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Synthesis of triazole-fused tetracyclic spirooxindole derivatives *via* metal-free Huisgen cycloaddition†

Sandip Maiti, Nabin Parui, Joydev Halder and Jyotirmayee Dash *

We report an efficient, metal free method for synthesizing tetracyclic spirooxindole derivatives from *N*-protected isatins and propargyl bromide *via* Huisgen cycloaddition. This simple and practicle method provides access to spirooxindoles containing five-, six-, or seven-membered rings fused to a triazole ring.

The spirooxindole core holds significance due to its prevalence in numerous natural products[1] and biologically active compounds.[1–4] The tricyclic skeleton as seen in horsfiline (**Ia**; Fig. 1), linked with a pyrrolidine, is known for its traditional use in herbal medicine for its antitumor properties.[5] Similarly, coerulescine (**Ib**; Fig. 1) and elacomine (**II**, Fig. 1) exhibit antitumor activities.[5] Compound **III** (Fig. 1) is a promising lead compound for inhibitors of β-secretase (**BCAE-1**) involved in Alzheimer's disease,[6] while spirotryprostatin B (**IV**; Fig. 1) inhibits G2/M progression of mammalian tsFT210 cells.[7] Spirooxindoles fused with piperidine systems are used to treat anaemia (**HIF PHD 1–3**, **V**).[8] Compounds **VI**,[9] **VII**,[10] and **VIII**[11](Fig. 1) are known as selective anticancer agents. Given their widespread significance, several synthetic methods such as transition metal catalysis,[4a–d] organocatalysis,[4e,f] photocatalysis[4g] have been documented in the literature to access this class of compounds.

The synthesis of 3-spirooxindoles has been achieved using various methods,[12] including Ru-catalyzed ring-closing enyne metathesis and Co-mediated Pauson–Khand cyclization.[13] Morpholine-fused spirooxindole derivatives with 1,2,3-triazole moieties, like compound **VI** show cytotoxic effects against various cancer cell lines, highlighting their therapeutic potential.[9] Our work has focused on synthesizing hydantoin, thiazolidinedione, and oxindole-based spirocycles using ring-closing metathesis.[14] Building upon our work on AAC[15] and spirooxindoles,[14c] we aim to develop a unified method for synthesizing tetracyclic spirooxindoles with five-, six-, or seven-membered heterocycles fused to a triazole ring (Scheme 1).

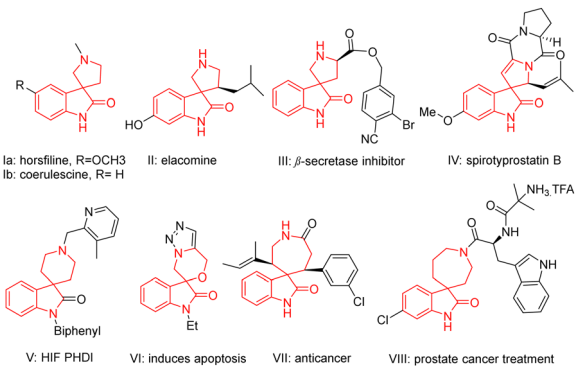
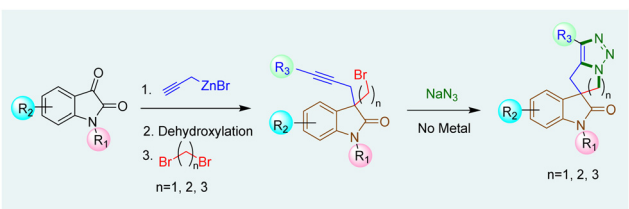


Fig. 1 Some bioactive and naturally occurring spirooxindoles.

The synthesis commenced with the zinc-mediated propargylation on *N*-protected isatin derivatives (**1a–k**) in tetrahydofuran, leading to the synthesis of 3-hydroxy-3-propargyl substituted 2-oxindole derivatives **2a–k** (Scheme 2). A catalytic amount of $HfCl_4$ was employed to enhance the yield. For *N*-methyl isatin **1a**, we obtained 91% yield of **2a**, comparable to the report by Alcaide and co-workers.[16] We then explored the scope and generality of this approach on several *N*-protected isatins (**1b–d**), as well as isatins having different types of electron withdrawing (**1i–k**) and electron donating (**1e–h**) groups on different positions of the aromatic ring (Scheme 2, see also ESI†). High yields of products (**2a–k**) were obtained overall. However, isatins



Scheme 1 Synthesis of 1,2,3-triazole fused spirooxindoles.

School of Chemical Sciences, Indian Association for the Cultivation of Science Jadavpur, Kolkata-7000032, India. E-mail: ocjd@iacs.res.in

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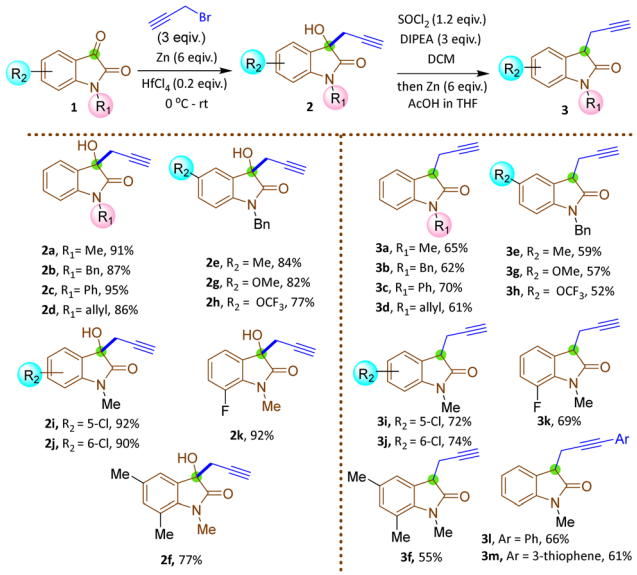
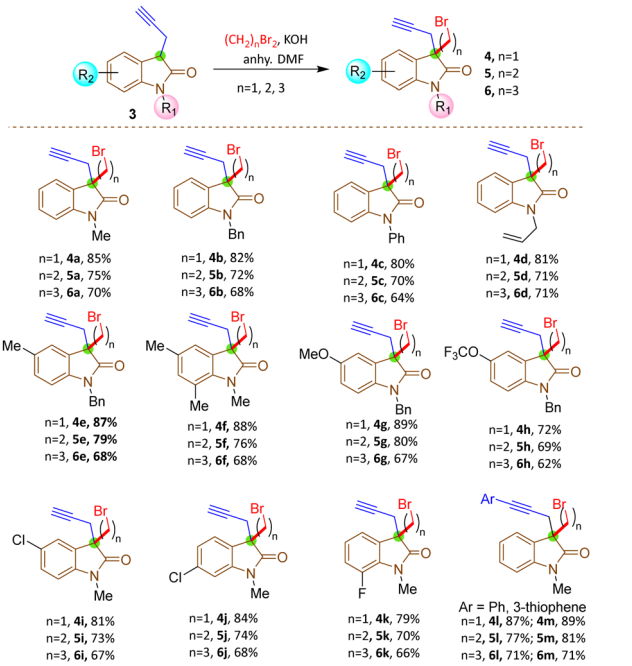


Scheme 2 Synthesis of 3-propargyl substituted oxindoles from isatins. Reaction conditions: (i) **1** (2 mmol), propargyl bromide (6 mmol), Zn dust (12 mmol), $HfCl_4$ (0.4 mmol), THF/aq. NH_4Cl (1 : 5, 20 mL) at 0 °C. (ii) **2** (1 mmol), $SOCl_2$ (1.2 mmol), DIPEA (3 mmol) in DCM (10 mL) at 0 °C-rt; (iii) Zn dust (6 mmol), AcOH (3 mL) in THF (10 mL) at 0 °C.

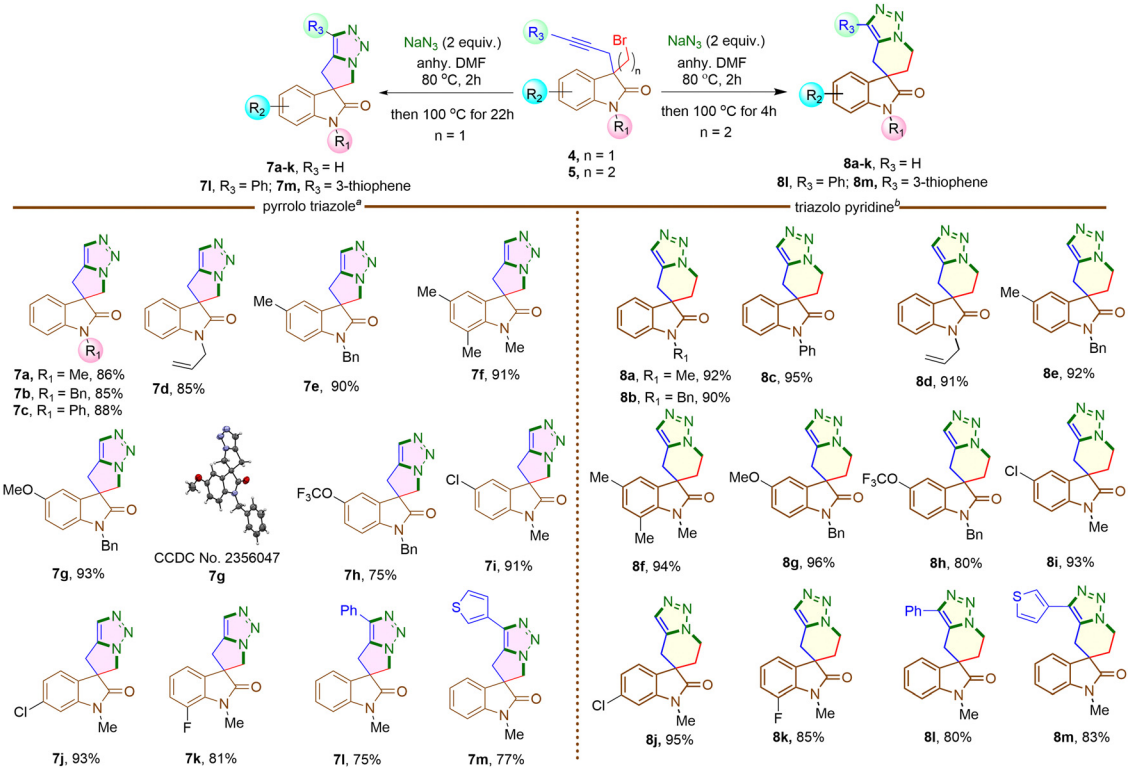


Scheme 3 Synthesis of 3,3-disubstituted oxindoles from 3-propargyl substituted oxindole. Reaction conditions: **3** (0.25 mmol), dibromoalkane (0.50 mmol), powdered KOH (0.50 mmol) in DMF (0.5 mL) at 0 °C-rt. Isolated yields.

with electron-donating groups on the aromatic ring gave slightly lower yields than those with electron-withdrawing substituents, as expected due to increased electrophilicity of the carbonyl group when electron withdrawing groups are present. To carry out dehydroxylation of **2**, we first adopted a procedure similar to our previously reported $SnCl_2$ in HCl/glacial AcOH method for *N*-protected 3-allyl-3-hydroxy-2-oxindole derivatives.[17] However, a low yield of *N*-methyl protected 3-propargyl-2-oxindole **3a** was obtained (Scheme 2). To overcome the problem, we converted the hydroxy group to chloro using thionyl chloride and DIPEA in dichloromethane. The reaction mixture was immediately utilized for the next step after workup without any purification. Upon treatment with Zn/AcOH in anhydrous tetrahydofuran, dechlorination occurred with moderate to good yield of the produced 3-propargyl-2-oxindole derivatives (**3a–m**) (Scheme 2).[18] The yield of **3** was quite a bit higher for *N*-phenyl substituted 2-oxindole **3c** compared to the yields obtained with Me, benzyl or allyl protections **3a–b**, **3d**. The substrate **2h** containing OCF_3 produced a relatively low yield of **3h**, probably due to the decomposition of the starting material to some extent. Subsequently, 3-propargyl substituted 2-oxindoles **3a–m** were treated with dibromides of different chain lengths in the presence of solid KOH in DMF. The reaction took place at the active hydrogen site resulting in the formation of 3,3-disubstituted 2-oxindoles **4–6** (Scheme 3). When dibromomethane was employed as the electrophile for **3a**, the corresponding 3-bromomethyl-3-propargyl-2-oxindole **4a** was obtained in 85% yield. However, upon using 1,2-dibromoethane and 1,3-dibromopropane, the yields of the corresponding oxindoles, **5a** with a 2-bromoethyl substituent and **6a** with a 3-bromopropyl group, decreased to 75% and 70%, respectively. A comparable decrease in yield was observed for substrates having different nitrogen protecting groups (**3b–d**) and functional groups in the aromatic ring (**3e–k**). This may be attributed to side reactions like S_N2/E2 reactions becoming more prominent with longer alkyl chains, leading to undesired by-products or the partial reactant decomposition, reducing the overall yield of the desired product.

Next, 3-bromomethyl-3-propargyl 2-oxindole **4a** was treated with NaN_3 in DMF at 80 °C for two hours initially, then increased to 100 °C for another 22 hours (Scheme 4). The reaction led to the formation of a triazole fused five-membered spirooxindole derivative **7a** in 86% yield. The reaction involved a nucleophilic substitution, replacing the bromine atom with an azide group, followed by a metal-free intramolecular Huisgen cycloaddition,[19] resulting in the formation of a triazole-fused spirooxindole derivative **7a** (Scheme 4). Under identical conditions, the reaction was conducted on different *N*-protected 3-bromomethyl substituted 2-oxindoles (**4b–d**), as well as substrates having different functional groups on the aromatic rings (**4e–k**). Impressively, each reaction yielded good to excellent results. The structure of compound **7g** was confirmed by single crystal X-ray analysis.‡ However, substrates **4h**, **4k** containing F and OCF_3 groups afforded comparatively lower yields of the corresponding products **7h** and **7k**, possibly due to some extent of decomposition of the starting materials.

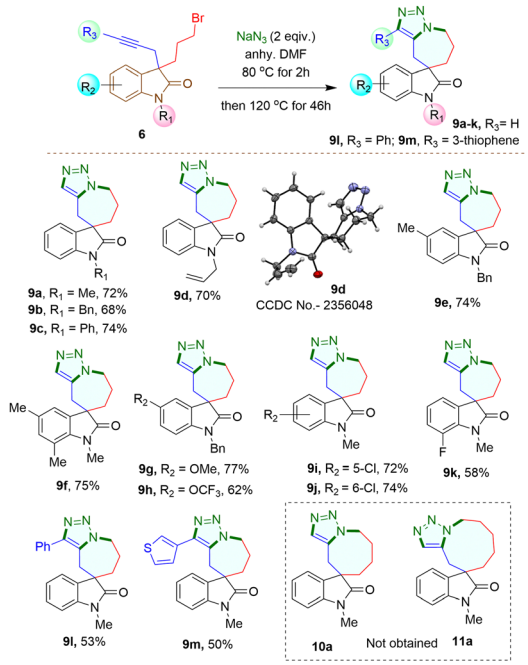
When 3-bromomethyl-2-oxindoles containing internal alkynes such as **4l–m** were treated with NaN_3, a slightly lower yield of the cycloaddition products **7l–m** was obtained. We next performed the one-pot azide formation and intramolecular cycloaddition of 3-(2-bromoethyl) oxindole derivatives **5a–l** with two equivalents of NaN_3 (Scheme 4). The reaction mixture was heated at 80 °C in DMF for two hours, following the same procedure as with 3-(bromomethyl) derivatives **4a–m**. However, upon increasing the temperature to 100 °C, the cycloaddition of **5a–m** completed



Scheme 4 Synthesis of pyrrolo triazoles and triazolo pyridine containing spirooxindole from 3,3-disubstituted 2-oxindoles. Reaction conditions: [a] **4** (0.15 mmol), NaN_3 (0.30 mmol) in anhy. DMF (1 mL) at 80 °C for the 1st 2 hours then temperature raised to 100 °C for another 22 hours; [b] **5** (0.15 mmol), NaN_3 (0.30 mmol) in anhy. DMF (1 mL) at 80 °C for 2 hours then temperature raised to 100 °C for another 4 hours. Isolated yields.

after four hours, resulting in triazole-containing piperidine-fused spirooxindole derivatives **8a–m** in 80–96% yields. The generality of the reaction was explored with substrates containing different *N*-protecting groups **5a–d** as well as electron-withdrawing **5i–k** and electron-donating substituents **5e–h** on different positions of the aromatic ring. In each case, good to excellent yields of cycloaddition products **8a–k** were obtained. The oxindoles containing internal alkynes **5l–m** also furnished the desired products **8l–m** in 80% and 83% yields, respectively, slightly lower than the terminal alkyne **5a–k**. Thus, the substituents had minimal effect on the overall yield of the cycloaddition reaction. The yields and reaction rates were significantly influenced by the ring size of the heterocyclic compounds formed during the cycloaddition reaction; 6-membered heterocyclic ring-fused spirooxindoles **8a–m** were formed more readily compared to the synthesis of five-membered rings **7a–m**, which required longer reaction times. After successfully synthesizing triazole-containing five and six-membered ring-fused spirooxindole derivatives (**7a–m**, **8a–m**), we explored our methodology for synthesizing seven-membered ring fused spirooxindole derivatives due to the limited number of reports available in the literature for this class of compounds.[1c] Compound 3-bromopropyl 3-propargyl 2-oxindole **6a** was treated with 2 equivalents of NaN_3 at 80 °C for two hours and then at 120 °C for another 46 hours (Scheme 5) for complete conversion. The desired 2-spirooxindole fused to triazoloazepine **9a** was obtained in 72% yield. We then explored the scope of the reaction on various *N*-protected (**6b–d**) as well as different substituents at the different positions of the benzene ring of 3-bromopropyl 2-oxindoles (**6e–k**). In each case, triazole-fused seven-membered rings spiro-linked to 2-oxindoles (**9a–k**) were obtained in moderate to good yields. However, these yields were lower compared to the corresponding five and six-membered counterparts. The structure of compound **9d** was established through single crystal X-ray analysis.‡ Following the successful synthesis of five, six and seven membered ring-fused spirooxindoles, we attempted to apply our methodology for the synthesis of eight and nine membered ring fused spirooxindoles. Unfortunately, we were unable to isolate any eight or nine membered ring-fused spirooxindoles from the reaction mixture under the optimized conditions (see ESI† for the synthesis of the substrates).

In summary, we have devised a novel and efficient approach for synthesizing spirooxindole-derived pyrrolidine, piperidine, and azepine-fused-1,2,3-triazole derivatives. This method involves propargylation at C-3 of isatin, dehydroxylation, one-pot substitution at C-3 with dibromoalkane and metal-free Huisgen cycloaddition. We found that spirooxindoles fused with 6-membered rings are formed more readily, while those with 7-membered rings result in lower yields. While existing reports mainly focus on 5 and 6-membered rings, our method effectively produces 5, 6, and 7-membered spirooxindole derivatives. Spirooxindoles fused to 6-membered rings are formed more readily than those with 5 or 7 membered rings. Our ongoing research will further explore these structures and evaluate their bioactivity.



Scheme 5 Synthesis of triazolo azepine-containing spirooxindoles from 3,3-disubstituted oxindoles. Reaction conditions: **6** (0.15 mmol), NaN_3 (0.30 mmol) in anhy. DMF (1 mL) at 80 °C for the 1st 2 hours, then another 46 hours at 120 °C. Isolated yields.

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Data availability

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

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ CCDC 2356047 and 2356048† contain the supplementary crystallographic data for compounds 7g and 9d (see also ESI†)

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