-containing

heterocyclic moieties are currently discovered in the more than 75% of drugs available in the market approved by the FDA. Thus, the reaction process with synthetic efficiency and operational simplification is a critical factor in the construction of nitrogen-based heterocycles. Normally, some advantageous approaches in green synthesis are in favor of innovating the synthetic methods, optimizing the reaction process and eliminating the step of intermediate purification to save resource and reduce waste [10-12]. The pot, atom, step and economic (PASE) approach [13-17] is one of the most distinguished representatives in the efficient synthesis of nitrogen-based heterocycles, such as multicomponent reactions (MCRs) [18-23], one-pot cascade reactions [24-32] as good examples of PASE synthesis. We have reported a series of multicomponent reactions, like Groebke-Blackburn-Bienayme for making BET inhibitors UMB32 and UMB136 [33, 34], and Zhang 4-Aminoquinolines synthesis for developing fluorinated analogues of acetylcholinesterase (AChE) inhibitors [35], cascade reactions, such as one-step synthesis of quinolines and quinolin-4-ols involving Histone acetyltransferases (HAT) inhibitors [36, 37], as well as one-pot reactions, for example, amino acids(esters)-based [3+2] cycloadditions [38-48] in the synthesis of pyrrolidine-containing systems [49-59].

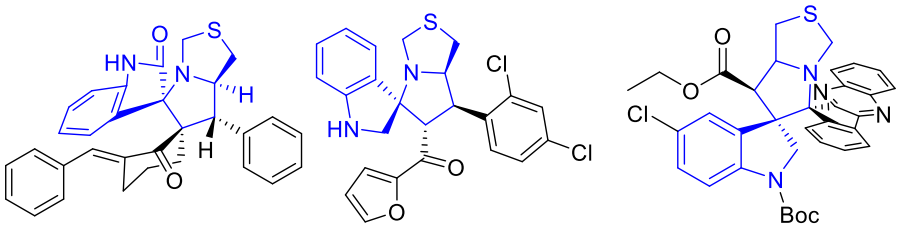
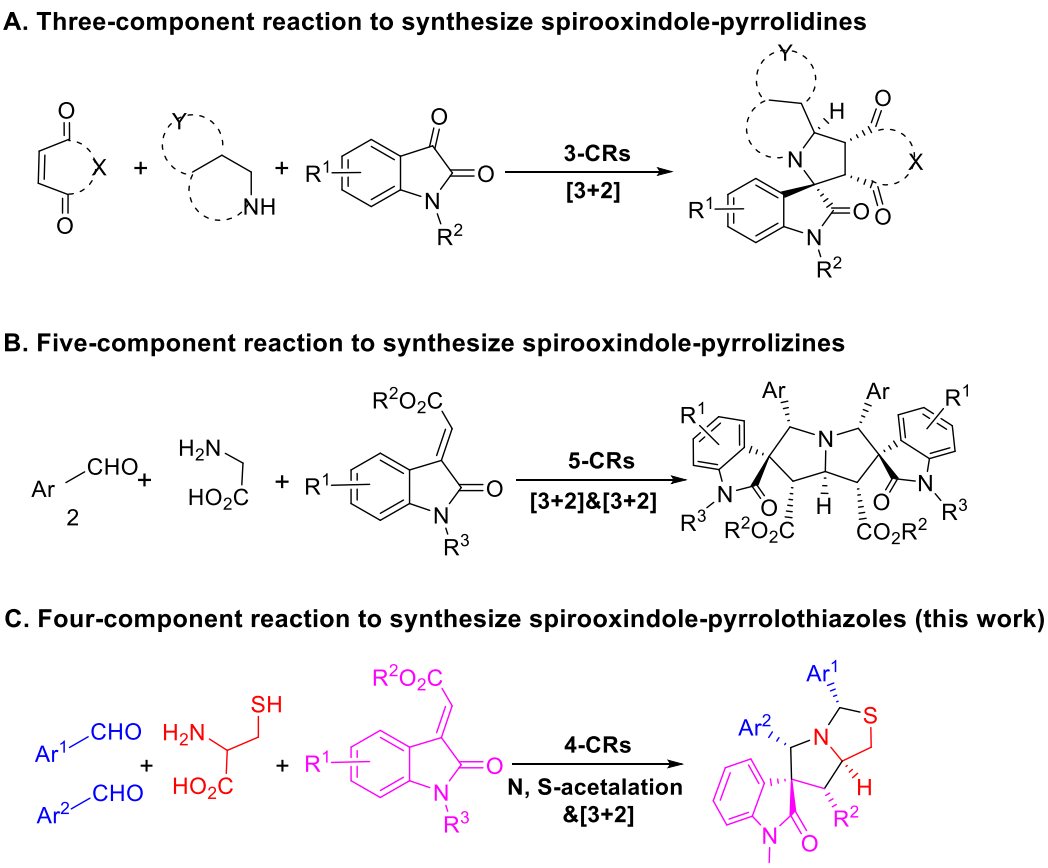


Figure 1: Bioactive Spirooxindole-pyrrolothiazoles

Pyrrolothiazole and spirooxindole moieties occupy exclusive positions as valuable source of natural products and therapeutic agents in organic synthesis and drug discovery [60-68].

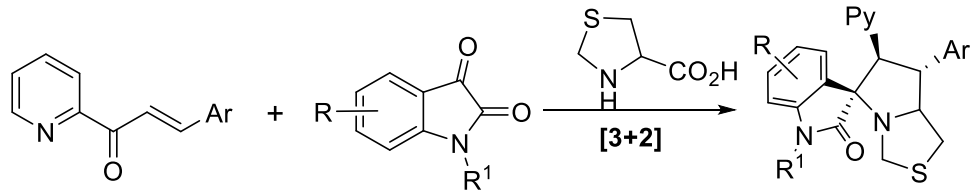


Scheme 1: The diastereoselective synthesis of spirooxindoles through MCRs.

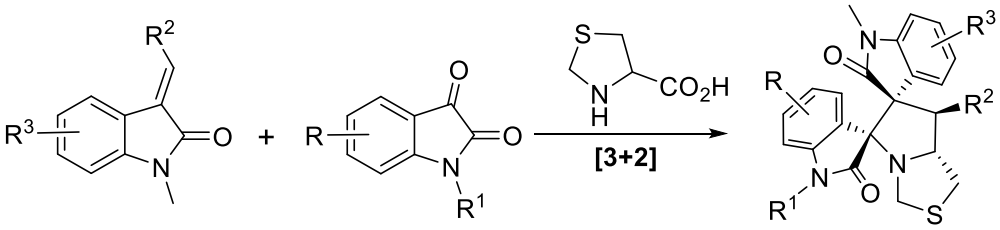
We have developed a number of asymmetric reaction to construct spirooxindole-based scaffolds through one-pot reactions with recyclable organocatalysts [69]. Notably, we conferred K10 acid to promote the C-H activation in the synthesis of spirooxindole-pyrrolidines, and used Zeolite HY catalyst to synthesize diastereoselective dispiro[oxindole-pyrrolidine]s with a butterfly shape (Scheme 1, A and B) [70, 71]. With the promising applications of spirooxindole-pyrrolothiazoles in drug discovery (Figure 1) [72-74], the structural integration of spirooxindole and pyrrolothiazole with diverse substituted groups via efficient synthesis is a challengeable research in green chemistry. The corresponding PASE reactions of making spirooxindole-pyrrolothiazoles are even more rare, which only involves three-component reactions with isatins and thioproline (Scheme 2, A and B) [75, 76].

Introduced in this paper is four-component double annulations through 2-substitutedthioprolines formed in N, S-acetalation of aldehyde and cysteine, and subsequently one equivalent of aldehyde and olefinic oxindole *in situ* followed by decarboxylative 1,3-dipolar cycloaddition for diastereoselective synthesis of spirooxindole-pyrrolothiazoles with generating 5 new bonds, 5 stereocenters and two heterocycles (Scheme 1, C and Scheme 2, C).

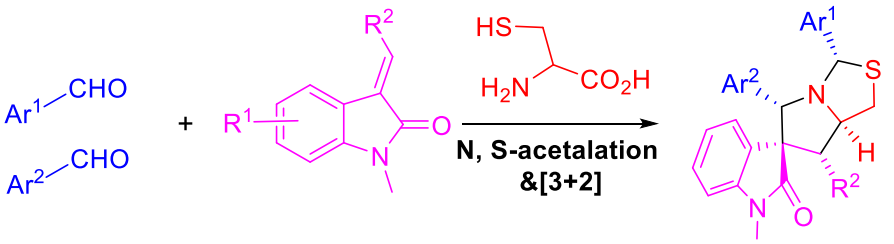
A. [3+2] cycloaddition of thioproline



B. [3+2] cycloaddition of thioproline



C. Sequential N, S-acetalation and [3+2] cycloaddition of cysteine (this work)



Scheme 2: The synthesis of spirooxindole-pyrrolothiazoles

Results and discussion

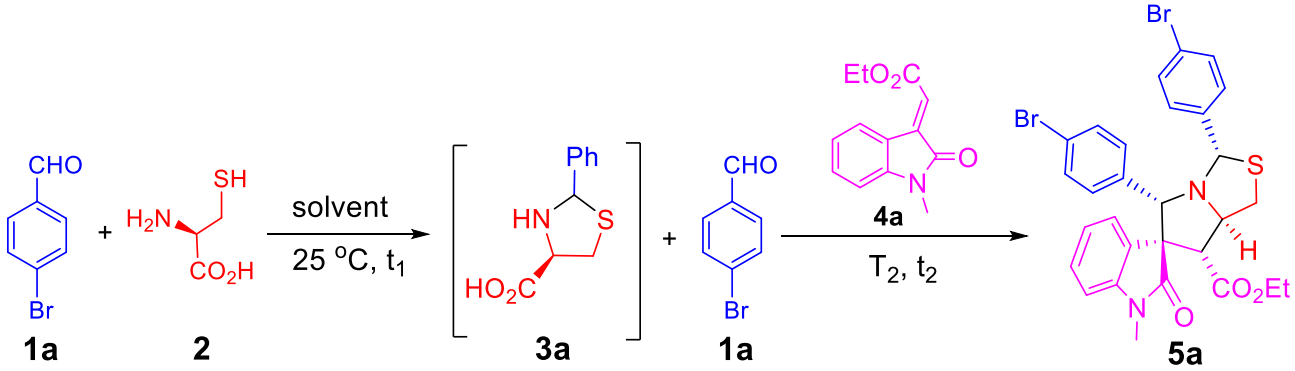
The optimized reaction conditions of stepwise, one-pot and cascade (two-step with one operational step) process for N, S-acetalation and decarboxylative 1,3-dipolar cycloaddition were developed by using two equivalents of 4-bromobenzaldehyde **1a**, L-cysteine **2** and

olefinic oxindole **4a** shown in Table 1. Taking the example by my reported work [54-59], we further evaluated the influence of protic solvents such as EtOH, ^{i}PrOH and MeOH, which only results in slightly different LC yield (93-95%) of compound **3a** and followed by decarboxylative [3+2] cycloaddition with olefinic oxindole **4a** under reflux heating, it indicates that the reactions with EtOH and ^{i}PrOH afforded the 81% of LC yield for compound **5a** slightly better than 78% yield using MeOH as a solvent (Table1, entries 1-4). After screening the reaction temperature in the 2nd step of one-pot process (Table 1, entries 4 and 5), it was found that thioproline **3a** without purification from N, S-acetalation with 1.0:1.15 of **1a:2** at 25 ^{o}C for 6 h with EtOH as solvent, *in situ* followed by addition of 1.1:1.0 of **1a:4a** for [3+2] cycloaddition at 90 ^{o}C for 9 h gave compound **5a** with the 81% of LC yield. Next, the stepwise process was also carried out by using the thioproline **3a** (1 eq.) with 86% of isolated yield and 1.1:1.0 of **1a:4a** through decarboxylative [3+2] cycloaddition (Table 1, entry 6), which afforded compound **5a** with 73% isolated yield at 90 ^{o}C for 9 h. Notably, we conferred cascade reaction process to synthesize compound **5a** with 70% isolated yield as one-step four-component reaction (4-CR) with 2.2:1.1:1.0 of **1a:2:4a** at 90 ^{o}C for 9 h in EtOH after variations of solvents, reaction time and temperature with one operational step (Table 1, entries 7-12). This 4-CR reaction is the first example of double annulations with sequential N, S-acetalation and [3+2] cycloaddition for diastereoselective spirooxindole-pyrrolothiazoles by the formation of two new rings, 5 bonds, and 5 stereocenters without intermediate purification.

To explore the reaction scope of 4-CR reaction, different aldehydes **1** (Ar^{1}) were used to react with L-cysteine **2** and olefinic oxindole **4a** in the synthesis of substituted spirooxindole-pyrrolothiazoles analogues **5a-5d** with 49-70% isolated yield (Table 2) under

the optimized reaction conditions (Table 1, entry 7).

Table 1: Optimized reaction conditions for double annulations of cysteine



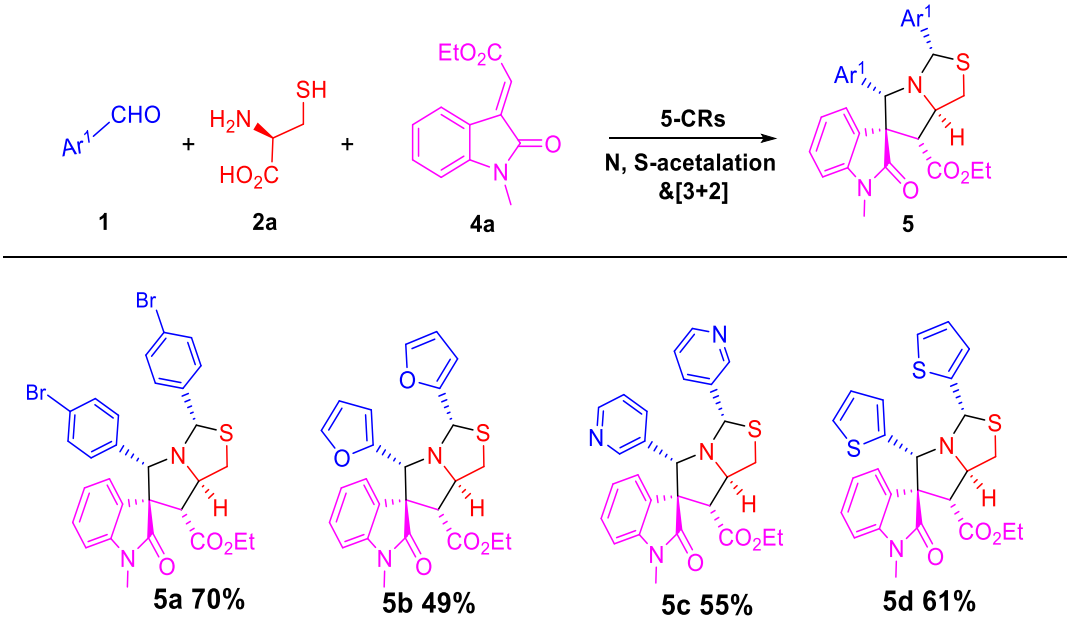
Entry	Solvent	t_1 (h)	**3a** (%)[b]	t_2 (h)	T_1(°C)	**5a** (%)[b]
1	EtOH	3	86			--
2	^{i}PrOH	6	95	12	105	81
3	MeOH	6	93	12	70	78
4	EtOH	6	95	12	90	81
5	EtOH	6	95	9	90	81
6[c]	EtOH	6	95(86)	9	90	83(73)
7[d]	EtOH			9	90	79(70)
8[d]	EtOH			6	90	67
9[d]	EtOH			18	90	75
10[d]	MeOH			9	70	76
11[d]	^{i}PrOH			9	105	78
12[d]	MeCN			9	90	67

[a] One-pot reaction of 1.0:1.15 of **1a**:**2** for *N*, *S*-acetalation **3a** followed by addition of 1.1:1.0 of **1a:4a** for [3+2] cycloaddition.[b] Detected by LC, isolated yield in parenthesis. [c] intermediate **3a** was isolated in the two-step reaction. [d] Cascade reaction of 2.2:1.1:1.0 of **1a**:**2**:**4a**. [e] dr > 4:1, Determined by ^{1}H NMR analysis of the crude products after the reaction mixture filtered through a pad of silica gel and removal of solvent.

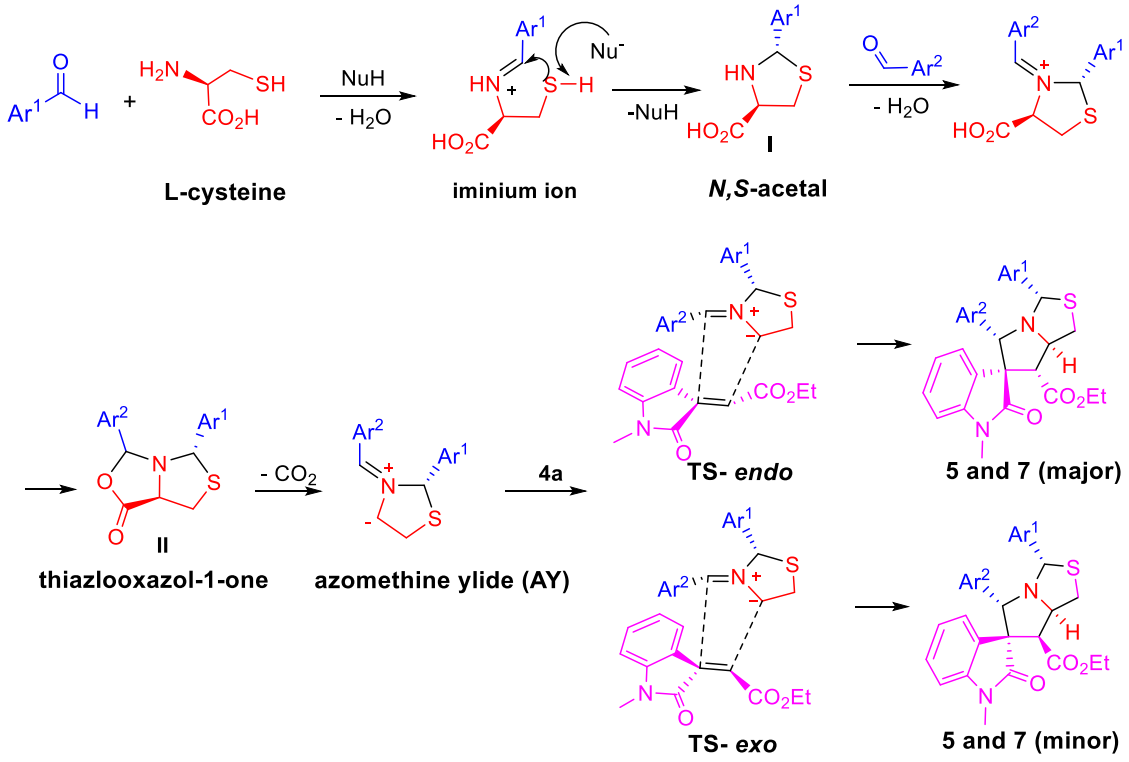
In addition, according to one-pot reaction process (Table 1, entry 5) with two operational steps using different aldehydes **1** and **6**, Products **7a-e** were synthesized in 43–72% isolated yields and up to 6:1 dr (Table 3). The results indicate that substituent on Ar^2 of the aldehydes could influence the product yield, such as **7c** (3-pyridinyl, 43% yield, 4.5:1 dr). In addition, oxindole **4** with different R^1 were employed for the synthesis to give **7f** with COMe

in the trace amount and no product **7g** with Ph, following aliphatic aldehydes to replace aromatic aldehydes, the reaction gave **7h** and **7i** as complex mixtures [54-59, 71].

Table 2: Four-component reaction for the synthesis of compound **5**

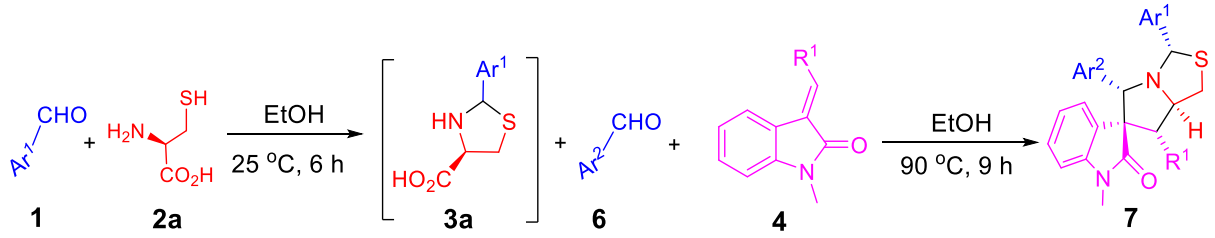


[a] Isolated yield. Reaction conditions are same as Table 1, entry 5



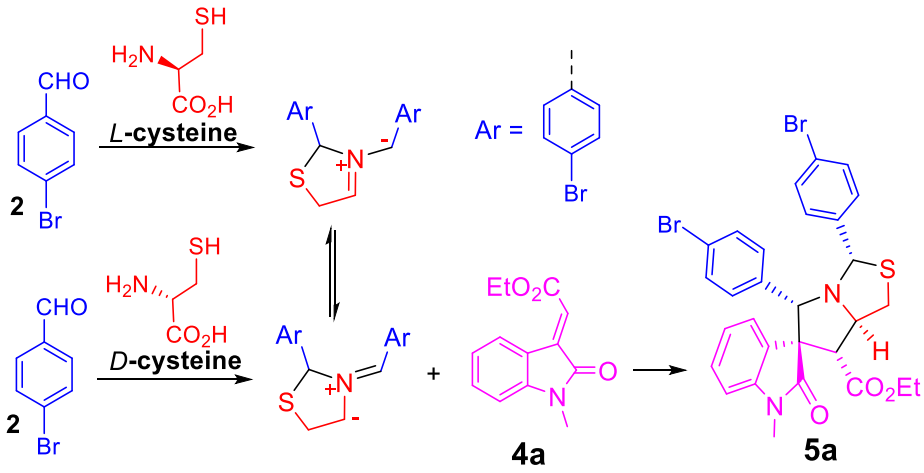
Scheme 3: Proposed mechanism for the double [3+2] cycloadditions.

Table 3: One-pot reaction for the synthesis of compound **7**



entry	Ar^1	Ar^2	R^1	product	yield (%)[b]
1	2-thiophenyl	3- OMe-4-FC_6H_3	CO_2Et	7a	66
2	2-thiophenyl	2-furanyl	CO_2Et	7b	51
3	2-thiophenyl	3-pyridinyl	CO_2Et	7c	43
4	2-FC_6H_4	4-ClC_6H_4	CO_2Et	7d	72
5	4-BrC_6H_4	4-ClC_6H_4	CO_2Et	7e	66
6	4-BrC_6H_4	Ph	COMe	7f	trace
7	4-BrC_6H_4	Ph	Ph	7g	--
8	4-BrC_6H_4	CO_2Et	CO_2Et	7h	messy
9	4-BrC_6H_4	Ethyl	CO_2Et	7i	messy

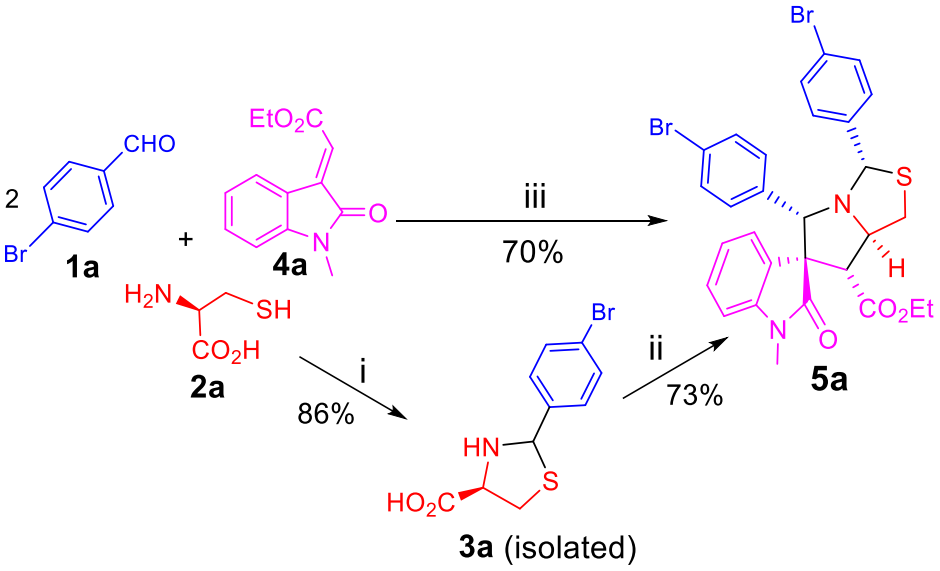
[a] Isolated yield. Reaction conditions are same as Table 1, entry 5.



Scheme 4: The synthesis of compound **5a** with D- and L-cysteine

The reaction mechanism of double annulations for sequential N, S-acetalation and decarboxylative [3+2] cycloaddition is shown in Scheme 3. With the promotion of protonic solvent EtOH, N, S-acetal **I** from the condensation of cysteine and an aldehyde reacts with second equivalent of aldehyde followed by cyclization to generate thiazlooxazol-1-one **II**. Subsequent decarboxylation of thiazlooxazol-1-one **II** affords non-stabilized azomethine

ylide (**AY**) for 1,3-dipolar cycloaddition with olefinic oxindole **4a** to give spirooxindole-pyrrolothiazoles **5** and **7**. The endo-TS is more favorable than exo-TS for 1,3-dipolar cycloaddition to afford major and minor products. The diastereochemistry of non-stabilized azomethine ylides for decarboxylative [3+2] cycloaddition could be identified in reported literature.[54-59, 71] Through the study of mechanism, it elucidates that the double annulations using L-cysteine undergoes three stages: N, S-acetal **I**, thiazlooxazol-1-one **II** and **AY** in the reducing stereocenter amount of 3 to 1. The mechanistic process indicates that the configuration of L-cysteine didn't affect the stereoselectivity in the formation of compound **5** and **7**. Thus, we further validated the hypothesis through the experimental results using D- and L-cysteine to synthesize compound **5a** (Scheme 4).



Scheme 5: Two-step (Process I) vs. Cascade (Process II) synthesis of 5a. i) 1.0:1.15 of **1a:2**, EtOH (0.05 M), 25 ^{o}C, 6 h. ii) 1.1:1.0:1.0 of **1a:3a:4a**, EtOH (0.5 M), 90 ^{o}C, 9 h (Table 1, entry 6). iii) 2.2:1.1:1.0 of **1a:2:4a**, EtOH (0.5 M), 90 ^{o}C, 9 h (Table 1, entry 7).

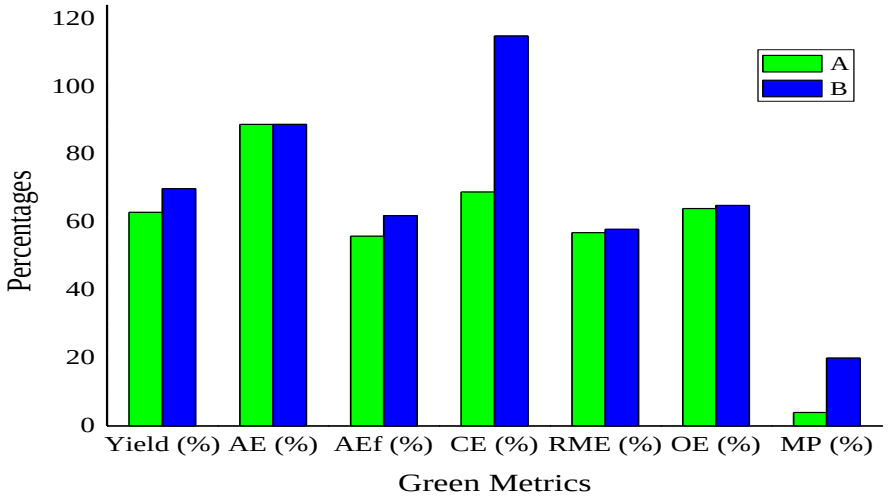
We conferred green chemistry metrics to evaluate the process efficiency of four-component reaction via comprehensive and quantitative calculation [77]. The metrics analysis is

carried out for the two-step synthesis with intermediate separation (Process I) and the single-step method (Process II) for the synthesis of spirooxindole-pyrrolothiazoles **5a** according to the reaction conditions shown in Scheme 5. Green chemistry metrics data including atom economy (AE), atom efficiency (AEf), carbon efficiency (CE), reaction mass efficiency (RME), optimum efficiency (OE), mass productivity (MP), mass intensity (MI), process mass intensity (PMI), E factor (E), and solvent intensity (SI) are listed in Table 4 and 5 (the green metrics and detailed calculation process in supporting information).

Table 4: Green metrics (AE, AEf, CE, RME, OE and MP) analysis for processes A and B.

Process	Isolation steps	Yield (%)	AE (%)	AEf (%)	CE (%)	RME (%)	OE (%)	MP (%)
I	2	63	88.9	56	64.4	57	64.1	4
II	1	70	88.9	62	115	58	65	20

The higher the value, the greener the process



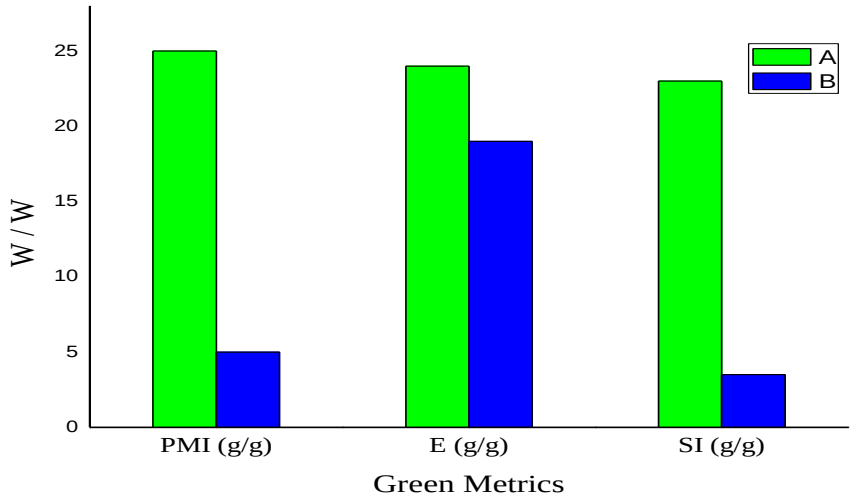
Process I is a two-step method involving intermediates isolation, in which compound **3a** was purified before 1,3-dipolar cycloaddition. Process II is a single-step approach without

isolation of intermediate **3a**. The same substrates for synthesizing product **5a** in Process I and II results in 88.9% of AE. The AEf, RME and OE for one-step Processes II are 62%, 58% and 65%, a little better than those for process I (56%, 57% and 64.1%). In addition, CE and MP are significant references to elucidate reaction process consumption. The CE and MP for process II (115% and 20%) are much better than that for Process I (64.4% and 4%). PMI for Process I (25) is 5 times larger than that for Process II (5). The E for Process I (24) is worse than that for Process II (19). Solvent consumption (SI, 3.5) for Process II is clearly lower than that for Process I (23) with more solvent for intermediate separations.

Table 5: Green metrics (PMI, E-factor, and SI) analysis for processes A and B.

Process	PMI(g/g)	E (g/g)	SI (g/g)
A	25	24	23
B	5	19	3.5

The lower value, the better the reaction process



Conclusions

A readily and efficient four-component synthesis for spirooxindole-pyrrolothiazoles is introduced, which involves sequential N, S-acetalation and decarboxylative [3+2] cycloaddition reactions. This one-pot and two-step process with four components generates 5 bonds, 5 stereocenters and two heterocyclesin a diastereoselective fashion, and without intermediate purification. One-pot four-component synthesis ingreen metrics analysis is compared with the stepwise reaction process to pinpoint the overwhelming advantages of one-pot approach in the CE, MP, PMI, and SI by eliminating the intermediate purification. It is an efficient way to build up novel spirooxindole-pyrrolothiazolesfor drug discovery screening.

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Conflicts of interest

There are no conflicts to declare

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