One-pot double annulations to confer diastereoselective spirooxindolepyrrolothiazoles

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Abstract
A novel four-component reaction in one pot as an atom- and step-economic process was developed to synthesize diastereoselectively spirooxindolepyrrolothiazoles through sequential N,S-acetalation of aldehydes with cysteine and decarboxylative [3 + 2] cycladdition with olefinic oxindoles. High synthetic efficiency, operational simplification and reaction process economy using EtOH as solvent, and only releasing CO₂ and H₂O as side products confer this approach favorable in green chemistry metrics analysis.

Introduction
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 more than 75% of the 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 resources 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]. Zhang developed 4-aminquinolines for the synthesis of fluorinated analogues of acetylcholin-
esterase (AChE) inhibitors [35] in cascade reactions, such as one-step syntheses of quinolines. Quinolin-4-ols involving histone acetyltransferases (HAT) inhibitors [36,37], as well as one-pot reactions were also developed by Zhang using the 4-aminoquinoline synthesis, for example, in amino acids(esters)-based [3 + 2] cycloadditions [38-48] and in the synthesis of pyrrolidine-containing systems [49-59]. Pyrrolothiazole and spirooxindole moieties occupy exclusive positions as valuable source of natural products and therapeutic agents in organic synthesis and drug discovery [60-68].

We have developed a number of asymmetric reactions 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 spirooxindolepyrrolidines, and used Zeolite HY catalyst to synthesize diastereoselective dispiro[oxindolepyrroli-dine]s with a butterfly shape (Scheme 1A and 1B) [70,71]. With the promising applications of spirooxindolepyrrolothiazoles in drug discovery (Figure 1) [72-74], the structural integration of spirooxindole and pyrrolothiazole with diverse substituted groups via an efficient synthesis is a challengeable research in green chemistry. The corresponding PASE reactions of making spirooxindolepyrrolothiazoles are even more rare, which only involves three-component reactions with isatins and thioproline (Scheme 2A and 2B) [75,76].

Scheme 1: The diastereoselective synthesis of spirooxindoles through MCRs.

Figure 1: Bioactive Spirooxindole-pyrrolothiazoles.
Scheme 2: The synthesis of spirooxindolepyrrolothiazoles.

Four-component double annulations through 2-substituted thioprolines formed in N,S-acetalation of aldehyde and cysteine was introduced in this study. Subsequently one equivalent of aldehyde and olefinic oxindole in situ were followed by decarboxylative 1,3-dipolar cycloaddition for diastereoselective synthesis of spirooxindolepyrrolothiazoles with generating 5 new bonds, 5 stereocenters and two heterocycles (Scheme 1C and Scheme 2C).

Results and Discussion
The optimized reaction conditions of stepwise, one-pot and cascade (two-step with one operational step) processes 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. In our continuous effort on the reaction optimization of benign solvents, we firstly evaluated the influence of reaction time and protic solvents such as EtOH, iPrOH and MeOH at 25 °C for 6 h, which only results in slightly different LC yield (93–95%) of compound 3a (Table 1, entries 2–4) superior to 86% yield for 3 h (Table 1 entry 1), and followed by decarboxylative [3 + 2] cycloaddition with the second equivalent of compound 1a and olefinic oxindole 4a under reflux heating for 12 h. It indicates that the one-pot reaction process with EtOH and iPrOH afforded the 81% of LC yield for compound 5a slightly better than 78% yield using MeOH as a solvent (Table 1, entries 2–4).

After screening the reaction temperature in the 2nd step of the one-pot process (Table 1, entries 4 and 5), it was found that the diastereomeric mixture of thioproline 3a without purification from N,S-acetalation with 1.0:1.15 of 1a/2 at 25 °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 °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 equiv) 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 °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 °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 is the first example of double annulations with sequential N,S-acetalation and [3 + 2] cycloaddition for diastereoselective spirooxindolepyrrolothiazoles by the formation of two new rings, 5 bonds, and 5 stereocenters without intermediate purification.

To explore the reaction scope of 4-CR, different aldehydes 1 (Ar1) were used to react with L-cysteine (2) and olefinic oxindole 4a in the synthesis of substituted spirooxindolepyrrolothiazole analogues 5a–d with 49–70% isolated yield (Scheme 3).
Table 1: Optimization of reaction conditions for double annulations of cysteine.\(^a\)

| entry | solvent | \(t_1\) (h) | \(3a\) (%)\(^b\) | \(t_2\) (h) | \(T_1(°C)\) | \(5a\) (%)\(^b\) |
|-------|---------|-------------|----------------|-------------|-------------|----------------|
| 1     | EtOH    | 3           | 86             |             |             | –              |
| 2     | iPrOH   | 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\(^c,e\) | EtOH | 6           | 95 (86)        | 9           | 90          | 83 (73)        |
| 7\(^d,e\) | EtOH | 9           | 90             | 79          | 70          | 79 (70)        |
| 8\(^d\) | EtOH | 6           | 90             | 67          |             |                |
| 9\(^d\) | EtOH | 18          | 90             | 75          |             |                |
| 10\(^d\) | MeOH | 9           | 70             | 76          |             |                |
| 11\(^d\) | iPrOH | 9           | 105            | 78          |             |                |
| 12\(^d\) | MeCN | 9           | 90             | 67          |             |                |

\(^a\)One-pot reaction of 1.0:1.15 of 1a/2 for N,S-acetilation 3a followed by addition of 1.1:1.0 of 1a/4a for [3 + 2] cycloaddition.\(^b\)Detected by LC–MS, 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.

Scheme 3: Four-component reaction for the synthesis of compound 5.
under the optimized reaction conditions (Table 1, entry 7). Compounds 5b–d with using heteroaromatic aldehydes resulted in lower yield than 5a.

In addition, according to the 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 2).

The results indicate that the substituent on Ar2 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 R1 was employed for the synthesis to give 7f with COMe in a trace amount and no product 7g with a Ph group. The following reactions with aliphatic aldehydes gave 7h and 7i as complex mixtures [54-59,71]. The reaction mechanism of the double annulations for sequential N,S-acetalation and decarboxylative [3 + 2] cycloaddition is shown in Scheme 4. With the promotion of the protonic solvent EtOH, compound 3 (N,S-acetal) from the condensation of cysteine and an aldehyde reacts with a second equivalent of aldehyde followed by cyclization to generate thiazolooxazol-1-one I.

Subsequent decarboxylation of thiazolooxazol-1-one I affords non-stabilized azomethine ylide (AY) for 1,3-dipolar cycloaddition with olefinic oxindole 4a to give spirooxindolepyrrolothiazoles 5 and 7. The endo-TS is more favorable than exo-TS for the 1,3-dipolar cycloaddition to afford the major and minor products. The diastereochemistry of non-stabilized azomethine ylides for decarboxylative [3 + 2] cycloaddiction could be identified in reported literature [54-59,71]. Through the study of the mechanism, it elucidates that the double annulations using l-cysteine undergoes three stages: compound 3, thiazolooxazol-1-one I and AY in the reducing stereocenter in an ratio 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 5).

Process A is a two-step method involving isolation of intermediates, in which compound 3a was purified before 1,3-dipolar

| entry | Ar1 | Ar2 | R1 | product | yield (%)b |
|-------|-----|-----|----|---------|------------|
| 1     | 2-thiophenyl | 3-OMe-4-FC6H3 | CO2Et | 7a | 66 |
| 2     | 2-thiophenyl | 2-furanyl | CO2Et | 7b | 51 |
| 3     | 2-thiophenyl | 3-pyridinyl | CO2Et | 7c | 43 |
| 4     | 2-FC6H4 | 4-ClC6H4 | CO2Et | 7d | 72 |
| 5     | 4-BrC6H4 | 4-ClC6H4 | CO2Et | 7e | 66 |
| 6     | 4-BrC6H4 | Ph | COMe | 7f | trace |
| 7     | 4-BrC6H4 | Ph | Ph | 7g | – |
| 8     | 4-BrC6H4 | CO2Et | CO2Et | 7h | messy |
| 9     | 4-BrC6H4 | ethyl | CO2Et | 7i | messy |

aIsolated yield. Reaction conditions are same as Table 1, entry 5.

Table 2: One-pot reaction for the synthesis of compound 7.
Scheme 4: Proposed mechanism for the double [3 + 2] cycloadditions.

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

cycloaddition. Process B is a single-step approach without isolation of intermediate 3a. The same substrates for synthesizing product 5a in processes A and B results in 88.9% of AE. The AEf, RME and OE for one-step process B are 62%, 58% and 65%, a little better than those for process A (56%, 57% and 64.1%). In addition, CE and MP are significant references to elucidate reaction process consumption. The CE and MP for process B (115% and 20%) are much better than that for process A (64.4% and 4%). PMI for process A (25) is 5 times larger than that for process B (5). The E-factor for process A (24) is less significant than that for process B (19). Solvent consumption (SI, 3.5) for process B is clearly lower than that for process A (23) with more solvent for intermediate separations.

Conclusion
A readily and efficient four-component synthesis for spirooxindolepyrrolothiazoles is introduced, which involves a sequential
Scheme 6: Two-step (process A) vs cascade (process B) synthesis of 5a. i) 1.0:1.15 of 1a/2, EtOH (0.05 M), 25 °C, 6 h. ii) 1.1:1.0:1.0 of 1a/3a/4a, EtOH (0.5 M), 90 °C, 9 h (Table 1, entry 6). iii) 2.2:1.1:1.0 of 1a/2/4a, EtOH (0.5 M), 90 °C, 9 h (Table 1, entry 7).

Table 3: 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 (%) |
|---------|----------------|-----------|--------|---------|--------|---------|--------|--------|
| A       | 2              | 63        | 88.9   | 56      | 64.4   | 57      | 64.1   | 4      |
| B       | 1              | 70        | 88.9   | 62      | 115    | 58      | 65     | 20     |

Figure 2: Graphical representation of the green metrics (AE, AEf, CE, RME, OE and MP) analysis for processes A and B. The higher the value, the greener the process.

N,S-acetalation and decarboxylative [3 + 2] cycloaddition reaction. This one-pot and two-step process with four components generates 5 bonds, 5 stereocenters and two heterocycles in a diastereoselective fashion, and without intermediate purification. The one-pot four-component synthesis in green metrics analysis is compared with the stepwise reaction process.
to pinpoint the overwhelming advantages of the one-pot approach in the CE, MP, PMI, and SI by eliminating the intermediate purification. It is an efficient way to build up novel spirooxindolepyrrolothiazoles for drug discovery screening.

Supporting Information
Supporting Information File 1
Experimental and analytical data, copies of NMR spectra, green metrics and the detailed calculation process. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-171-S1.pdf]

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