RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 30620

A [3 + 2] cycloaddition/C-arylation of isatin *N,N′*-cyclic azomethine imine 1,3-dipole with arynes†

Qiaomei Jin, ‡*[ab] Dongjian Zhang‡[ab] and Jian Zhang *[ab]

Received 23rd July 2020
Accepted 13th August 2020

DOI: 10.1039/d0ra06404a

rsc.li/rsc-advances

A [3 + 2] annulation/C-arylation of isatin *N,N′*-cyclic azomethine imine 1,3-dipole **1** with *in situ* generated arynes has been established for the synthesis of 3,3-disubstituted oxindole scaffolds. These highly functionalized scaffolds were assembled in moderate yields (up to 85% yield). The novel spirooxindole scaffolds displayed moderate antitumor activities, which represented promising lead compounds for antitumor drug discovery.

The construction of new heterocyclic architectures is of great importance because such privileged scaffolds that widely occur in natural products and drugs increase the returns of drug-discovery studies.[1] Among these scaffolds, the 3,3-disubstituted oxindoles are associated with interesting biological properties (Fig. 1). For instance, nelivaptan could be used as an orally active non-peptide vasopressin receptor antagonist.[2] NITD609 has been identified for potential treatment of malaria based on *in vivo* activity, having single dose efficacy in a rodent malaria model.[3] Moreover, other bioactive 3,3-disubstituted oxindoles have also attracted considerable attention due to their high activities, such as poliovirus inhibitor,[4] MDM2 inhibitor SAR405838 (ref. 5) and anti-bacterial agents.[6] Given the biological significance of functionalized 3,3-disubstituted oxindoles, synthesis of this class of compounds with high structural diversity from readily available starting materials by using simple manipulations is highly desirable.

Recently, 1,3-dipolar cycloadditions (1,3-DCs) are among the most powerful approaches for the construction of carbon–carbon bonds and heterocycles.[7] And the Wang's group reported an abnormal [3 + 2] cycloaddition of a new isatin *N,N′*-cyclic azomethine imine 1,3-dipoles with maleimides, an unusual Michael reaction between these 1,3-dipoles with β-nitrostyrenes and an abnormal [3 + 2] cycloaddition between these 1,3-dipoles and 3-methyleneoxindole, which are very scarce examples of 1,3-dipolar cycloaddition reaction (Scheme 1a).[8] After that, we disclosed an DMAP-catalyzed direct alkylation at the *α*-position of the cyclic amine of these isatin *N,N′*-cyclic azomethine imine 1,3-dipoles with Morita–Baylis–Hillman carbonates and developed an efficient way to synthesize seven-membered heterocyclic spirooxindoles *via* a [3 + 4] cycloaddition reaction of these 1,3-dipoles with *N*-(*ortho*-chloromethyl)aryl amides (Scheme 1a).[9] Furthermore, the

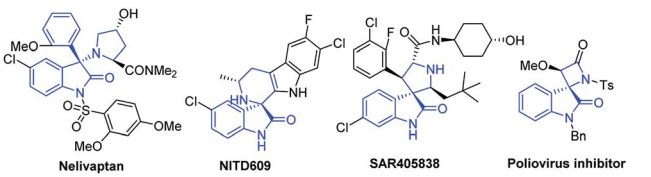
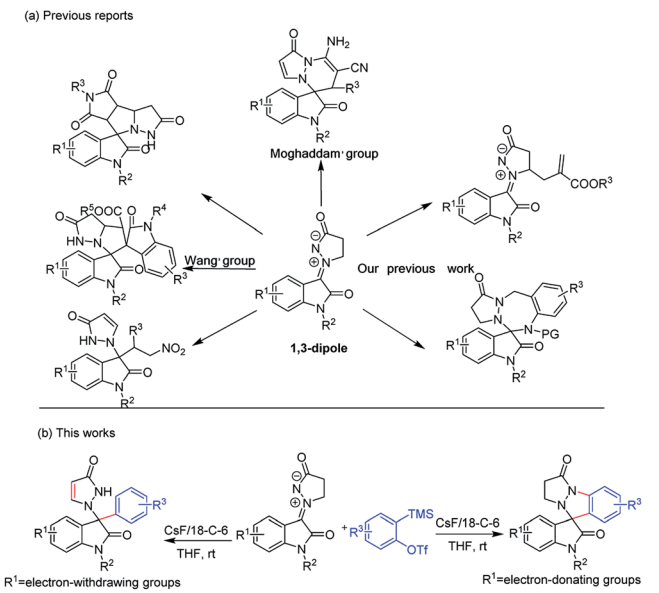


Fig. 1 Representative biologically active compounds containing the 3,3-disubstituted oxindole skeleton.



Scheme 1 (a) Previous reports of isatin *N,N′*-cyclic azomethine imine 1,3-dipoles. (b) Design of the new [3 + 2] cycloaddition.

[a]*Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210028, Jiangsu, China. E-mail: jqmxy@163.com; zjwonderful@hotmail.com*

[b]*Laboratories of Translational Medicine, Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing 210028, Jiangsu, China*

† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/d0ra06404a

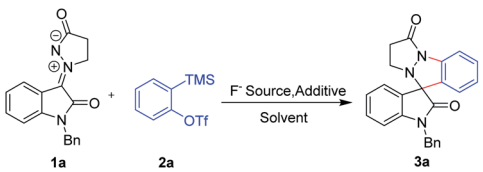
‡ These authors contributed equally to this work.

Moghaddam's group reported an unexpected abnormal [3 + 3] tandem Michael addition/*N*-cyclization of these 1,3-dipoles and 2-arylidenemalononitrile under DABCO catalysis (Scheme 1a).[10] During the course of the studies on these isatin *N*,*N*′-cyclic azomethine imine 1,3-dipoles, the related studies envisioned that these 1,3–dipoles have been utilized as valuable building blocks in cycloaddition reactions with alkenes. Given our ongoing interest in 1,3-dipolar cycloaddition and spirooxindole alkaloids, we envisioned the reaction of the isatin *N*,*N*′-cyclic azomethine imine 1,3-dipoles and arynes would be one approach to obtaining new pyrazole-spirooxindole derivatives *via* [3 + 2] cycloadditions (Scheme 1b).

Our investigations started with the screening of the reaction between the isatin *N*,*N*′-cyclic azomethine imine 1,3-dipole **1a** and the unsubstituted aryne precursor **2a** in the presence of CsF in CH_3CN at room temperature for 2 h. To our delight, the desired product **3a** was obtained in 20% yield (entry 1, Table 1). In order to improve the yield of the reaction product we used TBAF and KF instead of CsF as the fluoride source. Unfortunately, these two fluoride sources did not perform well (entries 2 and 3, Table 1). Performing the reaction in the presence of 18-crown-6 and CsF increased the yield to 55% (entry 4, Table 1). This result indicates that the 18-crown-6 has a remarkable influence on the yield. When the reaction was carried out at 50 °C, the reaction yields were not improved (entry 5, Table 1). Subsequently, a few more experiments were performed by changing the amount of CsF and 18-crown-6 (entries 6–9, Table 1). Interestingly, an improved yield of 67% was observed when the reaction was performed using 2.5 equiv. of CsF as a fluoride source and 3.0 equiv. of 18-crown-6 as an additive (entry 9, Table 1). And no improvements were observed with increasing the loadings of CsF (entries 7 and 8, Table 1). Finally, we investigated the reaction media by screening some common solvents, such as DMF, CH_2Cl_2, THF, 1,4-dioxane, EA, DCE and MeOH (entries 10–17, Table 1). The brief screening of the reaction solvent proved that THF was the best choice with respect to yields (entry 12, Table 1). Thus, the best reaction conditions utilized the isatin *N*,*N*′-cyclic azomethine imine 1,3-dipole **1a** (1.0 equiv.), aryne precursor **2a** (1.25 equiv.), CsF (2.5 equiv.) as the fluoride source and 18-crown-6 (3.0 equiv.) as the additive at room temperature.

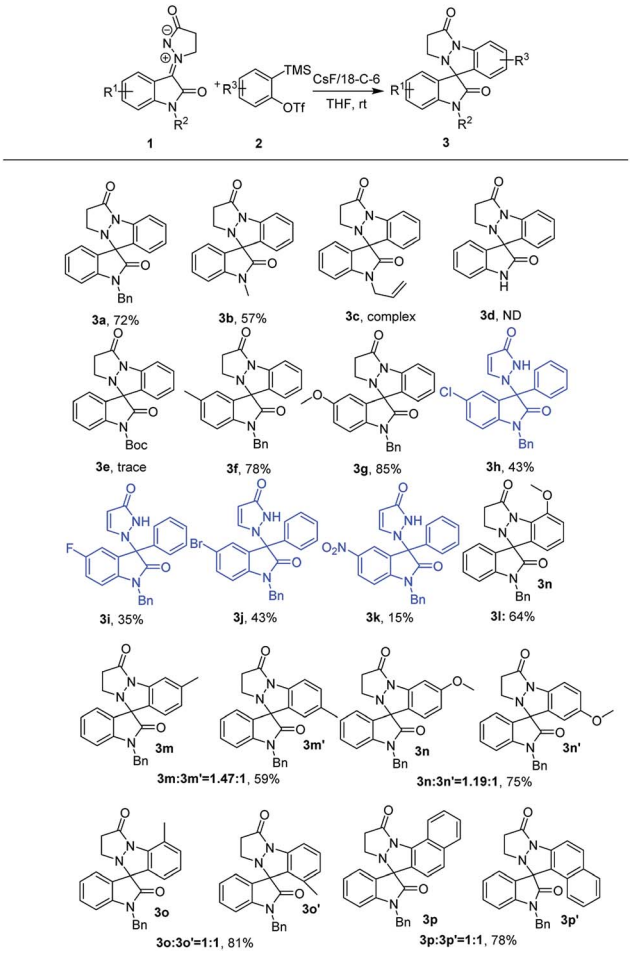
With the favorable reaction conditions established, the substrate scope and limitations of this catalyst-free self [3 + 2] cycloaddition of isatin *N*,*N*′-cyclic azomethine imine 1,3-dipole **1** with aryne precursors **2** were explored (Scheme 2). To our delight, most isatin *N*,*N*′-cyclic azomethine imines **1** and aryne precursors **2** were well tolerated. First, we evaluated the different 1,3-dipoles **1** with diverse substituents. It seems that the electronic nature of the substituents had intriguingly impact on the reaction. In general, substrates with electron-donating groups at the 5-position of **1** resulting in the formation of the cycloaddition products in good yields (**3f:** 78%; **3g:** 85%). In addition, a few 1,3-dipoles **1** with diverse N-substituted groups, including that with a free NH group, showed inert reactivity and failed to deliver the expected product. Only *N*-

Table 1 Optimization of the reaction conditions[a]



Entry	F-source (equiv.)	Additive (equiv.)	Solvent	Temp (°C)	Time (h)	Yield of **3a**[b] (%)
1	CsF (2.0)	—	MeCN	rt	2	20
2	TBAF (2.0)	—	MeCN	rt	2	Trace
3	KF (2.0)	—	MeCN	rt	2	15
4	CsF (2.0)	18-C-6 (2.0)	MeCN	rt	2	55
5	CsF (2.0)	18-C-6 (2.0)	MeCN	50	1	53
6	CsF (2.5)	18-C-6 (2.0)	MeCN	rt	2	64
7	CsF (3.0)	18-C-6 (2.0)	MeCN	rt	2	51
8	CsF (4.0)	18-C-6 (2.5)	MeCN	rt	2	53
9	CsF (2.5)	18-C-6 (3.0)	MeCN	rt	2	67
10	CsF (2.5)	18-C-6 (3.0)	DMF	rt	2	45
11	CsF (2.5)	18-C-6 (3.0)	CH_2Cl_2	rt	2	33
12	**CsF (2.5)**	**18-C-6 (3.0)**	**THF**	**rt**	**2**	**72**
13	CsF (2.5)	18-C-6 (3.5)	THF	rt	2	69
14	CsF (2.5)	18-C-6 (3.0)	1,4-Dioxane	rt	2	Trace
15	CsF (2.5)	18-C-6 (3.0)	EA	rt	4	55
16	CsF (2.5)	18-C-6 (3.0)	DCE	rt	4	27
17	CsF (2.5)	18-C-6 (3.0)	MeOH	rt	4	0

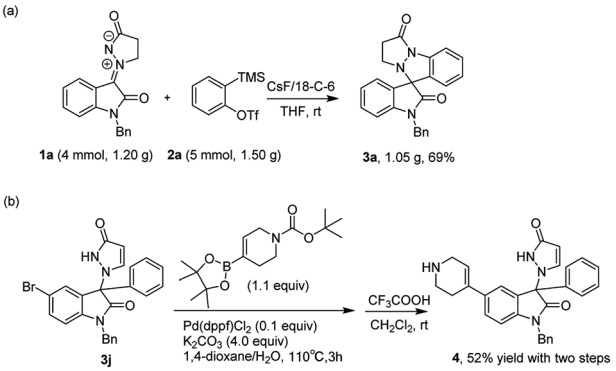
[a] Unless noted otherwise, reaction of **1a** (0.2 mmol), **2a** (0.25 mmol), fluoride source (0.5 mmol) and 18-C-6 (0.6 mmol) was performed in 3.0 mL of solvent under Ar. [b] Isolated yield based on **1a**.



Scheme 2 The reaction scope.[a,b] [a]Typical conditions: reaction of **1** (0.2 mmol), **2** (0.25 mmol), CsF (0.5 mmol) and 18-C-6 (0.6 mmol) was performed in 3.0 mL of THF at room temperature under Ar. [b]Isolated yield based on **1**.

methyl could smoothly afford the desired products with good results (**3b:** 57%). Interestingly, reactions carried out using the 1,3-dipoles **1** with electron-withdrawing groups resulted in the formation of the 3,3-disubstituted oxindole products in moderate yields (products **3h–3k**), probably because the latter substituent would lower the nucleophilicity of the 1,3-dipoles **1.** Next, the tolerance of substituents on the aryne moiety was also studied.

The cycloaddition products **3l–3o** are formed in moderate to good yields when this reaction was performed using unsymmetrical 3-substituted or 4-substituted arynes generated from the precursors. The unsymmetrical 4-methyl aryne afforded an inseparable mixture of regioisomers **3m** and **3m′** in 59% yield and a 1.47 : 1 regioisomer ratio. Similarly, inseparable regioisomeric products were formed when the reaction was carried out using unsymmetrical 4-methoxy, 3-methyl and 3-methoxy arynes. Moreover, the unsymmetrical naphthalyne was well tolerated to furnish the separable regioisomeric products **3p** and **3p′** in 78%.

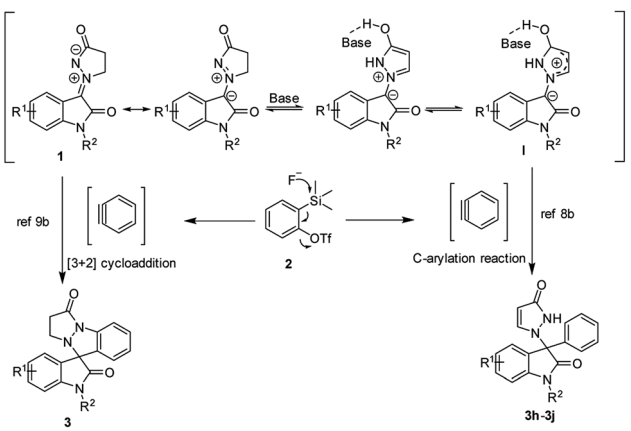


Scheme 3 Follow-up Chemistry.

In order to address the viability and potential synthetic application of this reaction, a gram-scale scale-up and several applications were carried out (Scheme 3). Under identified conditions, product **3a** was obtained without a significant loss of efficiency (69%) with a 4 mmol scale (Scheme 3a). To further illustrate synthetic applications of this method, we conducted a Suzuki coupling of product **3j** with *N*-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester, and then deprotection of the Boc group, which afforded product **4** in 52% yield (Scheme 3b).

On the basis of our results and the previous studies,[7d,8–10] two plausible mechanisms was proposed as illustrated in Scheme 4. One approach, the *in situ* generated aryne (formed by the fluoride induced 1,2-elimination from **2**) reacts with the isatin *N*,*N*′-cyclic azomethine imines **1** to generate the final product **3** through a thermal [3 + 2] annulation. The other, the more stable intermediate **I** was formed by the tautomerism of **1** in the presence of a base. Then intermediate **I** underwent C-arylation reaction with the *in situ* generated aryne with a double bond shift to generate the final product **3h**, **3i** and **3j** (Scheme 4).

Drawing inspiration from these 3,3-disubstituted oxindoles, a number of new drugs and lead compounds have been developed, especially in the field of anti-tumor.[11] Therefore, the target compounds were assayed for *in vitro* antitumor activity



Scheme 4 Plausible reaction mechanism.

Table 2 *In vitro* antitumor activities of the target compounds (IC_{50}, nM)

Compounds	IC_{50} (nM) Hep3B
3a	N.D.[a]
3b	N.D.
3f	N.D.
3g	N.D.
3h	>10 000
3i	>10 000
3j	4986.0
3k	>10 000
3l	N.D.
3m/**3m′**	N.D.
3n/**3n′**	N.D.
3o/**3o′**	N.D.
3p/**3p′**	N.D.
4	601.7
Infigratinib	224.2

[a] Not determined.

against hepatocellular carcinoma (Hep3B) using the standard MTT method (Table 2). Unfortunately, most compounds showed little bioactivity against Hep3B cells. Among all the compounds, only **3j** (4986.0 nM) and **4** (601.7 nM) showed good antitumor activities against Hep3B cells. And the results maybe suggest that these new 3,3-disubstituted oxindoles framework could be a new template for the design of novel anticancer molecules.

In summary, we have established an efficient method for the [3 + 2] annulation/C-arylation of isatin *N*,*N*′-cyclic azomethine imine 1,3-dipole **1** with *in situ* generated arynes, which constructed biologically important 3,3-disubstituted oxindoles in average good yields (up to 85% yield). The present methodology is both concise and mild, practical and one-pot method. The *in vitro* antitumor activity assay indicated that these scaffolds displayed moderate antitumor activities. Further chemical modification and biological exploration of these compounds are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (No. 21907053) and we also sincerely thank the China Pharmaceutical University for providing spectra.

Notes and references

1 (*a*) V. Polshettiwar and R. S. Varma, *Curr. Opin. Drug Discovery Dev.*, 2007, **10**, 723; (*b*) I. Sharma and D. S. Tan, *Nat. Chem.*, 2013, **5**, 157; (*c*) A. Padwa and S. K. Bur, *Tetrahedron*, 2007, **63**, 5341; (*d*) D. M. D'Souza and T. J. Muller, *Chem. Soc. Rev.*, 2007, **36**, 1095; (*e*) S. Dadiboyena, *Eur. J. Med. Chem.*, 2013, **63**, 347; (*f*) R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow and D. A. Pippin, *Comb. Chem. High Throughput Screening*, 2004, **7**, 473; (*g*) P. D. Leeson and B. Springthorpe, *Nat. Rev. Drug Discovery*, 2007, **6**, 881.

2 (*a*) K. Bernard, S. Bogliolo and J. Ehrenfeld, *Br. J. Pharmacol.*, 2005, **144**, 1037; (*b*) C. S. L. Gal, D. Sylvain, G. Brossard, M. Manning, J. Simiand, R. Gaillard, G. Griebel and G. Guillon, *Stress*, 2003, **6**, 199.

3 M. Rottmann, C. McNamara, B. S. K. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. Gonzalez-Paez, L. Lakshiminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H. P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler and T. T. Diagana, *Science*, 2010, **329**, 1175.

4 J. W. Skiles and D. McNeil, *Tetrahedron Lett.*, 1990, **31**, 7277.

5 (*a*) Y. Zhao, S. Yu, W. Sun, L. Liu, J. Lu, D. McEachern, S. Shargary, D. Bernard, X. Li, T. Zhao, P. Zou, D. Sun and S. Wang, *J. Med. Chem.*, 2013, **56**, 5553; (*b*) A. Aguilar, J. Lu, L. Liu, D. Du, D. Bernard, D. McEachern, S. Przybranowski, X. Li, R. Luo, B. Wen, D. Sun, H. Wang, J. Wen, G. Wang, Y. Zhai, M. Guo, D. Yang and S. Wang, *J. Med. Chem.*, 2017, **60**, 2819; (*c*) C. J. A. Ribeiro, J. D. Amaral, C. M. P. Rodrigues, R. Moreira and M. M. M. Santos, *MedChemComm*, 2016, **7**, 420; (*d*) A. Bertamino, M. Soprano, S. Musella, M. R. Rusciano, M. Sala, E. Vernieri, V. Di Sarno, A. Limatola, A. Carotenuto, S. Cosconati, P. Grieco, E. Novellino, M. Illario, P. Campiglia and I. Gomez-Monterrey, *J. Med. Chem.*, 2013, **56**, 5407.

6 G. Periyasami, R. Raghunathan, G. Surendiran and N. Mathivanan, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2342.

7 For selected 1,3-dipolar cycloaddition reviews, see: (*a*) L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887; (*b*) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863; (*c*) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366; (*d*) Y. Shi, G. G. Wang, Z. Y. Chen, M. H. Wu, J. Wang, L. Trigoura, H. B. Guo, Y. L. Xing and S. F Sun, *J. Heterocycl. Chem.*, 2020, **57**, 2044; (*e*) T. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, **12**, 1211.

8 (*a*) X. Wang, P. Yang, Y. Zhang, C. Z. Tang, F. Tian, L. Peng and L. X. Wang, *Org. Lett.*, 2017, **19**, 646; (*b*) X. Wang, L. Wu, P. Yang, X. J. Song, H. X. Ren, L. Peng and L. X. Wang, *Org. Lett.*, 2017, **19**, 3051; (*c*) X. J. Song, H. X. Ren, M. Xiang, C. Y. Li, F. Tian and L. X. Wang, *J. Org. Chem.*, 2020, **85**, 3921.

9 (*a*) S. Hu, J. Zhang and Q. Jin, *New J. Chem.*, 2018, **42**, 7025; (*b*) Q. Jin, J. Zhang, C. Jiang, D. Zhang, M. Gao and S. Hu, *J. Org. Chem.*, 2018, **83**, 8410.

10 F. M. Moghaddam, M. Eslami, A. Siahpoosh and G. Hoda, *New J. Chem.*, 2019, **43**, 10318.

11 (*a*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*b*) S. Peddibhotla, *Curr. Bioact. Compd.*, 2009, **5**, 20.