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Chemodivergent and diastereoselective synthesis of *syn*- and *anti*-cyclopentenyl spiroisoxazolones under ball-milling conditions†

Peng Xu,[a] Ming-Jun Li,[a] Honglin Diao,[b] Ning Shao,[b] Zeng-Yang He,[ab] Shi-Zhu Fan,[a] Ze Zhang ⓘ *[a] and Hui Xu ⓘ *[a]

A new cyclization pattern between arylidene isoxazolones and enamino esters has been demonstrated, efficiently affording various structurally novel cyclopentenyl spiroisoxazolones with high chemoselectivity in a ball mill. Interestingly, the diastereoselectivity of the spiro products is also controllable, with both *syn*- and *anti*-isomers generated selectively under different reaction conditions. The mechanochemical protocol features good chemo- and diastereoselectivity, high efficiency, mild reaction conditions and minimal solvent usage, providing rapid, environmentally benign and scalable access to spirocyclopentenes.

Introduction

It is well known that spiro compounds are a large and important class of organic compounds, widely present in bioactive molecules,[1] agrochemicals,[2] organo-catalysts[3] and functional materials.[4] Notably, spirocyclic compounds are of great significance in potential drug development due to their rigid structures, which can decrease conformational entropy cost during protein target binding.[5] Currently, several of the top 200 best-selling drugs feature spirocyclic frameworks.[6] Among numerous spirocycles, spiroisoxazolones also exhibit wide-ranging bioactivities including antitubercular, cytotoxic and antibacterial properties,[7] and have been used as versatile building blocks in organic synthesis due to their diverse reactivity.[8] Despite the significant research efforts focused on the synthesis of spiro compounds,[9] studies on spiroisoxazolone compounds remain relatively scarce.[10] In this context, exploring convenient and efficient methods for the construction of structurally diverse spiroisoxazolone derivatives is highly desirable.

Mechanochemical organic synthesis has gained increasing attention in recent years as a promising alternative to conventional solution-based methods. Traditionally, organic reactions require solvents and sometimes harsh conditions, contributing to environmental concerns such as solvent waste and energy consumption. Mechanochemistry addresses these challenges

by utilizing mechanical forces, such as ball-milling or grinding, to drive chemical reactions without or with minimal solvent use. This not only significantly reduces solvent waste but also improves reaction efficiency by enhancing molecular interactions. Additionally, mechanochemical processes often occur under milder conditions and in shorter timeframes, making them more energy-efficient. Therefore, mechanochemistry has demonstrated broad applicability across various fields of organic chemistry.[11] The growing interest in mechanochemical techniques reflects their potential to drive more efficient, greener and scalable synthetic processes, making them a valuable tool in the advancement of sustainable organic methodologies. Considering the great potential of mechanochemistry, we have explored several cyclization reactions driven by ball-milling, enabling the efficient synthesis of a vast variety of heterocyclic[12] and spirocyclic compounds.[13] Very recently, we disclosed a copper-catalyzed tandem reaction between arylidene isoxazolones and enamino esters under ball-milling conditions, yielding a series of pyrrole-2-carboxylic acids (Scheme 1a).[12b] The reaction initially proceeds through an N-

[a]School of Chemical and Environmental Engineering, Anhui Polytechnic University, Wuhu 241000, P. R. China. E-mail: zhangze@ustc.edu.cn; hxu@ahpu.edu.cn
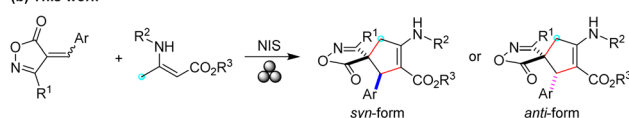
[b]Technology Center, China Tobacco Anhui Industrial Co., Ltd, Hefei 230088, P. R. China

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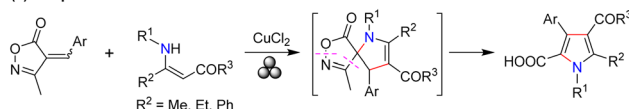
Scheme 1 Regulated annulation of arylidene isoxazolones with enamino esters under ball-milling conditions.

attacking cyclization to form spiropyrroline intermediates, which then undergo the ring-opening process to produce pyrrole products. Building on this work, we envisioned that a C-attacking cyclization could also occur under suitable conditions, leading to the formation of the rare spirocyclopentene scaffolds. With this goal in mind and following extensive exploration, we successfully controlled the chemoselectivity of the reaction to produce the desired cyclopentene–spiroisoxazolones, and also achieved high diastereoselective synthesis of both syn- and anti-isomers (Scheme 1b).
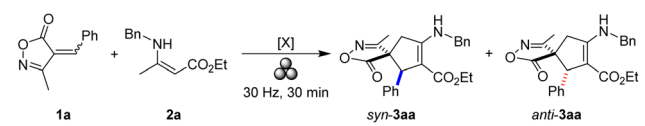
Results and discussion

4-Benzylidene isoxazol-5-one (**1a**) and ethyl 3-(benzylamino)but-2-enoate (**2a**) were selected as the model substrates to investigate the selective spiroannulation reaction. The optimized results are summarized in Table 1. When **1a** (0.2 mmol), 1.2 equiv. of **2a** and 1.2 equiv. of I_2 were introduced to a stainless steel jar (5 mL) containing four stainless steel balls (6 mm in diameter) and milled vigorously at 30 Hz for 30 min (Table 1, entry 1), another desired annulation product, namely cyclopentene-fused spiroisoxazolone (**3aa**), was obtained exclusively. Follow-up investigations confirmed its syn-configuration, where the phenyl group on the cyclopentene ring and the ester

moiety at the spiro atom are positioned on the same side. This initial result demonstrated that regulating the annulation process was feasible, though the product yield was somewhat low. Using N-iodosuccinimide (NIS) as the halogenating reagent promoted this C-attacking cyclization, affording product **3aa** in a moderate 56% yield (Table 1, entry 2). In addition to the syn-product, a minor anti-product was also generated. N-Bromo-succinimide (NBS) proved less efficient than NIS, delivering **3aa** in 36% yield with a syn-to-anti ratio of approximately 2 : 1 (Table 1, entry 3). Considering both efficiency and diastereoselectivity, NIS was selected as the promoter for further investigations. We then examined the reaction under liquid-assisted grinding (LAG) conditions by adding trace amounts of common solvents (Table 1, entries 4–9), as the LAG technique has been demonstrated to enhance reaction efficiency and, in some cases, modify selectivity.[11h,13b,14] To our delight, several solvents including acetonitrile (MeCN), toluene, dimethyl sulfoxide (DMSO) and N,N-dimethylformamide (DMF) were beneficial to this conversion. Notably, DMSO exhibited very high efficiency and diastereoselectivity, almost exclusively affording syn-configurational **3aa** with a 91% yield (Table 1, entry 8). Encouraged by the above results, we further explored the reaction using MeCN as the LAG solvent, aiming to achieve the selective synthesis of anti-spirocyclopentenes, as MeCN had shown the most favorable effect in the formation of anti-**3aa**. It was found that the introduction of bases such as Na_2CO_3, K_2CO_3, CH_3ONa, piperidine, 4-dimethylaminopyridine (DMAP) and 1,4-diazobicyclo[2,2,2]octane (DABCO) enhanced the diastereoselectivity towards the anti-product to some extent, with anti-**3aa** being isolated in moderate to good yields (Table 1, entries 10–15). Among these bases, CH_3ONa proved to be the optimal choice, affording anti-**3aa** in an impressive yield of 83%, along with 10% of syn-**3aa** (Table 1, entry 12). In addition, the milling parameters, including the materials, count and sizes of milling balls as well as the amount of LAG solvents and grinding auxiliaries, were evaluated, with the details presented in Table S1 (see the ESI).†

To compare the mechanochemical protocol with its solution-based counterpart, we then conducted this diastereoselective reaction in the corresponding solvents. The reaction of **1a** with **2a** in DMSO at room temperature also predominantly afforded syn-**3aa** with an excellent 88% yield (Table 1, entry 16 vs. entry 8). Nevertheless, when the reaction was performed in MeCN with CH_3ONa as the base, it exhibited lower diastereoselectivity towards the anti-product (Table 1, entry 17 vs. entry 12), with anti-**3aa** and syn-**3aa** isolated in 64% and 21% yields, respectively. From these results, it is clear that the LAG method offers several advantages, including enhanced diastereoselectivity, higher efficiency and minimal solvent usage.

After establishing the optimal reaction conditions, we proceeded to examine the universality and substrate scope of the diastereoselective spiroannulation. We first explored the substrate scope for the synthesis of syn-spirocyclopentenes from unsaturated isoxazolones and enamino ester derivatives under ball milling conditions (Table 2). Unsaturated isoxazolones bearing either electron-withdrawing groups (Me and OMe) or electron-donating groups (Cl, Br, CF_3 and NO_2) on the phenyl

Table 1 Optimization of the reaction conditions[a]

Entry	[X]	LAG solvent	Base	syn-**3aa**	anti-**3aa**
1	I_2			14	Trace
2	NIS			41	15
3	NBS			25	11
4	NIS	EtOH		27	12
5	NIS	MeCN		67	27
6	NIS	DCE		35	14
7	NIS	Toluene		75	Trace
8	NIS	DMSO		91	Trace
9	NIS	DMF		54	11
10	NIS	MeCN	Na_2CO_3	35	59
11	NIS	MeCN	K_2CO_3	27	61
12	NIS	MeCN	CH_3ONa	10	83
13	NIS	MeCN	Piperidine	21	58
14	NIS	MeCN	DMAP	22	69
15	NIS	MeCN	DABCO	29	55
16[c]	NIS			88	Trace
17[d]	NIS		CH_3ONa	21	64

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol, 1.2 equiv.), halogenating reagent (0.24 mmol, 1.2 equiv.), base (0.2 mmol, 1 equiv.), LAG solvent (30 μL) and four stainless steel balls (6 mm in diameter) were milled in a mixer mill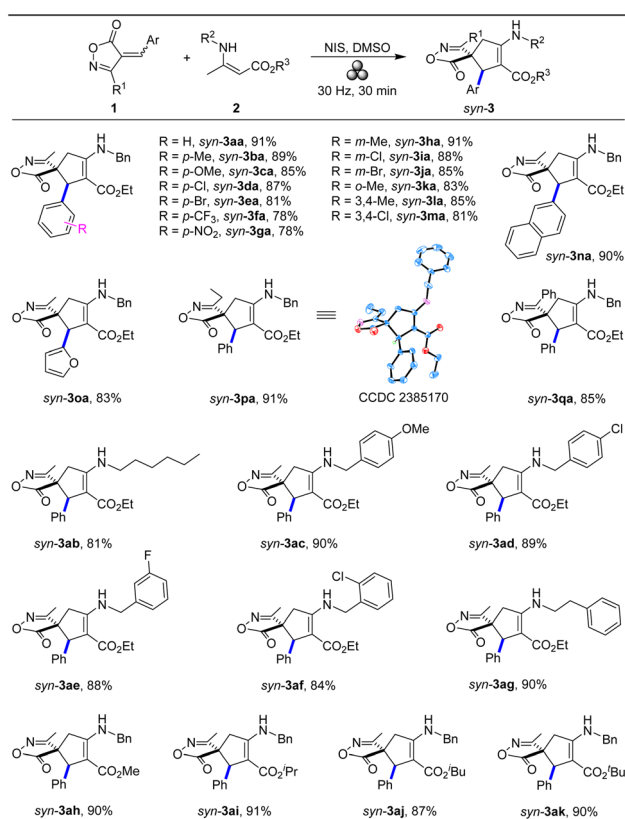. [b] Isolated yields based on **1a**. [c] The reaction was performed in DMSO (2 mL) at room temperature for 5 h. [d] The reaction was performed in MeCN (2 mL) at room temperature for 5 h.

ring reacted smoothly with **2a**, affording a series of *syn*-products **3ba–ma** in satisfactory yields of 78–91%. β-Naphthyl- and α-furanyl-substituted arylidene isoxazolones were also well tolerated in the reaction, with the corresponding products *syn*-**3na** and *syn*-**3oa** obtained in 90% and 83% yields, respectively. Additionally, methyl and phenyl group substituted substrates **1p** and **1q** were compatible in this transformation. Furthermore, the reaction exhibited impressive flexibility with variations in the enamino esters, where the benzyl group in R^2 was replaced by *n*-hexyl, substituted benzyl and phenethyl groups, and the ethyl group in the ester moiety was substituted with other alkyl groups (Me, ^{i}Pr, ^{i}Bu and ^{t}Bu), highlighting the excellent functional group tolerance of the reaction.
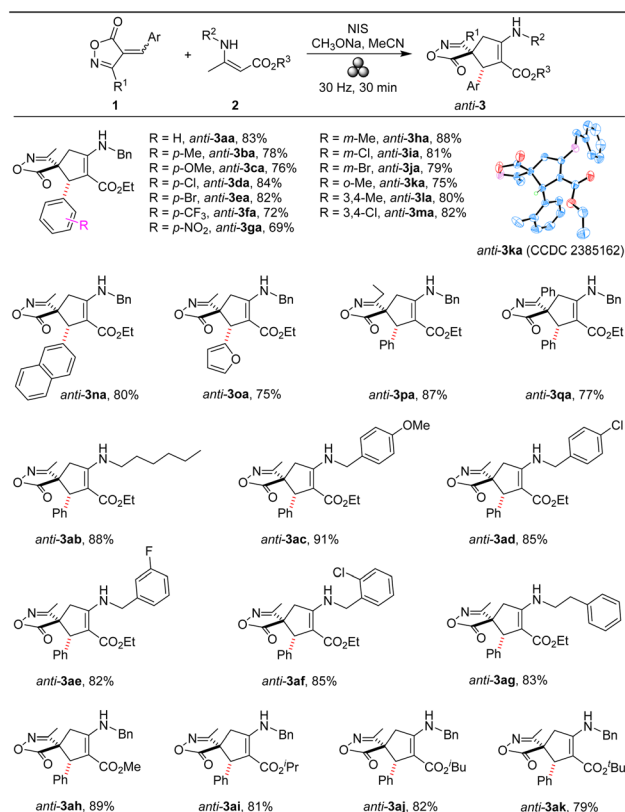
Next, we investigated the substrate scope for the selective synthesis of *anti*-spirocyclopentenes under the given conditions (Table 1, entry 12). The results are displayed in Table 3. It was found that all of the employed unsaturated isoxazolones **1b–q** and enamino esters **2b–k** proceeded well in the transformation, affording the corresponding *anti*-products in yields ranging from 69% to 91%. Overall, the yields of the *anti*-products were slightly lower than those of the *syn*-products, as small amounts of *syn*-isomers were generated in most cases during the selective synthesis of the *anti*-products. Despite this, the reaction

Table 3 Diastereoselective synthesis of *anti*-spirocyclopentenes under liquid-assisted grinding conditions^{a,b}

anti-3ka (CCDC 2385162)

R = H, anti-3aa, 83%	R = m-Me, anti-3ha, 88%	
R = p-Me, anti-3ba, 78%	R = m-Cl, anti-3ia, 81%	
R = p-OMe, anti-3ca, 76%	R = m-Br, anti-3ja, 79%	
R = p-Cl, anti-3da, 84%	R = o-Me, anti-3ka, 75%	
R = p-Br, anti-3ea, 82%	R = 3,4-Me, anti-3la, 80%	
R = p-CF₃, anti-3fa, 72%	R = 3,4-Cl, anti-3ma, 82%	
R = p-NO₂, anti-3ga, 69%		

anti-3na, 80%   anti-3oa, 75%   anti-3pa, 87%   anti-3qa, 77%

anti-3ab, 88%   anti-3ac, 91%   anti-3ad, 85%

anti-3ae, 82%   anti-3af, 85%   anti-3ag, 83%

anti-3ah, 89%   anti-3ai, 81%   anti-3aj, 82%   anti-3ak, 79%

^{a} Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv.), NIS (0.24 mmol, 1.2 equiv.), CH$_3$ONa (0.2 mmol, 1 equiv.), MeCN (30 μL) and four stainless steel balls (6 mm in diameter) were milled in a Retsch MM400 mixer mill. ^{b} Isolated yields based on **1**.

Table 2 Diastereoselective synthesis of *syn*-spirocyclopentenes under liquid-assisted grinding conditions^{a,b}

R = H, syn-3aa, 91%	R = m-Me, syn-3ha, 91%	
R = p-Me, syn-3ba, 89%	R = m-Cl, syn-3ia, 88%	
R = p-OMe, syn-3ca, 85%	R = m-Br, syn-3ja, 85%	
R = p-Cl, syn-3da, 87%	R = o-Me, syn-3ka, 83%	
R = p-Br, syn-3ea, 81%	R = 3,4-Me, syn-3la, 85%	
R = p-CF₃, syn-3fa, 78%	R = 3,4-Cl, syn-3ma, 81%	
R = p-NO₂, syn-3ga, 78%		

syn-3na, 90%

syn-3oa, 83%   syn-3pa, 91%   CCDC 2385170   syn-3qa, 85%

syn-3ab, 81%   syn-3ac, 90%   syn-3ad, 89%

syn-3ae, 88%   syn-3af, 84%   syn-3ag, 90%

syn-3ah, 90%   syn-3ai, 91%   syn-3aj, 87%   syn-3ak, 90%

^{a} Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv.), NIS (0.24 mmol, 1.2 equiv.), DMSO (30 μL) and four stainless steel balls (6 mm in diameter) were milled in a Retsch MM400 mixer mill. ^{b} Isolated yields based on **1**.

exhibited broad applicability across a wide range of substrates, demonstrating its potential for selective *anti*-spirocyclopentene synthesis under the given conditions.

The configurations of both the *syn*- and *anti*-products **3** were unequivocally confirmed by single-crystal X-ray analysis, using *syn*-**3pa** and *anti*-**3ka** as representative examples, respectively. Additionally, the *syn*- and *anti*- configurational products can be easily distinguished based on their ^{1}H NMR spectra (see the ESI†), as the chemical shifts of the tertiary hydrogen in the cyclopentene ring are distinctly different, ranging from 4.0–4.5 ppm for *syn*-products and 4.5–5.0 ppm for *anti*-products.

To demonstrate the practicality of this diastereoselective spiroannulation reaction, we then carried out scale-up experiments (Scheme 2). When the reaction of **1a** with **2a** towards the selective synthesis of *syn*-**3aa** was amplified to a 2 mmol scale, the corresponding *syn*-product was obtained with nearly exclusive diastereoselectivity and excellent yield (88%, 714 mg). In addition, scaling up the reaction for *anti*-product synthesis under the corresponding conditions also maintained good stereochemical selectivity, delivering *anti*-**3aa** in 76% yield (617 mg), along with a minor amount of the *syn*-isomer, which was isolated in 12% yield. These results confirmed that the
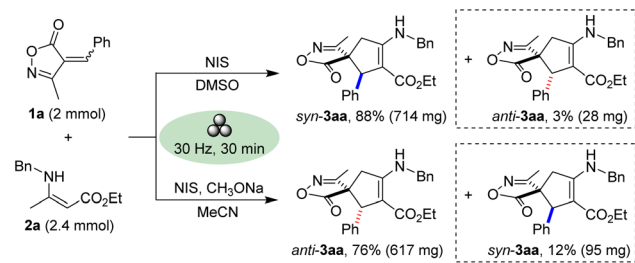
Scheme 2 Scale-up reaction of **1a** with **2a**.

spiroannulation reaction exhibits strong scalability in terms of stereoselectivity and efficiency, further highlighting their potential for larger-scale synthetic applications.

To elucidate the diastereoselectivity of the controllable spiroannulation, we proposed a possible reaction mechanism using the reaction of **1a** with **2a** as an example, as illustrated in Scheme 3. At first, **1a** reacts with **2a** *via* a Michael addition to form adduct **A** (detected by HRMS, see Fig. S111 in the ESI).† Then, intermediate **A** undergoes iodination in the presence of NIS, where the iodine atom is introduced at different positions under diverse conditions. In the absence of a base, **A** reacts with NIS at the methine position of the isoxazolone moiety, yielding a tertiary halide intermediate **B** (path a). Intermediate **B** subsequently undergoes an elimination reaction, producing (*E*)-alkene intermediate **C**, which then undergoes an intramolecular addition to yield *syn*-**3aa**. Under basic conditions, particularly in the presence of sodium methoxide, iodination occurs at the methyl group of the enamino ester segment, forming a primary halide.[15] Concurrently, the base abstracts a tertiary hydrogen from the isoxazolone ring, generating carbanion intermediate **D** (path b). This intermediate then undergoes an intramolecular nucleophilic substitution to produce spirocyclic product **3aa**. In this process, the bulky phenyl and methyl groups are positioned on the same side, creating sufficient space for the nucleophilic reaction to proceed efficiently. Consequently, the product formed through this pathway predominantly exhibits the *anti*-configuration.
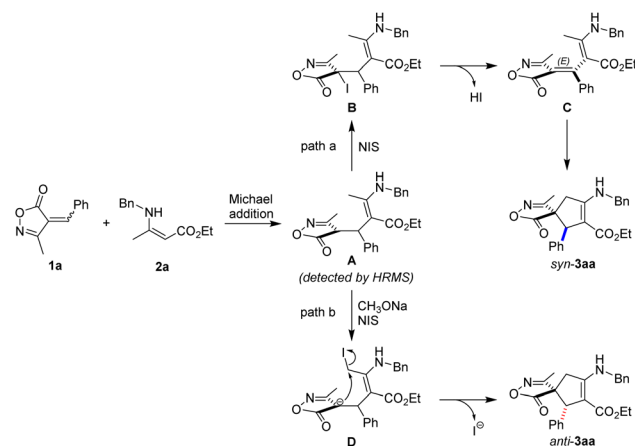
Scheme 3 Proposed reaction mechanism.

Conclusions

In summary, we have developed a novel and efficient mechanochemical method for the synthesis of structurally unique cyclopentenyl spiroisoxazolones through a selective C-attacking cyclization of arylidene isoxazolones and enamino esters. The ball-milling approach demonstrates excellent chemoselectivity and diastereoselectivity, allowing for the controlled synthesis of both *syn*- and *anti*-cyclopentene-spiroisoxazolone isomers under mild reaction conditions. The reaction exhibits several advantages, such as remarkable functional group tolerance, high efficiency, minimal solvent usage, scalability and ability to selectively produce stereoisomers. These strengths highlight the protocol's practicality and versatility in synthetic organic chemistry.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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