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Cu-mediated 1,3-dipolar cycloaddition of azomethine ylides with dipolarophiles: a faster access to spirooxindoles of potential pharmacological interest

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ABSTRACT

CuI facilitated three-component reaction of isatin derivatives, L-proline and terminal alkynes containing an amide or ester functional group. The multi-component reaction (MCR) afforded a faster and practical synthesis of spirooxindole derivatives. A range of novel spirooxindoles were synthesized by using this straightforward and one-pot efficient methodology. A representative compound showed significant inhibition of PDE4B enzyme in vitro and good interactions with this protein in silico.

The unique structural features of spiro heterocycles and the presence of spiro linkage as a basic skeleton in several natural products have increased their importance to a great extent. The naturally occurring spiro heterocycles for example spirooxindoles (with five membered nitrogen containing ring) present in horsfiline[1] (analgesic activity), spirotryprostatins **A**[2] (inhibitors of mammalian cell cycle at G2/M phase), and elacomine[3] showed interesting biological properties (Fig. 1). Mitraphylline (Fig. 1), a natural compound, containing the spirooxindole framework possesses anti-tumor activity against human brain cancer cell lines and malignant glioma GAMG.[4] Rhynchophylline, another natural product is used as antipyretic, anti-hypertensive, and anti convulsant medications for the treatment of headache, vertigo, and epilepsy.[5] The oxindole class of compounds attracted our particular attention due to their impressive PDE4 inhibitory properties reported earlier. For example, the PDE4 inhibitor **A** (Fig. 2) significantly reduced antigen-induced bronchoconstriction in animal models and in asthmatic patients.[6] This prompted us to synthesize and assess the PDE4 inhibitory properties of novel spiro derivatives of oxindoles **B** (Fig. 2) possessing an amide/ester at C-2′. We anticipated that this group may facilitate the interactions of **B** with PDE4B. To the best of our knowledge PDE4 inhibitory properties of **B** have not been reported in the literature earlier.

The most common synthetic routes reported so far for the synthesis of spiro cyclic compounds include alkylation methods, rearrangement based approaches, ring closure of geminally substituted compounds, radical cyclizations, organometallic processes (metals include Rh, Pd, Cu, Ir etc.,), organocatalytic approaches, cleavage of bridged ring systems, or cycloaddition reactions.[7] Recently, the

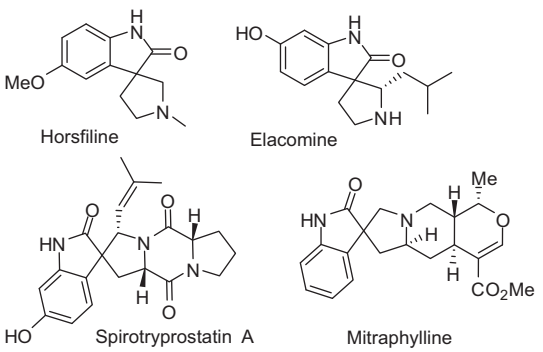

Figure 1. Structure of natural products containing spirooxindole framework.

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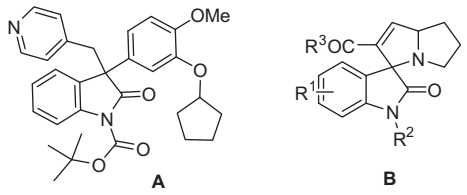
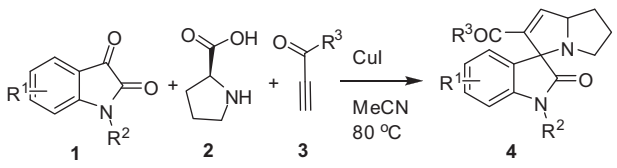


Figure 2. Known PDE4 inhibitor **A** and our target spirooxindoles **B**.

multi component reaction or MCR strategy has been successfully adopted by many researchers for the synthesis of spirooxindoles. This reaction involved 1,3-dipolar cycloaddition of azomethine ylide generated in situ with different dipolarophiles in a single pot. The azomethine ylides were efficiently generated by the reaction of isatin with L-proline. Chen et al. have reported the synthesis of the spirooxindole pyrrolidine ring by three-component coupling of isatin, L-proline, and 1,4-naphthoquinone in methanol under ultrasound.[8] Kang and co-workers reported a similar type of coupling in 1,4-dioxane by varying the dipolarophile for the synthesis of spiropyrrolidine oxindoles.[9] They used dimethyl maleate instead of 1,4-naphthoquinone. The synthesis of spiropyrrolidine was also reported by using terminal and internal alkynes as dipolarophiles in acetonitrile by Pardasani et al.[10] that required a relatively longer reaction time for example 20 h. Moreover, the use of only one terminal alkyne that is phenyl acetylene was examined in their study. Herein, we report a faster and efficient method leading to our target spiropyrrolidine oxindoles **B** or **4** (Scheme 1) using isatin (**1**), L-proline (**2**), and terminal alkynes (**3**) containing ester or amide substituents in the presence of catalytic CuI in acetonitrile. Notably the use of alkyne **3** in a similar MCR is not common in the literature.

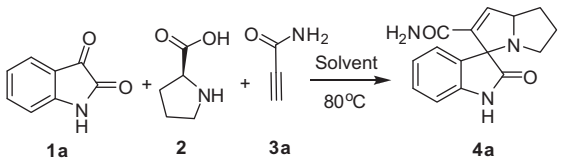
Initially, the coupling reaction was performed by heating a mixture of isatin (**1a**), L-proline (**2**), and propiolamide (**3a**) in DMF at 80 °C. After 24 h, the spiro compound **4a** was obtained in 60% yield (Table 1, entry 1). To improve the product yield the reaction was carried out in different solvents like ethanol (Table 1, entry 2) and acetonitrile (Table 1, entry 3). In case of ethanol, the yield decreased to 55%, but improved in acetonitrile (70%). However, the duration of the reaction was not satisfactory for a quick access to the compound library related to **4a**. After screening a range of catalysts a major improvement in yield (92%) as well as reaction time (2 h) was observed when catalytic amount of CuI was added to the reaction mixture in acetonitrile (Table 1, entry 4). While the reaction proceeded in the presence of other copper salts for example CuBr and CuCl, the yield of product **4a** was poor (Table 1, entries 5 and 6) in these cases. The MCR was found to be less effective in an aqueous media for example in 1:1 *i*-PrOH/H_2O when **4a** was obtained only in 32% yield (Table 1, entry 7). Thus based on the observation that CuI in acetonitrile decreased the reaction time from 20 to 2 h, the combination of CuI and acetonitrile was used for our further study.

The scope and generality of the reaction were further tested by performing the reactions using a range of isatin derivatives (**1**) and terminal alkynes (**3**) containing various carbonyl functionalities (Table 2).[11] Substituents such as Br, F, NO_2, and aryl group on the isatin ring were well tolerated. The terminal alkynes employed



Scheme 1. Cu-mediated faster synthesis of spirooxindoles **4**.

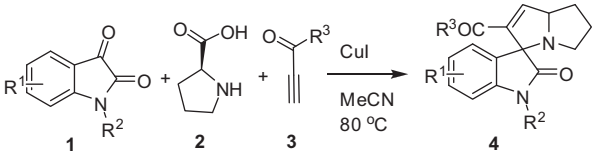
Table 1
Effect of reaction conditions on three-component reaction of **1a**, **2**, and **3a**[a]



Entry	Solvent	Catalyst	Time (h)	Temp (°C)	Yield[b] (%)
1	DMF	No catalyst	24	80	60
2	EtOH	No catalyst	24	80	55
3	CH_3CN	No catalyst	24	80	70
4	CH_3CN	CuI	2	80	92
5	CH_3CN	CuBr	8	80	78
6	CH_3CN	CuCl	12	80	75
7	*i*-PrOH:H_2O (1:1)	CuI	6	80	32

[a] Reactions were carried out using **1a** (1.0 mmol), **2** (1.0 mmol), and propiolamide (**3a**) (1.0 mmol) in a solvent (15 mL) under nitrogen.
[b] Isolated yield.

Table 2
Synthesis of spirooxindoles **4** via Cu-mediated MCR of **1**, **2**, and **3**[a]



Entry	Isatin derivative (R^1, R^2=) **1**	Alkyne (R^3=) **3**	Time (h)	Product **4**	Yield[b] (%)
1	H, H **1a**	NH_2 **3a**	2.0	**4a**	92
2	**1a**	NHMe **3b**	2.0	**4b**	90
3	**1a**	NHEt **3c**	2.0	**4c**	91
4	5-Br, H **1b**	**3a**	2.5	**4d**	85
5	**1b**	**3b**	2.5	**4e**	82
6	**1b**	**3c**	2.0	**4f**	85
7	5,7-Di-NO_2, H **1c**	**3a**	2.0	**4g**	90
8	5-F, H **1d**	**3a**	2.5	**4h**	80
9	**1a**	OEt **3d**	3.0	**4i**	81
10	**1b**	**3d**	2.5	**4j**	80
11	**1c**	**3d**	2.5	**4k**	85
12	H, $-CH_2C_6H_4Cl$-*m* **1e**	**3a**	3.0	**4l**	75

[a] Reactions were carried out using isatin (**1**) (1.0 mmol), proline (**2**) (1.0 mmol), alkyne (**3**) (1.0 mmol), and CuI (0.01 mmol) in acetonitrile (15 mL) at 80 °C under nitrogen.
[b] Isolated yield.

contained an N-unsubstituted or substituted amide (e.g. NH_2, NHMe, or NHEt) or an ester moiety. The reaction proceeded well in all these cases affording desired spirooxindoles **4** in good to excellent yield.

All the spirooxindole derivatives (**4a**–**l**) synthesized were characterized by their ^1H and ^{13}C NMR, IR, and mass spectral data. The sharp peak at ~3300 cm^{-1} in IR, a singlet at 10.0 ppm in ^1H NMR correspond to the spirooxindole NH group. Moreover, a sharp IR absorption at ~1640 cm^{-1} and appearance of a quaternary carbon signal at ~178.0 ppm in the ^{13}C NMR indicated the presence of the C=O group. While a sharp IR absorption at ~1735 cm^{-1} and a signal at ~161.0 ppm in the ^{13}C NMR indicated the presence of the ester carbonyl group (e.g. **4i**–**k**), the amide derivatives (**4a**–**h**)