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Communication

1,3-Dipolar cycloaddition for selective synthesis of functionalized spiro[indoline-3,3′-pyrrolizines]

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ABSTRACT

The 1,3-dipolar cycloaddition reaction of dimethyl hex-2-en-4-ynedioate with azomethine ylides derived from reaction of L-proline with various isatins in methanol selectively resulted in the formation of functionalized spiro[indoline-3,3′-pyrrolizine]acrylates as main products and spiro[indoline-3,3′-pyrrolizine]propiolates as minor products. This result indicated that the electron-deficient alkyne has higher reactivity than that of electron-deficient alkene in 1,3-dipolar cycloaddition reaction.

Spirooxindole is an important heterocyclic nucleus with broad biological activity and applications for pharmaceutical lead discovery [1–4]. Among the various spirooxindoles, the spirooxindole-pyrrolidine is one of the most frequently encountered in natural alkaloids and is often considered as attractive templates for drug discovery [5–8]. They have been widely studied on the antiviral, antibacterial, anti-cancer and cholinesterase inhibitory activities, *etc.* (Fig. 1) [9–11]. As a consequence, many efficient synthetic procedures have been developed for the preparation of the structurally diverse spirooxindole-pyrrolidine derivatives [12–18]. The 1,3-dipolar cycloaddition reaction is one of the most important method for the construction of spirooxindole-pyrrolidines [19–23]. For this purpose, the cycloaddition reaction of various azomethine ylides with active electron-deficient alkenes has become the convenient method for synthesis of various spirooxindole-pyrrolidines [24–27]. On the other hand, the electron-deficient alkynes were also employed to react with azomethine ylides generating from reaction of isatins with suitable amines in 1,3-dipolar cycloaddition [28–36]. In recent years, dialkyl hex-2-en-4-ynedioates have emerged as new reactive electron-deficient alkynes in various cycloaddition reactions [36–40]. Dialkyl hex-2-en-4-ynedioates can be easily prepared in nearly quantitative yields from base-catalysed dimerization of alkyl propiolates under mild reaction conditions [41–49]. We have also developed several domino reactions by employing nucleophilic triphenylphosphine addition to electron-deficient alkynes as key protocol for the efficient construction of diverse polycyclic and spiro compounds [50–55]. In this paper, we wish to report the 1,3-dipolar cycloaddition reaction of dimethyl hex-2-en-4-ynedioate with azomethine ylides derived from reaction of L-proline with various isatins in methanol and selectively synthesis of functionalized spiro[indoline-3,3′-pyrrolizines].

According to the previously established reaction conditions for the preparing of the spiro[indoline-3,3′-pyrrolizine] [28–33], a mixture of L-proline, isatin and dimethyl hex-2-en-4-ynedioate in methanol was stirred at room temperature. TLC analysis showed that the reaction was completed in 24 h. After workup, the spiro compound **1a** and the spiro compound **2a** were obtained in 62% and 20% yields, which can be separated out by column chromatography. The structural analysis indicated that the spiro compound **1a** has a unit of methyl acrylate, which was clearly come from the reaction of 1,3-dipolar cycloaddition of azomethine ylide with the C$\equiv$C triple bond in dimethyl hex-2-en-4-ynedioate. On the other hand, the [3 + 2] reaction of the methylene ylide with the C=C double bond in dimethyl hex-2-en-4-ynedioate afforded the spiro compound **2a**. The much higher yield of **1a** to that of **2a** showed that the C$\equiv$C triple bond has higher reactivity than that of C=C double bond in dimethyl hex-2-en-4-ynedioate. In order to increase the selectivity of the reaction, the three-component reaction was carried out in ethanol, acetonitrile at room temperature and at the elevated temperature. But similar yields of the spiro compounds **1a** and **2a** were obtained. Then various

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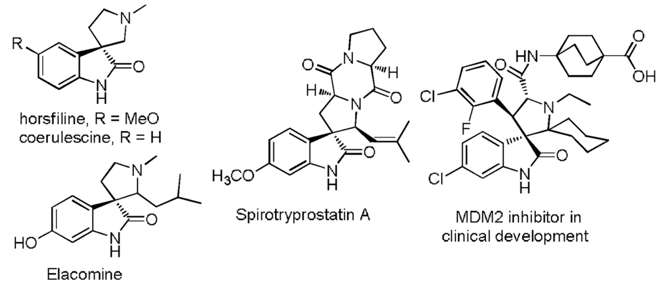
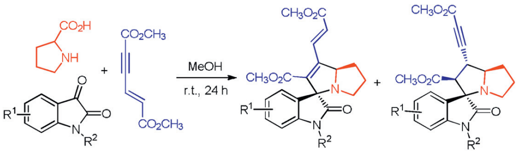


Fig. 1. Representative of bioactive natural and synthetic products having spirooxindole-pyrrolidine.

Table 1
Synthesis of spiro[indoline-3,3′-pyrrolizines] *via* cycloaddition reaction.[a]



Entry	R^1	R^2	Compd.		Yield (%)[b]	
			1	2	1	2
1	5-Cl	H	**1a**	**2a**	62	20
2	H	H	**1b**	**2b**	54	–
3	5-F	H	**1c**	**2c**	48	–
4	5-CH_3	H	**1d**	**2d**	45	–
5	6-Cl	H	**1e**	**2e**	68	15
6	7-F	H	**1f**	**2f**	65	10
7	7-CF_3	H	**1g**	**2g**	67	13
8	H	Bn	**1h**	**2h**	52	16
9	5-Cl	Bn	**1i**	**2i**	58	
10	5-F	Bn	**1j**	**2j**	50	–
11	5-CH_3	Bn	**1k**	**2k**	49	
12	5-F	*n*-Bu	**1l**	**2l**	61	
13	5-CH_3	*n*-Bu	**1m**	**2m**	58	18
14	5-Cl	CH_3	**1n**	**2n**	45	–

[a] Reaction conditions: L-Proline (0.55 mmol), isatin (0.55 mmol), dimethyl hex-2-en-4-ynedioate (0.5 mmol), MeOH.
[b] Isolated yields.

substituted isatins were employed in the reaction. The results are summarized in Table 1 (Experimental section, ^1H and ^{13}C NMR spectra for all new compounds are listed in Supporting information). It can be seen that the reaction usually resulted in the spiro compounds **1a-1n** as main product and the spiro compound **2a-2n** as minor products. In some cases, the minor spiro compounds were not isolated due to too lower yields.

The molecular structures of the obtianed spiro compounds were fully characterized by IR, HRMS, ^1H and ^{13}C NMR spectra. The single crystal structures of the compounds **1h**, **1l** and **2h** (Fig. 2) were succesfully detemined by X-ray diffraction method. Crystallographic data **1h** (CCDC No. 1588730), **1l** (CCDC No. 1588731), **2h** (CCDC No. 1588732) have been deposited at the Cambridge Crystallographic Database Centre. In the compounds **1h** and **1l**, it can be seen that the acrylate unit exists in *E*-configuration. In the molecular structure of the compound **2h**, methyl carboxylate and methyl propiolate exist on the *trans*-position. On the other hand, the methyl carboxylate exist on the *cis*-position to the phenyl group of the oxindole scaffold. Thus, relative configurations of the obtained spiro compounds were clearly elucidated on the basis of NMR spectra and the single crystal structures.

For explaining the formation of the two kinds of spiro compounds, a plausible reaction mechanism was proposed on the basis of the similar 1,3-dipolar cycloaddition reaction (Scheme 1). At first, the condensation of L-proline with isatin afforded known intermediate azomethine ylide (**A**). Because the C≡C triple bond and C=C double bond connected to the electron-withdrawing ester group in dimethyl hex-2-en-4-ynedioate, both of them could react as the reactive 1,3-dipolarophiles. Thus, the 1,3-dipolar cycloaddition of azomethine ylide (**A**) with more reactive C≡C triple bond according to the path a gave the spiro compound **1** as main product. On the other hand, the 1,3-dipolar cycloaddition of azomethine ylide (**A**) with less reactive C=C double bond according to the path b resulted in the spiro compound **2** as minor product. Due to the concerted reaction of 1,3-dipolar cycloaddition, the two substituents retained the *trans*-configuration in the newly-formed ring of pyrrole in the spiro compound **2**. Thus, dimethyl hex-2-en-4-ynedioate provided an ideal example for comparing the reactivity of electron-deficient C=C double bond and C≡C triple bond as the active 1,3-dipolarophiles in cycloaddition reaction. Our experimental results clearly revealed that the electron-deficient alkyne has much high reactivity than that of electron-deficient alkene in 1,3-dipolar cycloaddition reaction.

For developing the scope of this reaction, acenaphthylene-1,2-dione was also employed to react with proline and dimethyl hex-2-en-4-ynedioate in methanol at room temperature. The spiro compound **3a** was successfully obtained in 51% yields, in which the C=C double bond was remained in the molecule (Scheme 2). On the other hand, the reaction with ninhydrin resulted in the product **3b**. It was obviously produced from the further ring-opening of the initially formed spiro[indene-2,3′-pyrrolizine] *via* [3+2] cycloaddition reaction. The single crystal structure of the compound **3b** (Fig. 3) has been determined by X-ray diffraction method. Crystallographic data **3b** (CCDC No. 1972418) has been deposited at the Cambridge Crystallographic Database Centre.

For demonstrating the synthetic values of this three-component reaction, the variety of amino acids were also examined.

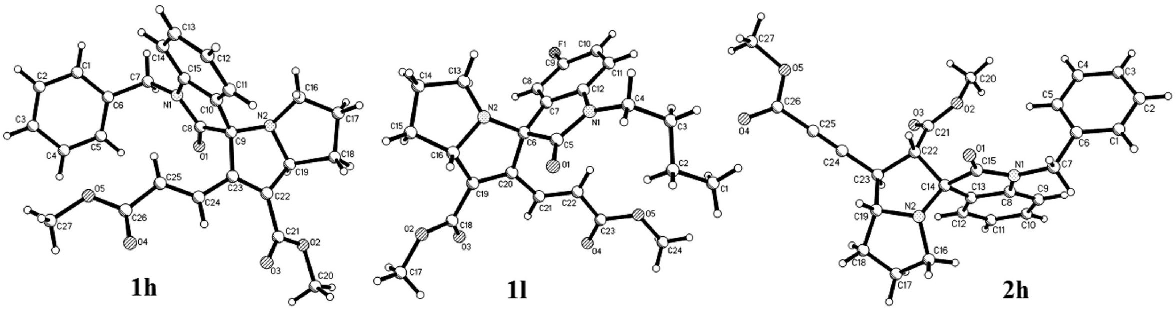
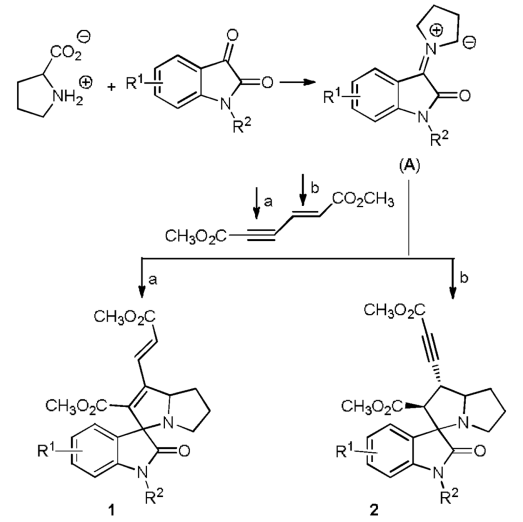
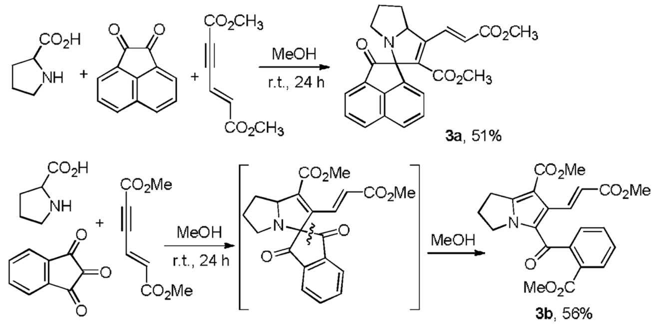

1h **1l** **2h**

Fig. 2. Molecular structures of the compounds **1h, 1l** and **2h**.



Scheme 1. Proposed formation mechanism for spiro compounds.



Scheme 2. Reactions with acenaphthylene-1,2-dione and ninhydrin.

Therefore, thioproline, 4-hydroxyproline and sarcosine were also employed to replace proline in the three-component reaction under same reaction conditions (Scheme 3). The similar spiro compounds **4a-4c** were formed as main products. In each case, the C≡C triple bond took part in the reaction and the C=C double bond was remained in the molecule. These results indicated again the electron-deficient C≡C triple bond is more reactive than the electron-deficient C=C double bond in 1,3-dipolar cycloaddition reaction.

In summary, we have investigated 1,3-dipolar cycloaddition reaction of dimethyl hex-2-en-4-ynedioate with azomethine ylides derived from reaction of L-proline with various isatins in methanol. This reaction successfully provided an convenient synthetic protocol for functionalized spiro[indoline-3,3′-pyrrolizine]acrylates as main products and spiro[indoline-3,3′-pyrrolizine]propiolates as minor products. The stereochemistry of the spiro compounds were clearly elucidated by determination of several single crystal structures. Additionally, this reaction provided an example to reveal the relative reactivity of the electron-deficient alkyne and electron-deficient alkene in 1,3-dipolar cycloaddition reaction.

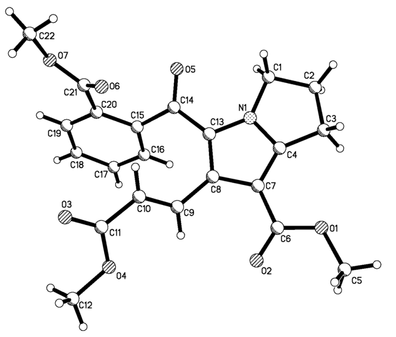
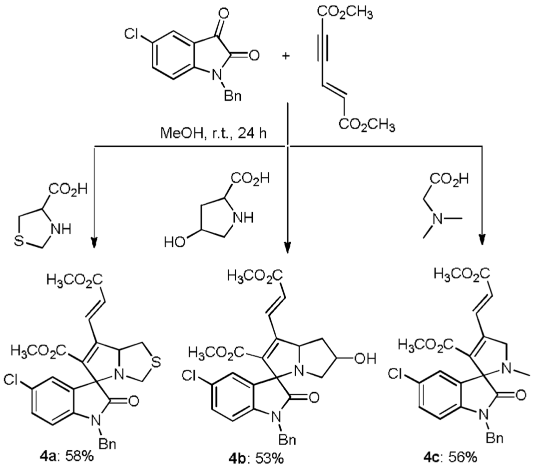


Fig. 3. Molecular structures of the compounds **3b.**



Scheme 3. Reactions with other amino acids.

Declaration of competing interest

We declared there is no conflict of interest in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.12.028.

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