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1,3-Dipolar Cycloadditions of Isatin *N,N′*-Cyclic Azomethine Imines with Alkynes for the synthesis of spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazoles]

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Abstract

$CuCO_3$ catalyzed 1, 3-dipolar cycloaddition of isatin *N,N′*-cyclic azomethine imine has been developed. Biologically active heterocyclic spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazoles] were prepared as single regioisomers in good yields and functional group compatibility.

Keywords

Cycloaddition; isatin *N,N′*-Cyclic Azomethine; Imines heterocycles; 1,3-Dipolar

Introduction

Heterocyclic molecules bearing *N,N′*-bicyclic pyrazolidinones have been found to possess a wide range of important biological activities (Figure 1).[1]As a result of their facilitating biological activities, the synthesis of this particular class of heterocyclic molecules is highly attractive to the synthetic community. Among various synthetic methods, 1, 3-dipolar cycloaddition reactions of azomethine imines with alkynes have been widely utilized as an efficient strategy for the preparation of *N,N′*-bicyclic pyrazolidinones structures (Scheme 1, 1).[2]

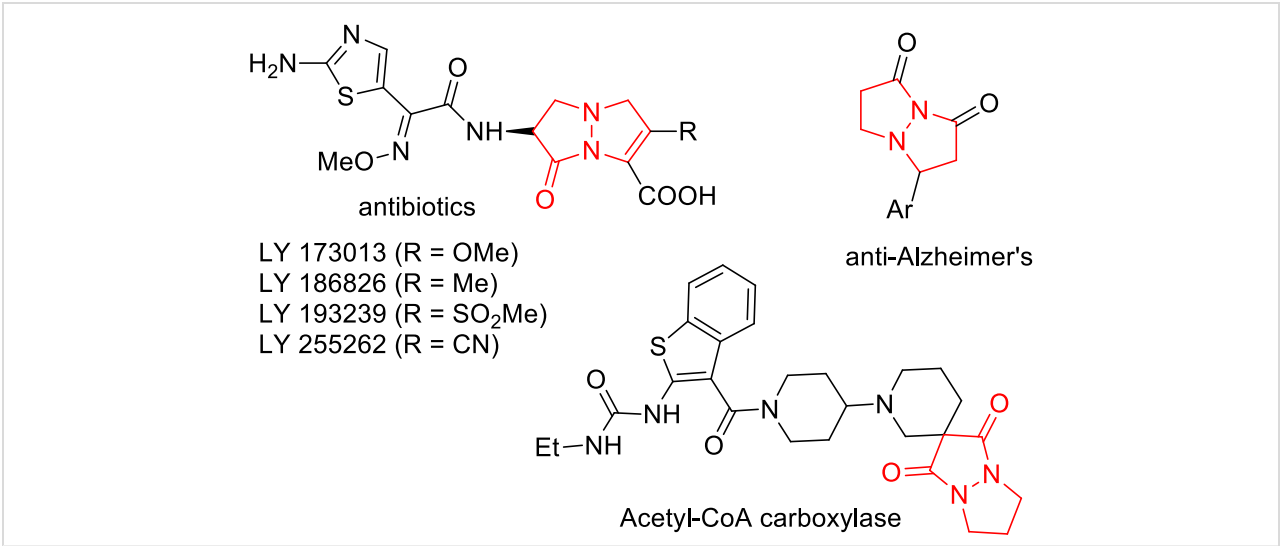
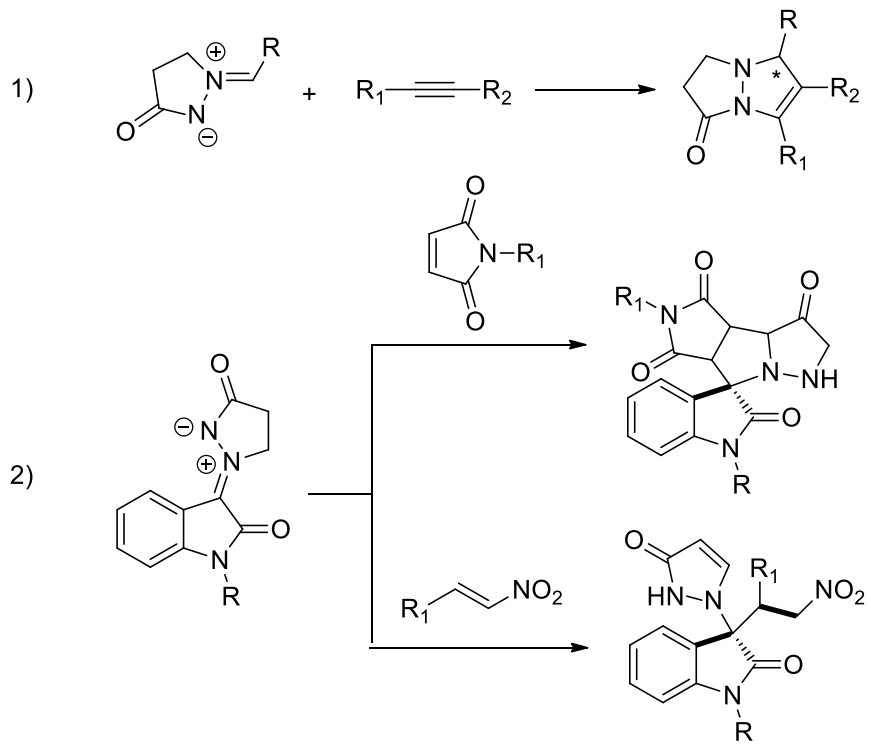


Figure 1: Bioactive compounds containing N,N'-bicyclic pyrazolidinones

Our research team has been interested in the development of novel dipolar cycloaddition reactions for the synthesis of biologically active heterocycles. Recently, a new type of azomethine imine dipolar, isatin *N,N′*-cyclic azomethine imine, has caught our attention due to its unique structure. In 2017, Wang and coworkers reported a 1,3-dipolar cycloaddition of maleimide and isatin *N,N′*-cyclic azomethine imine to obtain interesting spirooxindole scaffolds (Scheme 1, 2). They also reported a Michael addition in lieu of cycloaddition of isatin *N,N′*-cyclic azomethine imine with *β*-Nitrostyrene (Scheme 1,2). Inspired by these advances, we aimed to explore the reactivity of isatin *N,N′*-cyclic azomethine imine as a dipolar towards electron

deficient alkynes. To the best of our knowledge, the 1, 3 dipolar cycloaddition of isatin *N,N′*-cyclic azomethine imine and alkynes has not been previously reported.



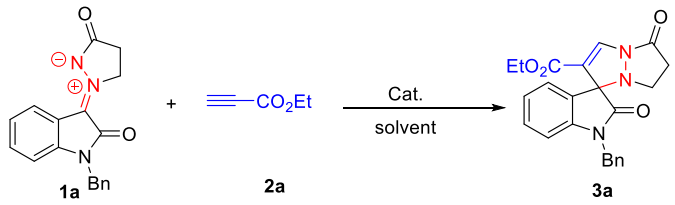
Scheme 1: Previous Work

Results and Discussion

Our investigation began with a model reaction of *N,N′*-cyclic azomethine imine (**1a**) and ethyl propiolate (**2a**) (Table 1). Initially, chloroform was utilized as the solvent and a variety of metal salts were screened as the catalyst for the cycloaddition reaction. To our delight, it was found that 5 mol % $CuCO_3$ catalyzed the reaction at 50 ^oC and generated the desired cycloaddition product (**3a**) as a single regioisomer in 83% yields (entry 6). Other Cu (I) and Cu (II) salts such as $Cu(OAc)_2$, $CuCl_2$, Cu_2O, CuCl, $Cu(CF_3SO_3)_2$, and CuI, as well as Ag_2O, all gave lower yields. Next, we tested a

variety of solvents in the presence of our optimal catalyst, $CuCO_3$. However, both dichloromethane (entry 9) and toluene (entry 10) produced the desired products in relatively lower yields (80% and 78% respectively). Afterwards, the reaction temperature was reduced to 25 ^oC to further optimize the reaction conditions. Unfortunately, the resulting reaction yield dramatically decreased to 18%, even when the reaction time was increased to 24 hours (entry 11). In addition, a control reaction was tested without any catalyst. As expected, no desired product formation was observed (entry 12), indicating the importance of a catalyst. Therefore, $CuCO_3$ was identified as the optimal catalyst, providing the best results at 50 ^oC in the presence of $CHCl_3$.

Table 1. Optimization of Reaction Conditionsa



Entry[a]	Cat.	Solvent	T/h	T/^oC	Yield[b]
1	$Cu(OAc)_2$	$CHCl_3$	12	50	17
2	$CuCl_2$	$CHCl_3$	12	50	51
3	Cu_2O	$CHCl_3$	12	50	32
4	CuCl	$CHCl_3$	12	50	18
5	$Cu(CF_3SO_3)_2$	$CHCl_3$	12	50	23
6	$CuCO_3$	$CHCl_3$	12	50	83
7	CuI	$CHCl_3$	12	50	57
8	Ag_2O	$CHCl_3$	12	50	59
9	$CuCO_3$	DCM	12	50	80
10	$CuCO_3$	Tol.	12	50	78
11	$CuCO_3$	$CHCl_3$	24	25	18
12	-	$CHCl_3$	24	50	<5

[a] Reaction conditions: a mixture of 1 (1.0 mmol), 2 (1.5 mmol), and cat. (5 mol%) in solvent (2 mL) was stirred at the set temperature in a high pressure vessel for a certain period of time. [b] Yield of isolated product.

To confirm the structure of the spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazoles] product and regiochemistry of this [3+2] cycloaddition reaction, we successfully obtained the X-ray crystallography of **3a** which clearly indicated spiro-bicyclic structure (Figure 2).[4]

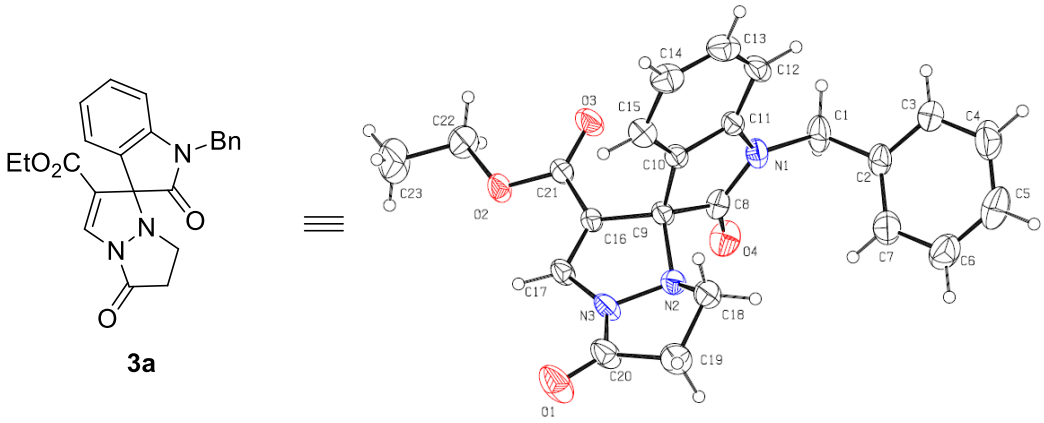
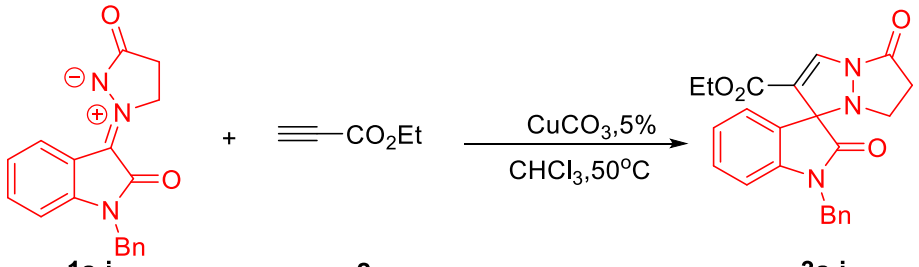


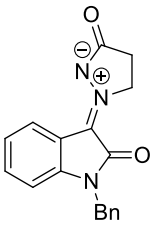
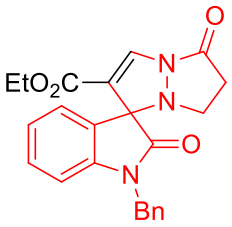
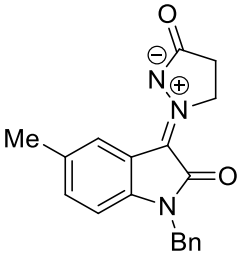
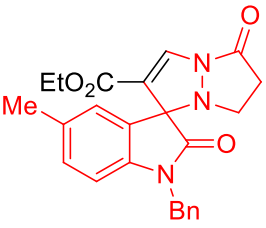
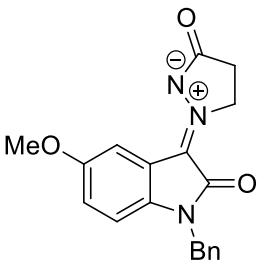
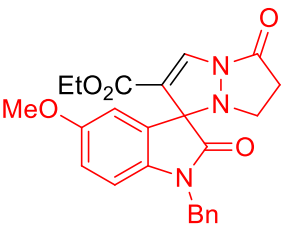
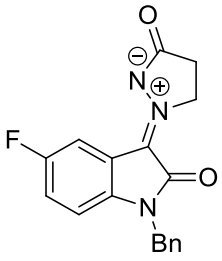
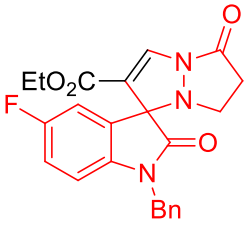
Figure 2 X-ray structure of 3a

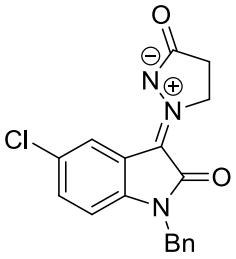
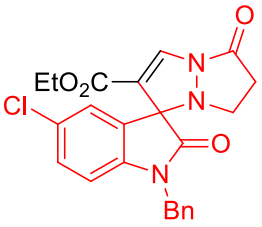
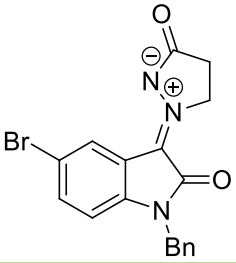
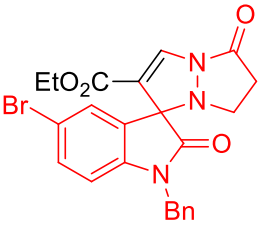
With the optimal conditions in hand, we started our study on the substrate scope and limitations of this cycloaddition reaction. As shown in Scheme 2, ethyl propiolate (**2a**) was utilized as the dipolarophile. A variety of *N,N'*-cyclic azomethine imines with different substituents on the aromatic ring were tested under the optimal [3+2] cycloaddition reaction conditions. Electron withdrawing groups such as methyl and methoxyl groups (**3b**, **3c**, and **3j**), and electron donating groups such as halogen, nitro, and trifluoromethyl groups (**3d**, **3e**, **3f**, **3h**, and **3i**), substituted on the aromatic ring, were well tolerated and resulted in good yields. It is noticeable that the number and the position of the substituents do not affect the reaction outcome. For instance, both **3b** with one methyl group and **3j** with two methyl groups gave the same yields of the desired products.

Scheme 2. Substrate scope

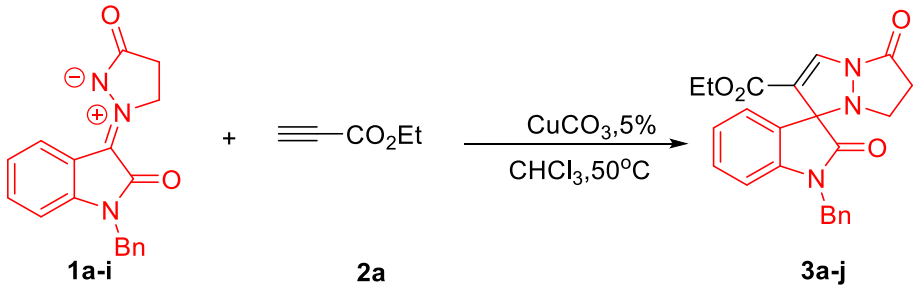


1a-i **2a** **3a-j**

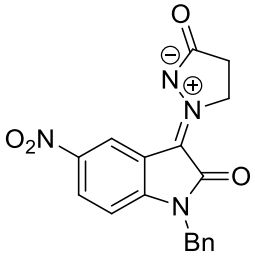
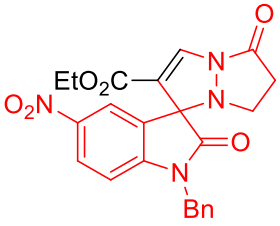
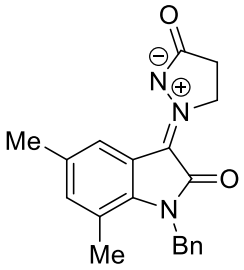
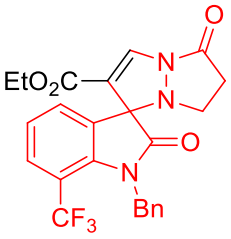
Entry	substrate		Product		Yield[b](%)
1		**1a**		**3a**	83
2		**1b**		**3b**	78
3		**1c**		**3c**	80
4		**1d**		**3d**	77

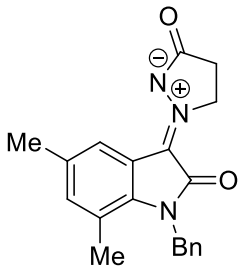
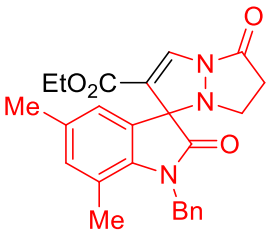
5		**1e**		**3e**	77
6		**1f**		**3f**	75

Scheme 2. Substrate scope(continued)



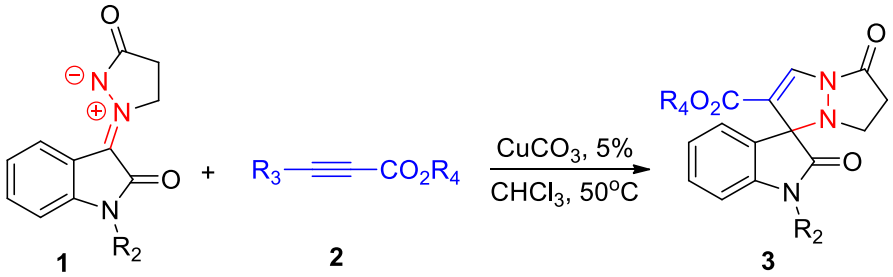
1a-i **2a** **3a-j**

Entry	substrate		Product		Yield[b]
7		**1h**		**3h**	70
8		**1i**		**3i**	76

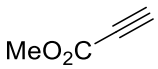
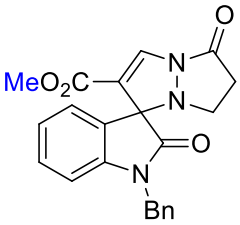
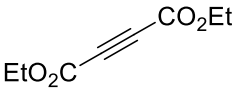
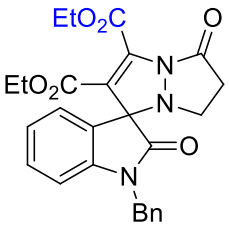
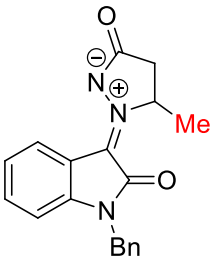
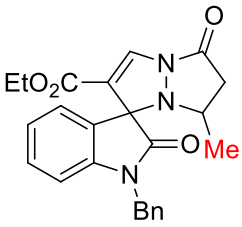
9		**1j**		**3j**	78

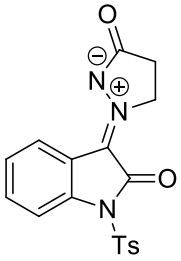
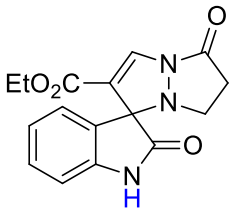
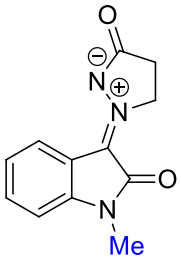
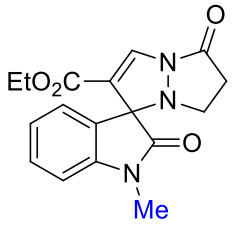
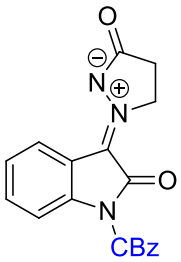
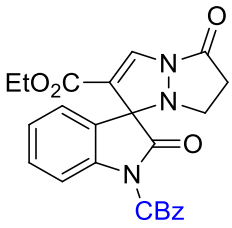
[a] Reaction conditions: a mixture of **1** (1.0 mmol), **2** (1.0 mmol), and cat. (5mol%) in solvent (2 mL) was stirred at the set temperature for a certain period of time. [b]Yield of isolated product.

Scheme 3. Substrate scope



1 **2** **3**

Entry	substrate		Product		Yield[b]
1		**2k**		**3k**	80
2		**2l**		**3l**	73
3		**1m**		**3m**	80

4		**1n**		**3n**	65
5		**1o**		**3o**	75
6		**1p**		**3p**	80

[a] Reaction conditions: a mixture of **1** (1.0 mmol), **2** (1.0 mmol), and cat. (5mol%) in solvent (2 mL) was stirred at the set temperature for a certain period of time. [b]Yield of isolated product.

Afterwards, we turned our attention to the study of substrate scopes and limitations of ethyl propiolate (**2a**) and the R_2 group of *N,N'*-cyclic azomethine imines (Scheme 3). We found that methyl propiolate produced the desired product (**3k**) in similar yield as ethyl propiolate. Also, diethyl but-2-ynedioate participated in the reaction smoothly and generated the cycloaddition product **3l** in good yield (73%). When the R_2 substituent was changed to methyl, and Cbz groups, the desired products were obtained in good yields. It is worth to mention that when R2 was a Ts group, Ts was removed during the reaction and **3n** (R_2 = H) was obtained as the product in 65% yield.

Conclusion

In conclusion, we have developed an efficient and straightforward synthesis of spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazoles]. This reaction offers a unique approach

to access bio-active *N,N′*-spirobicyclic pyrazolidinones structure motifs in both good yield and mild conditions.

Experimental

A mixtureof isatin *N,N′*-cyclic azomethine imines **1** (0.1 mmol, 1.0 equiv), alkyne ester **2** (0.15 mmol, 1.5 equiv), and $CuCO_3$ (5 mol%) was stirred in 2 mL $CHCl_3$ at 50^oC for the indicated time. filtered and evaporated to dryness. The products were obtained by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1-3/1).

Acknowledgements

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4.Crystallographic data for **3a** has been deposited with the Cambridge Crystallographic Data Centre as deposition no. 1903766 CCDC . Detailed information can be found in the Supporting Information.