Chinese Chemical Letters 32 (2021) 413–416

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

Mn(III)-mediated radical reaction of 2-isocyano-6-alkenyl(alkynyl) benzonitriles with arylboronic acids: Synthesis of pyrroloisoquinoline derivatives

Pei Xu[1], Yi-Ming Zhu[1], Xin-Yu Liu, Xiao-Zhou Zhou, Shun-Yi Wang*, Shun-Jun Ji*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou 215123, China

ARTICLE INFO

Article history:
Received 19 January 2020
Received in revised form 17 February 2020
Accepted 7 March 2020
Available online 9 March 2020

Keywords:
2-Isocyano-6-alkenyl(alkynyl)benzonitriles
Arylboronic acids
Pyrroloisoquinoline derivatives
Radical reaction

ABSTRACT

A Mn(III) mediated radical reaction of new designed multi-functionalized 2-isocyano-6-alkenyl(alkynyl) benzonitriles with arylboronic acids has been developed. This reaction provides a method for the synthesis of pyrroloisoquinoline derivatives through the formation of two C—C bonds and one C—N bond *via* radical cascade cyclization in one step.

Cyano group is one of the most powerful group in chemical synthesis because it can participate in many reactions and transform into various functional groups, such as amino, amido, and carboxyl [1]. Very recently, the radical reactions involving cyano group have attracted increasing attention for their efficient and diversity applications. These reactions not only led to the carbonyl group [2], but also construct the *N*-heterocylic compounds [3]. Notably, the radical-mediated cyano group migration strategies which afford the new cyano-containing compounds have been well studied in the past few years [4]. On the other hand, isocyanides, which are isomer with cyano groups, are highly reactive groups and can participate in transition-metal-catalyzed reaction [5] and radical reaction [6]. Especially, the reactions utilizing *o*-functionalized arylisocyanides to construct the *N*-heterocylic compounds *via* radical cascade cyclization strategy in one step have received increasing attention of researchers. There are many *o*-functionalized arylisocyanides as radical acceptors, such as 2-isocyanobiaryls [7], 2-alkenyl arylisocyanides [8], 2-alkynyl arylisocyanides [9], 1-azido-2-isocyanoarenes [10], *o*-diisocyanoarenes [11], 2-isocyanothioanisoles [12].

It is of particular interest to develop the reactions of the arylisocyanides which modified by cyano group in the *ortho* position to afford the *N*-heterocylic compounds. However, only two relevant works have been reported in the literature. In 1999, Ito and his collaborators reported the reaction of *o*-isocyanobenzonitile to give the 2-diethylaminoquinazoline (only one example, Scheme 1a) [13], In addition, our group developed the novel method to construct the pyrrolopridin derivatives in this year (Scheme 1b). As our ongoing interest in the reaction of *o*-isocyanobenzonitile, we designed and synthesized 2-isocyano-6-alkenylbenzonitrile and 2-isocyano-6-alkynylbenzonitrile, respectively. Herein, we demonstrate a radical cascade reaction of 2-isocyano-6-alkenyl(alkynyl)benzonitrile to construct pyrroloisoquinoline derivatives (Scheme 1c).

We started our investigations with the reaction of methyl (*E*)-3-(2-cyano-3-isocyanophenyl)acrylate (**1a**) and phenylboronic acid (**2a**) in the presence of 2.0 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ in toluene to optimize the reaction. To our delight, the reaction proceeded smoothly to form the target product methyl 2-phenylpyrrolo [2,3,4-*ij*]isoquinoline-4-carboxylate (**3a**) in 61% yield after 12 h (Table 1, entry 1). Alternative manganese salts such as $MnSO_4$ and $Mn(OAc)_2 \cdot 2H_2O$, no desired product was detected (Table 1, entries 2 and 3). When increase the loading amount of $Mn(OAc)_3 \cdot 2H_2O$ to 3.0 equiv., the reaction proceed smoothly to give **3a** in 78% yield (Table 1, entry 4). While, the yield of **3a** reduce to 72% in the presence of 4.0 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ (Table 1, entry 5). Other solvents including DCE, DMSO, CH_3CN and DMF were also investigated under similar reaction conditions. However, all these solvents could not improve the yield of **3a** (Table 1, entries 6–9). Notably, either elevating or lowering the temperature resulted in

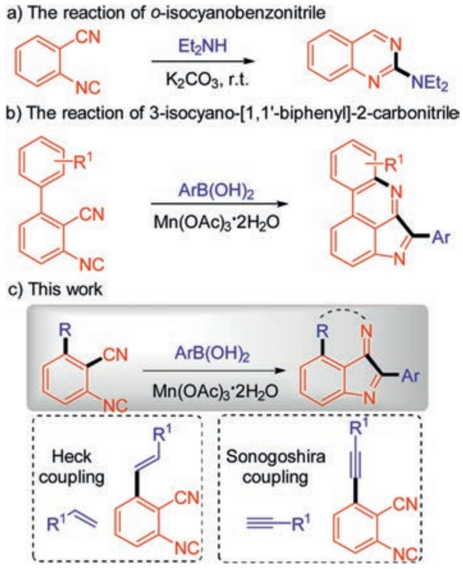
---

* Corresponding authors.

E-mail addresses: shunyi@suda.edu.cn (S.-Y. Wang), shunjun@suda.edu.cn (S.-J. Ji).

[1] These authors made equal contributions.

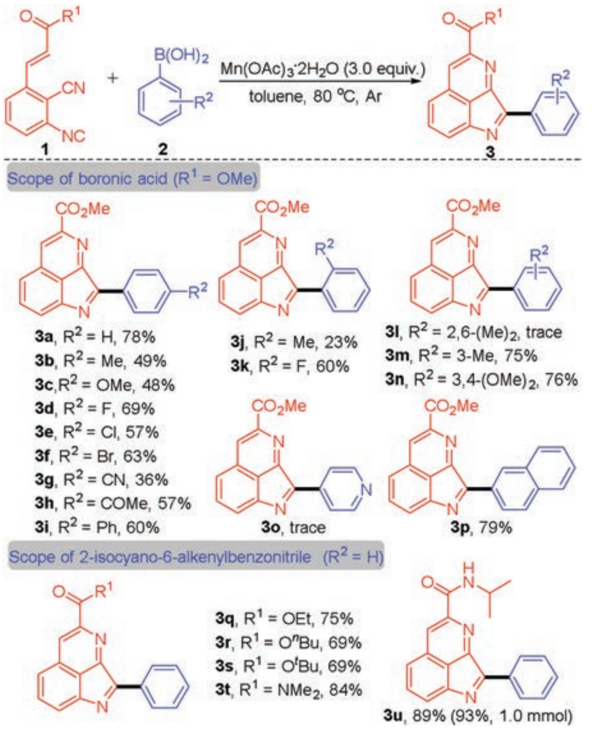
https://doi.org/10.1016/j.cclet.2020.03.023



Scheme 1. The reaction of isocyanides.

lower yields (Table 1, entries 10 and 11). Therefore, the optimized reaction conditions is following: methyl (*E*)-3-(2-cyano-3-isocyanophenyl)acrylate (**1a**) and phenylboronic acid (**2a**) in the presence of 3.0 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ in 2.0 mL toluene at 80 °C.

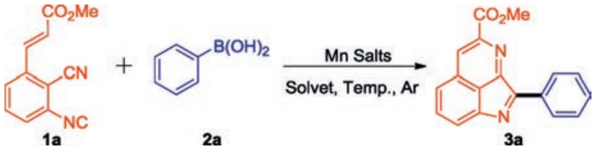
After having established the optimal reaction conditions, we investigated the substrate scope of 2-isocyano-6-alkenylbenzonitriles and arylboronic acids (Scheme 2). The reactions of arylboronic acids which substrates with electron-doating (Me, OMe) or electron-withdrawing groups (F, Cl, Br, CN, COMe) in the *para* position could proceed smoothly to afford the corresponding products **3b**-**3h** in 36%–69% yields. When the methyl group shifted to the *ortho* or *meta* position of the aryl ring, the reaction proceeded smoothly to give the desired products **3j** and **3m** in 23% and 75% yields, respectively. While, when the (2,6-dimethylphenyl)boronic acid **2l** was applied to the reaction with **1a**, the reaction failed to give the desired product **3l**.



Scheme 2. The reaction of 2-isocyano-6-alkenylbenzonitrile with arylboronic acids. Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (3.0 equiv.), toluene (2 mL), 80 °C, 12 h, argon atmosphere. Isolated yield. **3 u** was synthesized in 1.0 mmol scale by **1f** (1.0 mmol), **2a** (2.0 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (3.0 equiv.), toluene (20 mL), 80 °C, 12 h, argon atmosphere.

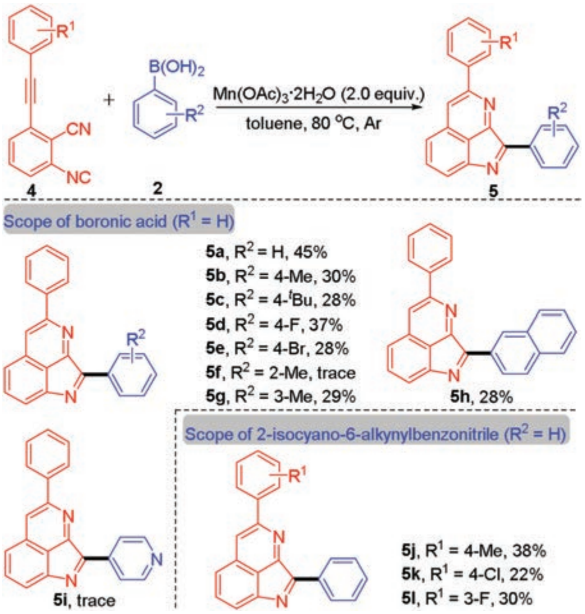
It is worth noting that when the F atom as an *ortho* substituent of the arylboronic acid, the yield of the corresponding product **3k** increased to 60%. The results indicate that steric effects have a significant effect on the reaction. In addition, the reactions of the (3,4-dimethylphenyl)boronic acid and naphthalen-2-ylboronic acid

Table 1
Optimization of the reaction conditions[a].

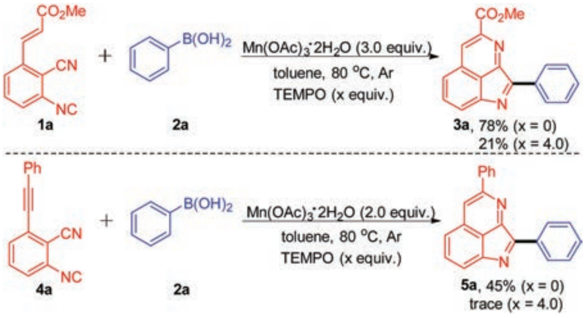


Entry	Mn salts (equiv.)	Solvent (2 mL)	T (°C)	Yield (%)[b]
1	$Mn(OAc)_3 \cdot 2H_2O$ (2)	Toluene	80	61
2	$MnSO_4$ (2)	Toluene	80	0
3	$Mn(OAc)_2 \cdot 2H_2O$ (2)	Toluene	80	0
4	$Mn(OAc)_3 \cdot 2H_2O$ (3)	Toluene	80	78
5	$Mn(OAc)_3 \cdot 2H_2O$ (4)	Toluene	80	72
6	$Mn(OAc)_3 \cdot 2H_2O$ (3)	DCE	80	68
7	$Mn(OAc)_3 \cdot 2H_2O$ (3)	DMSO	80	11
8	$Mn(OAc)_3 \cdot 2H_2O$ (3)	CH_3CN	80	56
9	$Mn(OAc)_3 \cdot 2H_2O$ (3)	DMF	80	26
10	$Mn(OAc)_3 \cdot 2H_2O$ (3)	Toluene	60	30
11	$Mn(OAc)_3 \cdot 2H_2O$ (3)	Toluene	100	70

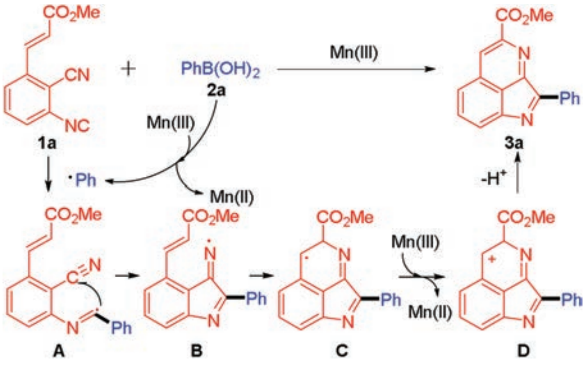
[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), manganese salts, solvent, 80 °C, 12 h.
[b] Isolated yields.



Scheme 3. The reaction of 2-isocyano-6-alkynylbenzonitrile with arylboronic acids. Reaction conditions: **4** (0.2 mmol), **2** (0.4 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (2.0 equiv.), toluene (6 mL), 80 °C, 12 h, argon atmosphere. Isolated yield.



Scheme 4. Control experiment.



Scheme 5. Plausible mechanism.

with **1a** could furnish the corresponding products **3n** and **3p** in 76% and 79% yield, respectively. Unfortunately, when the pyridin-4-ylboronic acid was employed in the reaction with **1a** and failed to obtain the desired product **3o** under the standard conditions. Then, a series of 2-isocyano-6-alkenylbenzonitrile were synthesized and have been subjected to the reactions with **2a** under the optimized conditions. It should be noted that the corresponding products **3q**-**3u** were obtained in moderate to excellent yields. To show the potential applications of our method, we tried the reactions of **1f** with **2a** in 1.0 mmol scale under the standard reaction conditions. To our delight, the reaction proceeded smoothly to afford **3u** in 93% yield.

Next, we turned our attention to the reaction of 2-isocyano-6-alkynylbenzonitrile with arylboronic acid (Scheme 3). After extensive optimization, we were able to identify conditions which included 2-isocyano-6-(phenylethynyl)benzonitrile (**4a**) and phenylboronic acid (**2a**) in the presence of 2.0 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ in toluene at 80 °C that delivered the desired product **5a** in 45% isolated yield. To further evaluate the scope of this method, differently substituted arylboronic acids were examined. It is worth mentioning that several functional groups, including electron-rich (Me, ^{t}Bu) or halogen groups (F, Br) of the arylboronic acid as the substrate the corresponding products **5b**, **5c**, **5d**, **5e**, **5g** were obtained in 28%–37% yields. It is notable that **5f** could not be observed when *o*-tolylboronic acid reacted with **4a** due to the steric effect. Additionally, the desired product **5h** could be obtained in 28% yield when using naphthalen-2-ylboronic acid as the substrate. Unfortunately, the reaction of pyridin-4-ylboronic acid with **4a** failed to give the corresponding product **5i**. We also explored the scope of 2-isocyano-6-alkynylbenzonitrile. Different groups on the aryl ring including methyl (**5j**), chloro (**5k**), and fluoro (**5l**) were also tolerated under the reaction conditions.

To gain insight into the reaction mechanism, a series of radical capture experiments have been carried out (Scheme 4). When 4.0 equiv. of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) was employed in the reaction system under the optimized conditions, we could isolated the desired product in 21% yield. The above results which suggest a radical process is probably involved in the reaction of 2-isocyano-6-alkenylbenzonitrile and arylboronic acid. After that, a similar result was observed when 4.0 equiv. of TEMPO was applied to the reaction of **4a** and **2a**.

On the basis of the results above and related literatures [3,14], we proposed a plausible reaction mechanism (Scheme 5). First, the Mn(III) promotes the phenylboronic acid to give the phenyl radical. Next, the radical intermediate **A** is generated by the reaction of methyl (*E*)-3-(2-cyano-3-isocyanophenyl)acrylate (**1a**) and the phenyl radical. Subsequently, the radical intermediate **A** adds to the cyano group to furnish the corresponding N-centered radical **B**. The N-centered radical **B** undergoes intramolecular cyclization with the C—C double bond to afford the radical intermediate **C**. Then, the intermediate **D** is afforded *via* single-electron oxidation of C by Mn(III). Finally, the corresponding product **3a** is formed by hydrogen abstraction from the intermediate **D**.

In summary, we have developed a radical cascade reaction of 2-isocyano-6-alkenyl(alkynyl)benzonitriles with arylboronic acid in the presence of Mn(III). This reaction provides a novel strategy for the construction of pyrroloisoquinoline derivatives in one step *via* the formation of two C—C bonds and one C—N bond, which has high step and atomic economy.

Declaration of competing interest

The authors declare no completing financial interest.

Acknowledgments

We gratefully acknowledge the National Natural Science Foundation of China (Nos. 21971174, 21772137, 21542015 and 21672157), PAPD, the Project of Scientific and Technologic Infrastructure of Suzhou (No. SZS201708), the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (No. 16KJA150002), Soochow University for financial support.

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.2020.03.023.

References

[1] (a) M.X. Wang, Acc. Chem. Res. 48 (2015) 602–611;
(b) P. Anbarasan, T. Schareina, M. Beller, Chem. Soc. Rev. 40 (2011) 5049–5067.
[2] (a) S.S. Wang, H. Fu, Y. Shen, M. Sun, Y.M. Li, J. Org. Chem. 81 (2016) 2920–2929;
(b) X.T. Zhu, Q. Zhao, F. Liu, et al., Chem. Commun. 53 (2017) 6828–6831;
(c) J. Yu, H.X. Sheng, S.W. Wang, et al., Chem. Commun. 55 (2019) 4578–4581.
[3] (a) J. Zheng, Y. Zhang, D. Wang, S. Cui, Org. Lett. 18 (2016) 1768–1771;
(b) X. Li, X. Fang, S. Zhuang, P. Liu, P. Sun, Org. Lett. 19 (2017) 3580–3583;
(c) L.J. Wu, Y. Yang, R.J. Song, et al., Chem. Commun. 54 (2018) 1367–1370;
(d) X.H. Shan, H.X. Zheng, B. Yang, et al., Nat. Commun. 10 (2019) 908.
[4] (a) Z. Wu, R. Ren, C. Zhu, Angew. Chem. Int. Ed. 55 (2016) 10821–10824;
(b) N. Wang, L. Li, Z.L. Li, et al., Org. Lett. 18 (2016) 6026–6029;
(c) Y. Chen, J. Du, Z. Zuo, Chem 6 (2020) 266–279.
[5] (a) B. Song, B. Xu, Chem. Soc. Rev. 46 (2017) 1103–1123;
(b) P. Xu, F. Wang, T.Q. Wei, et al., Org. Lett. 19 (2017) 4484;
(c) Y. Fang, J.M. Yang, R. Zhang, S.Y. Wang, S.J. Ji, Org. Chem. Front. 6 (2019) 3383–3386;
(d) P. Xu, Y.M. Zhu, X.J. Li, et al., Adv. Synth. Catal. 361 (2019) 4909–4913;
(e) G.S. Chen, S.J. Chen, J. Luo, et al., Angew. Chem. Int. Ed. 59 (2020) 614–621.
[6] (a) B. Zhang, A. Studer, Chem. Soc. Rev. 44 (2015) 3505–3521;
(b) J.J. Cao, T.H. Zhu, S.Y. Wang, et al., Chem. Commun. 50 (2014) 6439–6442;
(c) J.J. Cao, X. Wang, S.Y. Wang, S.J. Ji, Chem. Commun. 50 (2014) 12892–12895;
(d) Y. Fang, C. Liu, F. Wang, et al., Org. Chem. Front. 6 (2019) 660–663.
[7] (a) M. Tobisu, K. Koh, T. Furukawa, N. Chatani, Angew. Chem. Int. Ed. 51 (2012) 11363–11366;
(b) Y. Li, T. Miao, P. Li, L. Wang, Org. Lett. 20 (2018) 1735–1739;
(c) A. Guo, J.B. Han, X.Y. Tang, Org. Lett. 20 (2018) 2351–2355;
(d) J. Wei, D. Gu, S. Wang, et al., Org. Chem. Front. 5 (2018) 2568–2572;
(e) S. Liu, F. Fan, N. Wang, et al., Adv. Synth. Catal. 361 (2019) 3086–3093;
(f) S. Liu, W. Pan, S. Wu, et al., Green Chem. 21 (2019) 2905–2910.
[8] (a) B. Zhang, A. Studer, Org. Lett. 16 (2014) 1216–1219;
(b) C.J. Evoniuk, M. Ly, I.V. Alabugin, Chem. Commun. 51 (2015) 12831–12834.
[9] T. Mitamura, K. Iwata, A. Ogawa, Org. Lett. 11 (2009) 3422–3424.
[10] (a) D. Li, T. Mao, J. Huang, Q. Zhu, Org. Lett. 19 (2017) 3223–3226;
(b) D. Li, J. Lei, Org. Biomol. Chem. 17 (2019) 9666–9671.
[11] (a) D. Leifert, A. Studer, Angew. Chem. Int. Ed. 55 (2016) 11660–11663;
(b) X. Sun, W. Wang, Y. Li, J. Ma, S. Yu, Org. Lett. 18 (2016) 4638–4641;
(c) Y. Liu, X.L. Chen, F.L. Zeng, et al., J. Org. Chem. 83 (2018) 11727–11735;
(d) Y. Fang, C. Liu, W. Rao, S.Y. Wang, S.J. Ji, Org. Lett. 21 (2019) 7687–7691.
[12] (a) W.C. Yang, K. Wei, X. Sun, J. Zhu, L. Wu, Org. Lett. 20 (2018) 3144–3147;
(b) Y. Yuan, W. Dong, X. Gao, X. Xie, Z. Zhang, Org. Lett. 21 (2019) 469–472;
(c) K. Luo, W.C. Yang, K. Wei, et al., Org. Lett. 21 (2019) 7851–7856;
(d) Y. Liu, X.L. Chen, K. Sun, et al., Org. Lett. 21 (2019) 4019–4024.
[13] M. Suginome, T. Fukuda, Y. Ito, Org. Lett. 1 (1999) 1977–1979.
[14] P. Xu, Y.M. Zhu, F. Wang, S.Y. Wang, S.J. Ji, Org. Lett. 21 (2019) 683–686.