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Advanced Synthesis & Catalysis

PPTS-Catalyzed Bicyclization Reaction of 2-Isocyanobenzaldehydes with Various Amines: Synthesis of Diverse Fused Quinazolines

Xiang-He Meng,[a] Dan-Ni Wu,[a] Yu-Jia Zhang,[a] and Yu-Long Zhao[a,*]

[a] Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Faculty of Chemistry, Northeast Normal University, Changchun 130024, People's Republic of China
E-mail: zhaoyl351@nenu.edu.cn

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Abstract: A PPTS (pyridinium *p*-toluenesulfonate)-catalyzed bicyclization reaction of 2-isocyanobenzaldehydes as 1,5-dielectrophiles with various amines has been developed. The reaction not only provides a simple and efficient strategy for the assembly of structurally diverse fused quinazoline derivatives from readily available substrates under metal-free and mild conditions in a single step with only water and hydrogen as the by-products, but also opens the way to the application of *o*-formyl arylisocyanides in the synthesis of nitrogen-containing heterocycles.

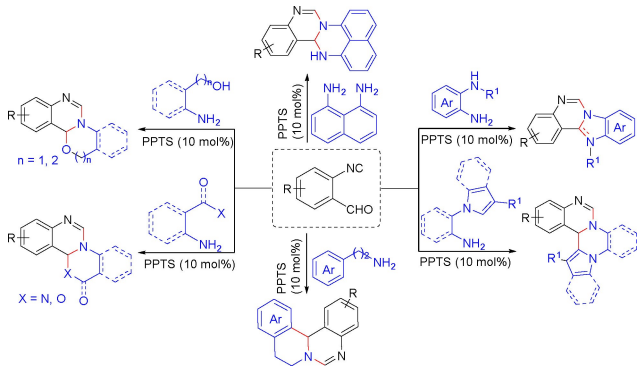
Keywords: PPTS; 2-Isocyanobenzaldehydes; Amines; Bicyclization; Fused quinazolines

Introduction

Due to the significance of molecular diversity and complexity in drug discovery and other research fields, development of efficient synthesis toward valuable complex and diverse compounds from easily available starting materials, along with minimum environmental impacts, has attracted great interest in academia and industry.[1] Among various synthetic routes to these compounds, metal-free bicyclization reactions are highly attractive due to their inherent advantages of step- and atom-economy and sustainability as well as no heavy metal residue.[2] On the other hand, nitrogen-containing heterocycles are the most remarkable motifs found in a wide range of natural products and pharmaceuticals.[3] Among the vast array of heterocycle compounds, various fused quinazoline derivatives, such as benzo[4,5]imidazo[1,2-*c*]quinazolines, quinazolino[3,4-*a*]perimidines, quinazolinoquinazolinones, isoquinolino[2,1-*c*]quinazolines and other polycyclic fused quinazoline derivatives, are particularly fascinating skeletons and show a broad spectrum of medicinally profound bioactivities.[4] Moreover, polycyclic fused quinazoline derivatives are also used as core components of various functional materials and ligands.[5] Consequently, various prevalent and useful methods for the synthesis of fused quinazoline derivatives based on different synthetic strategies have been developed.[6–10] However, most of methods suffer from the limited substrate scope, tedious synthetic procedures, hard reaction conditions or use of transition metal catalysts. Thus, development of new and systematical methods for the diversity-oriented construction of polycyclic fused quinazoline derivatives from readily available substrates, especially from the same starting materials, in the absence of transition metals under mild conditions is an appealing and challenging for chemists.

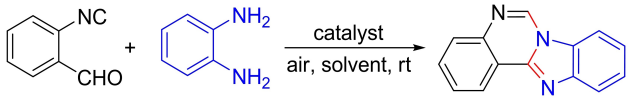
Because of their unique and versatile reactivities, isocyanides are very useful building blocks and have been extensively applied in organic chemistry.[11] Among the various functionalized arylisocyanides, *o*-carbonyl arylisocyanides have been employed as valuable precursors for the synthesis of diverse classes of heterocycles.[12] As important members of these families, although the preparation of *o*-formyl arylisocyanides had been achieved,[13] report on application of *o*-formyl arylisocyanides is considerably rare. To the best of our knowledge, so far only one application based on the *o*-formyl arylisocyanides was described. Very recently, our group reported a silver-catalyzed coupling cyclization reaction of *o*-formyl arylisocyanides, amines, and 2,2,2-trifluorodiazoethane for the first time.[14] As part of our continuing research on the

synthesis of nitrogen-containing compounds,[14,15] herein we reported a PPTS-catalyzed bicyclization reaction of 2-isocyanobenzaldehydes as 1,5-dielectrophiles with various amines for the first time (Scheme 1). The advantages of the current protocol can be summarized as follows: (1) the reaction provides a simple and efficient strategy for the assembly of structurally diverse fused quinazoline derivatives; (2) this strategy allows the formation of two rings and three new bonds with only water and hydrogen as the by-products in a single step; (3) this protocol is characterized by a broad substrate scope, readily available starting materials, mild reaction conditions, and high scalability.



Scheme 1. Bicyclization reaction of *o*-formyl arylisocyanides with amines for the synthesis of diverse fused quinazolines.

Table 1. Optimization of reaction conditions.[a]



1a 2a 3aa

Entry	Catalyst [mol%]	Addition	Solvent	t	Yield[b] [%]
1	PPTS (10)	–	DMSO	1	52
2	PPTS (10)	4ÅMS (100 mg)	DMSO	1	91
3	PPTS (5)	4ÅMS (100 mg)	DMSO	1	86
4	PPTS (15)	4ÅMS (100 mg)	DMSO	1	90
5	AcOH (10)	4ÅMS (100 mg)	DMSO	1	33
6	TsOH (10)	4ÅMS (100 mg)	DMSO	1	45
7	TfOH (10)	4ÅMS (100 mg)	DMSO	1	57
8	PPTS (10)	4ÅMS (100 mg)	DMF	1	74
9	PPTS (10)	4ÅMS (100 mg)	MeCN	1	58
10	PPTS (10)	4ÅMS (100 mg)	THF	2	46
11	PPTS (10)	4ÅMS (100 mg)	dioxane	2	51
12	PPTS (10)	4ÅMS (100 mg)	toluene	2	38
13	PPTS (10)	4ÅMS (100 mg)	DCE	2	41

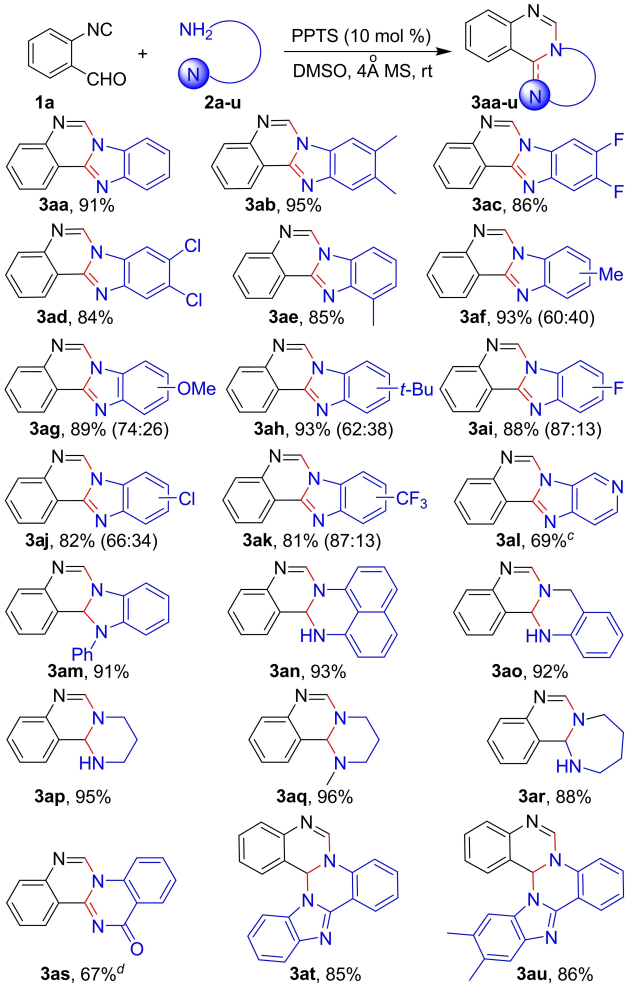
[a] **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (5–15 mol%), 4Å MS (100 mg), solvent (0.5 mL), at room temperature for 1–2 h.
[b] Isolated yield.

Results and Discussion

Initially, the reaction of 2-isocyanobenzaldehyde **1a** and *o*-phenylenediamine **2a** was investigated to optimize the reaction conditions (Table 1). We found that the benzo[4,5]imidazo[1,2-*c*]quinazoline **3aa** was obtained in 52% yield when the reaction of **1a** (0.2 mmol) with **2a** (0.5 mmol) was performed in the presence of pyridinium *p*-toluenesulfonate (PPTS, 10 mol%) at room temperature for 1 h (Table 1, entry 1). To our delight, the yield of **3aa** was raised to 91% by the addition of 4Å molecular sieves (100 mg) under otherwise identical conditions (entry 2). Decreasing the amount of PPTS led to comparatively lower yield (entry 3). Further increasing the amount of PPTS did not improve the yield of **3aa** (entry 4). Other acid catalysts, such as AcOH, TsOH, and TfOH were less effective than PPTS (entries 5–7). Among the solvents tested, DMSO turned out to be the best choice. Other solvents, such as DMF, MeCN, THF, 1,4-dioxane, toluene and DCE gave lower yields.

With the optimized reaction conditions in hand, the scope of the bicyclization reaction was examined and the results are summarized in Table 2. We found that the bicyclization showed broad tolerance to various diamines. All selected *o*-phenylenediamines **2a–k** bearing either electron-withdrawing or electron-donating groups on the aromatic rings and pyridine-3,4-diamine **2l** reacted smoothly with 2-isocyanobenzaldehyde **1a** to give the corresponding benzo[4,5]imidazo[1,2-*c*]quinazolines **3aa–l** in high to excellent yields. In this transformation, symmetrical *o*-phenylenediamines **2a–d** gave single isolated products **3aa–d** as expected. Reactions of *o*-phenylenediamines **2f–k** with **1a** provided inseparable regioisomers **3af–k**. In the case of 3-methylbenzene-1,2-diamine **2e** and pyridine-3,4-diamine **2l**, the bicyclization reaction showed exclusive regioselectivity and produced the desired products **3ae** and **3al** in 85% and 69% yields, respectively. Similarly, N^1-phenylbenzene-1,2-diamine **2m** could react efficiently with **1a** to produce desired product **3am** in 91% yield. When naphthalene-1,8-diamine **2n** was employed as reaction partner, the dihydroquinazolino[3,4-*a*]perimidine **3an** was produced in 93% yield. In addition, the bicyclization of 2-(aminomethyl)aniline **2o** with **1a** also proceeded efficiently in a highly regioselective manner, resulting in the expected single product **3ao** in 92% yield.[16] Besides to aromatic amines, a range of aliphatic diamines, such as propane-1,3-diamine **2p**, N^1-methylpropane-1,3-diamine **2q**, and butane-1,4-diamine **2r** also proved to be efficient partners, and the desired fused quinazoline derivatives **3ap–r** were obtained in high to excellent yields. Notably, even using 2-aminobenzamide **2s** as dinucleophile, the bicyclization also worked well, yielding the desired product **3as** in 67% yield. More importantly, 2-(1*H*-benzo[*d*]imidazol-2-yl)

Table 2. PPTS-Catalyzed bicyclization of 2-isocyanobenzaldehyde **1a** and diamines **2**.[a,b]

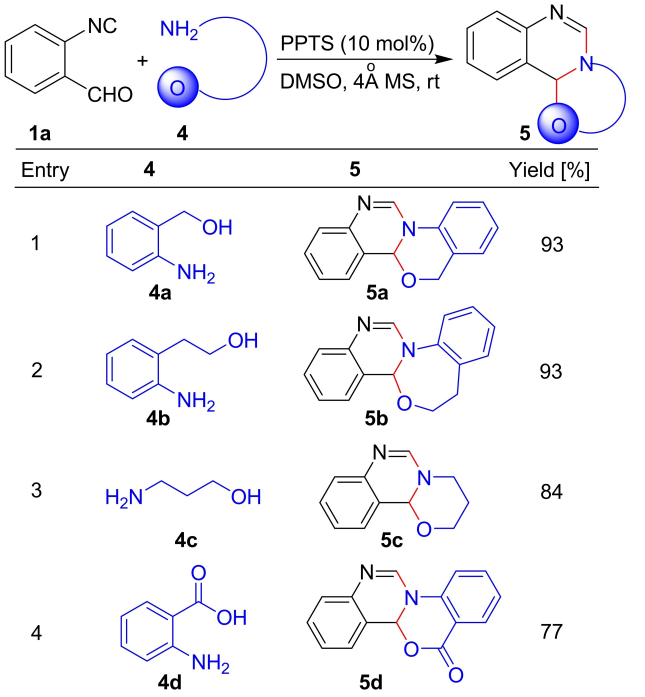


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), PPTS (10 mol%), 4Å MS (100 mg), DMSO (0.5 mL), at room temperature for 1–2 h.
[b] Isolated yield.
[c] The reaction was performed at 100 °C for 1.5 h.
[d] The reaction was performed at 120 °C for 12 h.

anilines **2t** and **2u** were also tolerant, with the generation of polycyclic fused quinazolines **3at** and **3au** in 85% and 86% yields, respectively (Table 2). In addition, a scale-up reaction of **1a** (5.0 mmol) and **2n** (5.0 mmol) was carried out for 2 h under otherwise identical conditions as above, furnishing 1.10 g of the desired product **3an** in 81% isolated yield, showing the practicality of the transformation.

To further explore the generality of this new reaction for dinucleophiles, the PPTS-catalyzed bicyclization reaction of 2-isocyanobenzaldehyde **1a** with various *N,O*-dinucleophiles **4** was investigated (Table 3). As a result, when the reaction of **1a** with (2-aminophenyl)methanol **4a** was carried out under the identical conditions as above, the desired quinazolino

Table 3. PPTS-Catalyzed bicyclization of 2-isocyanobenzaldehyde **1a** and *N,O*-dinucleophiles **4**.[a,b]

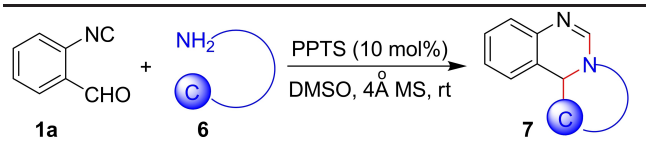


[a] Reaction conditions: **1a** (0.2 mmol), **4** (0.2 mmol), PPTS (10 mol%), 4Å MS (100 mg), DMSO (0.5 mL), at room temperature for 1–2 h.
[b] Isolated yield.

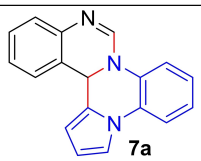
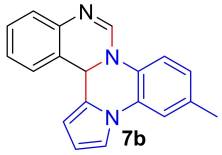
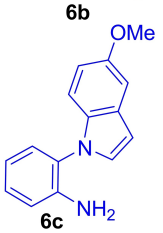
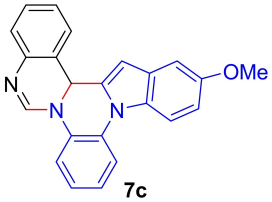
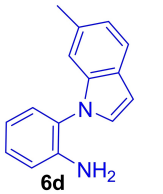
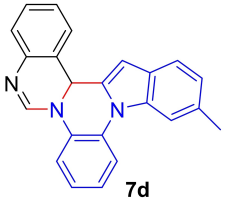
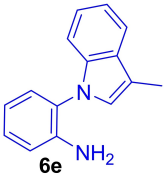
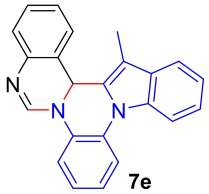
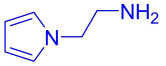
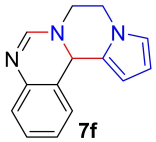
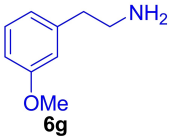
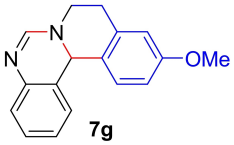
[3,4-*a*]-3,1-benzoxazine **5a** was generated in 93% yield. Similarly, other amino alcohols, such as 2-(2-aminophenyl)ethanol **4b** and 3-aminopropan-1-ol **4c**, were also compatible in this bicyclization reaction and the corresponding fused quinazoline derivatives **5b** and **5c** were obtained in 93% and 84% yields, respectively. Notably, when 2-aminobenzoic acid **4d** was used as *N,O*-dinucleophile, the bicyclization reaction also proceeded efficiently to give the desired product **5d** in 77% yield (Table 3).

On the basis of the above experimental results, along with the consideration of Friedel-Crafts alkylation reaction of imines with arenes,[17] we reasoned that the imine intermediate generated in situ from the reaction of 2-isocyanobenzaldehyde **1a** with 2-(1*H*-pyrrol-1-yl)aniline **6a** can undergo a sequential intramolecular Friedel-Crafts alkylation and intramolecular cyclization to afford polycyclic fused quinazoline derivatives (Table 4). As expected, the polycyclic fused quinazoline **7a** was obtained in 87% yield when 2-isocyanobenzaldehyde **1a** (0.2 mmol) was treated with **6a** (0.2 mmol) under the optimized reaction conditions as above. Similarly, fused pyrrole **7b** was produced in 83% yield when 4-methyl-2-(1*H*-pyrrol-1-yl)aniline **6b** was employed as *N,C*-dinucleophile. In addition, considering the importance of fused indole scaffold in

Table 4. PPTS-Catalyzed bicyclization of 2-isocyanobenzaldehyde **1a** and *N,C*-dinucleophiles **6**.[a,b]



1a 6 7

Entry	6	7	Yield [%]
1	 6a	 7a	87
2	 6b	 7b	83
3	 6c	 7c	80
4	 6d	 7d	78
5	 6e	 7e	84
6	 6f	 7f	85
7	 6g	 7g	64

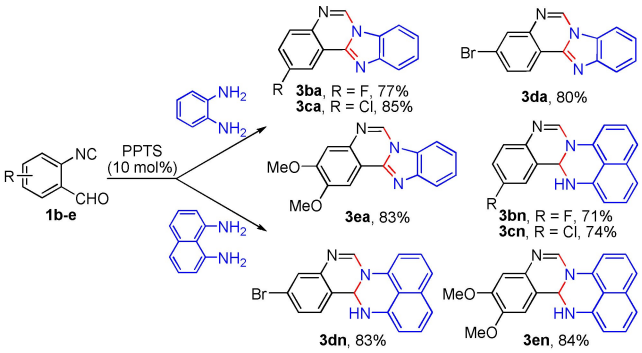
[a] Reaction conditions: **1a** (0.2 mmol), **6** (0.2 mmol), PPTS (10 mol%), 4Å MS (100 mg), DMSO (0.5 mL), at room temperature for 12 h.
[b] Isolated yield.

pharmaceuticals, fragrances, agrochemicals, and pigments,[18] the bicyclization reaction of 2-(1*H*-indol-1-yl)anilines **6c–e** with **1a** also was investigated As a result, fused indoles **7c–e** were formed in high yields. More importantly, ethylamines bearing an aromatic ring **6f** and **6g** were tolerated, with the generation of polycyclic fused quinazolines **7f** and **7g** in 85% and 64% yields, respectively (Table 4). The above results further indicate that the bicyclization reaction can tolerate various dinucleophiles and exhibit good flexibility.

Next, we turned to extend the scope of 2-isocyanobenzaldehydes **1**. As shown in Scheme 2, various 2-isocyanobenzaldehydes **1b–e** bearing either electron-withdrawing or electron-donating R groups on the aromatic ring could react smoothly with **2a** to give the corresponding benzo[4,5]imidazo[1,2-*c*]quinazolines **3b–ea** in high yields (Scheme 2). Similarly, dihydroquinazolino[3,4-*a*]perimidines **3b–en** were produced in high yields when 2-isocyanobenzaldehydes **1b–e** were treated with naphthalene-1,8-diamine **2n** under the optimized reaction conditions (Scheme 2).

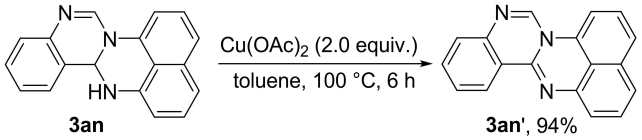
In addition, the oxidation reaction of **3an** was explored. We found that the oxidation reaction of **3an** (0.2 mmol) proceeded efficiently in the presence of $Cu(OAc)_2$ (2.0 equiv.) in toluene at 100 °C for 6 h to give the desired oxidation product **3an′** in 94% yield (Scheme 3).

To further probe the mechanism for the formation **3**, the reaction of **1a** with **2a** was carried out under an atmosphere of nitrogen under otherwise identical



[a] Reaction conditions: **1b-e** (0.2 mmol), **2a** or **2n** (0.2 mmol), PPTS (10 mol%), 4Å MS (100 mg), DMSO (0.5 mL), at room temperature for 1-2 h.
[b] Isolated yield.

Scheme 2. PPTS-Catalyzed bicyclization of 2-isocyanobenzaldehydes **1b–e** and **2a** or **2n.**[a,b]



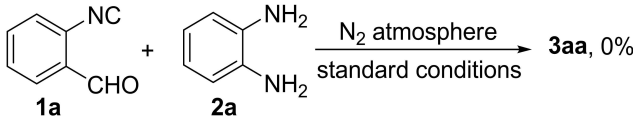
Scheme 3. Oxidation reaction of **3an**.

conditions. As a result, no desired product **3aa** was obtained, indicating that molecular oxygen as oxidant is required for the synthesis of **3aa** (Scheme 4).

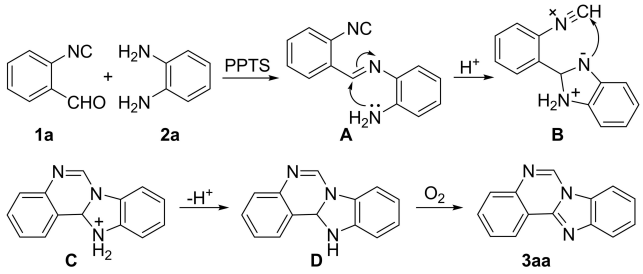
On the basis of the above experimental results together with related reports,[11–13,17] a possible mechanism for the formation of **3**, **5** and **7** is proposed in Scheme 5 (with the formation of **3aa** as example). Initially, in the presence of PPTS, the in situ condensation of 2-isocyanobenzaldehyde **1a** and *o*-phenylenediamine **2a** generates aldimine **A**. Subsequently, intermediate **A** undergoes an intramolecular cyclization, followed by the protonation of isocyano group to give intermediate **B**. The nitrogen anion of intermediate **B** attacks the terminal carbon atom of the isocyano group to produce intermediate **C**. Finally, benzo[4,5]imidazo[1,2-*c*]quinazoline **3aa** was produced via a sequential deprotonation and oxidative aromatization process (Scheme 5).

Conclusion

In summary, a new PPTS-catalyzed bicyclization reaction of 2-isocyanobenzaldehydes as 1,5-dielectrophiles with various amines has been developed for the first time. The reaction provides a simple and efficient strategy for the assembly of structurally diverse fused quinazoline derivatives by formation of two rings and three new bonds in a single step. This protocol features readily available starting materials, mild conditions, broad substrate scope, good functional tolerance, high reaction efficiency, and high product yields. The method will open the way to the application of *o*-formyl arylisocyanides in the synthesis of nitrogen-containing heterocycles. Further work on the applications and extension of *o*-formyl arylisocyanides are currently under investigation in our laboratory.



Scheme 4. Control experiment.



Scheme 5. Proposed mechanism for the formation of **3aa**.

Experimental Section

General Procedure for the Preparation of 3, 5 and 7 (3aa as Example)

An oven-dried vial equipped with a magnetic stir bar was charged with 2-isocyanobenzaldehyde **1a** (26.3 mg, 0.2 mmol), *o*-phenylenediamine **2a** (21.6 mg, 0.2 mmol), PPTS (5.6 mg, 10 mol%), 4 Å MS (100 mg), then DMSO (0.5 mL) was added. The resulting suspension was stirred at 25 °C for 1 h until **1a** disappeared. After the reaction was complete, the resulting mixture was filtered (Celite/EA), then was diluted with 30 mL brine and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed three times with brine and dried over anhydrous $MgSO_4$. The solid was recrystallized in ethyl acetate/*n*-hexane to afford pure product **3aa** (39.9 mg, 91%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.10 (s, 1H), 8.69–8.64 (m, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.80–7.76 (m, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 146.32, 144.00, 142.55, 136.11, 131.76, 128.63, 128.50, 128.13, 126.14, 124.19, 123.26, 120.29, 119.30, 110.06. HRMS (ESI-TOF): $[M+H]^+$ calculated for $C_{14}H_{10}N_3^+$: 220.0869, found: 220.0866.

Acknowledgements

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References

[1] For selected reviews, see: a) F.-L. Hong, L.-W. Ye, *Acc. Chem. Res.* **2020**, *53*, 2003; b) J.-Y. Wang, W.-J. Hao, S.-J. Tu, B. Jiang, *Org. Chem. Front.* **2020**, *7*, 1743; c) J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281; d) Y. Wang, H. Lu, P. F. Xu, *Acc. Chem. Res.* **2015**, *48*, 1832; e) A. C. Jones, J. A. May, R. Sarpong, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2014**, *53*, 2556; *Angew. Chem.* **2014**, *126*, 2590; f) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; g) W. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976.

[2] For selected reviews, see: a) R. Ardkhean, D. F. J. Caputo, S. M. Morrow, H. Shi, Y. Xiong, E. A. Anderson, *Chem. Soc. Rev.* **2016**, *45*, 1557; b) B.-H. Rotstein, S. Zaretsky, V. Rai, A.-K. Yudin, *Chem. Rev.* **2014**, *114*, 8323; c) S. V. Brauch, S.-S. Berkel, B. Westermann, *Chem. Soc. Rev.* **2013**, *42*, 4948; d) A. Domling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083; e) G. Koopmanschap, E. Ruijter, R.-V. Orru, *Beilstein J. Org. Chem.* **2014**, *10*, 544; f) M.-H. Huang, W.-J. Hao, B. Jiang, *Chem. Asian J.* **2018**, *13*, 2958.

[3] For selected reports: a) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 5th Edition; Wiley: Chichester, U. K., **2010**; b) P. A. Keller, *In Comprehensive Heterocyclic Chemistry III*; A. R. Katritzky, C. A. Ramsden, E. F. V.

Scriven, R. J. K. Taylor, Eds.; Elsevier: Oxford, U. K. **2008**; Vol. 7, pp 217; c) B. R. Brown, *The Organic Chemistry of Aliphatic Nitrogen Compounds*; Cambridge University Press: Cambridge, U. K., **2004**; d) G. A. Cordell, *The Alkaloids: Cehemistry and Biology*, Ed.; Academic Press: San Diego, CA.; Vol. 54, **2000**; e) N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso, A. F. Trindade, *Chem. Rev.* **2009**, *109*, 2703; f) A. T. Balaban, D. C. Oniciu, A. R. Katritzky, *Chem. Rev.* **2004**, *104*, 2777; g) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[4] For selected reports: a) O. M. O. Habib, H. M. Hassan, A. El-Mekabaty, *Med. Chem. Res.* **2012**, *22*, 507; b) C. Lamazzi, S. Leonce, B. Pfeiffer, P. Renard, G. Guillaumet, C. W. Rees, T. Besson, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2183; c) R. Rohini, K. Shanker, P. M. Reddy, Y. P. Ho, V. Ravinder, *Eur. J. Med. Chem.* **2009**, *44*, 3330; d) R. A. Smits, M. Adami, E. P. Istyastono, O. P. Zuiderveld, C. M. van Dam, F. J. de Kanter, A. Jongejan, G. Coruzzi, R. Leurs, I. J. de Esch, *J. Med. Chem.* **2010**, *53*, 2390; e) H. L. Gahlon, W. B. Schweizer, S. J. Sturla, *J. Am. Chem. Soc.*, **2013**, *135*, 6384; f) J. C. Li, R. X. Wang, Y. Sun, J. K. Zhu, G. F. Hu, Y. L. Wang, R. Zhou, Z. M. Zhao, Y. Q. Liu, J. W. Peng, Y. F. Yan, X. F. Shang, *Bioorg. Chem.* **2019**, *92*, 103266; g) P. S. Jadhavar, K. I. Patel, T. M. Dhameliya, N. Saha, M. D. Vaja, V. S. Krishna, D. Sriram, A. K. Chakraborti, *Bioorg. Chem.* **2020**, *99*, 103774.

[5] For selected reports: a) Y. H. Song, S. J. Yeh, C. T. Chen, Y. Chi, C. S. Liu, J. K. Yu, Y. H. Hu, P. T. Chou, S. M. Peng, G. H. Lee, *Adv. Funct. Mater.* **2004**, *14*, 1221; b) Y.-T. Chang, S.-L. Hsu, M.-H. Su, K.-H. Wei, *Adv. Mater.* **2009**, *21*, 2093; c) S. Sen, S. Sarkar, B. Chattopadhyay, A. Moirangthem, A. Basu, K. Dhara, P. Chattopadhyay, *Analyst* **2012**, *137*, 3335; d) B. Li, Z. Wang, S. J. Su, F. Guo, Y. Cao, Y. Zhang, *Adv. Opt. Mater.* **2019**, *7*, 1801496; e) B. Xu, S. Li, H. Jiao, J. Yin, Z. Liu, W. Zhong, *J. Mater. Chem. A.* **2020**, *8*, 3865.

[6] For the synthesis of benzo[4,5]imidazo[1,2-*c*] quinazolines, see: a) H. B. Zhao, Z. W. Hou, Z. J. Liu, Z. F. Zhou, J. Song, H. C. Xu, *Angew. Chem. Int. Ed.* **2017**, *56*, 587; *Angew. Chem.* **2017**, *129*, 12906; b) S. Xu, J. Lu, H. Fu, *Chem. Commun.* **2011**, *47*, 5596; c) X. Wu, S. Sun, S. Xu, J. Cheng, *Adv. Synth. Catal.* **2018**, *360*, 1111; d) L. Xu, T. Li, L. Wang, X. Cui, *J. Org. Chem.* **2019**, *84*, 560; e) N. K. Nandwana, S. Dhiman, G. M. Shelke, A. Kumar, *Org. Biomol. Chem.* **2016**, *14*, 1736; f) C. Shen, L. Wang, M. Wen, H. Shen, J. Jin, P. Zhang, *Ind. Eng. Chem. Res.* **2016**, *55*, 3177; g) P. D. Q. Dao, H. K. Lee, H. S. Sohn, N. S. Yoon, C. S. Cho, *ACS Omega.* **2017**, *2*, 2953; h) S. Ambethkar, M. Kalaiselvi, J. Ramamoorthy, V. Padmini, *ACS Omega.* **2018**, *3*, 5021; i) N. K. Nandwana, R. P. Singh, O. P. S. Patel, S. Dhiman, H. K. Saini, P. N. Jha, A. Kumar, *ACS Omega.* **2018**, *3*, 16338; j) P. D. Q. Dao, C. S. Cho, *Eur. J. Org. Chem.* **2020**, 330; k) C. Li, W. T. Zhang, X. S. Wang, *J. Org. Chem.* **2014**, *79*, 5847; l) A. H. Shinde, S. Arepally, M. D. Baravkar, D. S. Sharada, *J. Org. Chem.* **2017**, *82*, 331; m) W. Chen, Y. Du, M. Wang, Y. Fang, W. Yu, J. Chang, *Org. Chem. Front.* **2020**, *7*, 3705.

[7] For the synthesis of quinazolino[3,4-*a*]perimidines, see: a) M. Akita, H. Seto, R. Aoyama, J. Kimura, K. Kobayashi, *Molecules.* **2012**, *17*, 13879; b) P. Molina, A. Alías, A. Balado, A. Arques, *Liebigs Ann. Chem.* **1994**, 745.

[8] For the synthesis of quinazolinoquinazolinones, see: a) S. Chatterjee, R. Srinath, S. Bera, K. Khamaru, A. Rahman, B. Banerji, *Org. Lett.* **2019**, *21*, 9028; b) M. Ramanathan, S. T. Liu, *J. Org. Chem.* **2018**, *83*, 14138; c) J. Bergman, C. J. Arewang, P. H. Svensson, *J. Org. Chem.* **2014**, *79*, 9065; d) S. Venkateswarlu, M. Satyanarayana, K. Srinivas, K. N. V. V. Aadisudhakar, *Tetrahedron Lett.* **2013**, *54*, 128; e) F. Duan, M. Liu, J. Chen, J. Ding, Y. Hu, H. Wu, *RSC Adv.* **2013**, *3*, 24001; f) A. D. Roy, A. Subramanian, R. Roy, *J. Org. Chem.* **2006**, *71*, 382; g) S. Venkateswarlu, M. Satyanarayana, V. Lakshmikanthan, V. Siddaiah, *J. Heterocycl. Chem.* **2015**, *52*, 1631; h) S. Venkateswarlu, M. Satyanarayana, G. N. Murthy, V. Siddaiah, *Tetrahedron Lett.* **2012**, *53*, 2643; i) S. Venkateswarlu, M. Satyanarayana, V. Lakshmikanthan, V. Siddaiah, *J. Heterocycl. Chem.* **2015**, *52*, 1631.

[9] For the synthesis of isoquinolino[2,1-*c*]quinazolines, see: a) R. T. Sawant, M. Y. Stevens, C. Skold, L. R. Odell, *Org. Lett.* **2016**, *18*, 5392; b) Y. Wang, A. O. Madsen, F. Diness, M. Meldal, *Chem. Eur. J.* **2017**, *23*, 13869; c) F. Diness, J. Beyer, M. Meldal, *Chem. Eur. J.* **2006**, *12*, 8056.

[10] For the synthesis of other polycyclic fused quinazoline derivatives, see: a) P.-G. Li, C. Yan, S. Zhu, S.-H. Liu, L.-H. Zou, *Org. Chem. Front.* **2018**, *5*, 3464; b) Z. An, L. Zhao, M. Wu, J. Ni, Z. Qi, G. Yu, R. Yan, *Chem. Commun.* **2017**, *53*, 11572; c) C. Xie, Z. Zhang, D. Li, J. Gong, X. Han, X. Liu, C. Ma, *J. Org. Chem.* **2017**, *82*, 3491; d) H. Liu, T. Duan, Z. Zhang, C. Xie, C. Ma, *Org. Lett.* **2015**, *17*, 2932; e) T. Xu, H. Alper, *Org. Lett.* **2015**, *17*, 1569; f) J. Wu, H.-H. Kong, M.-W. Ding, *Chin. J. Org. Chem.* **2016**, *36*, 1662; g) C. H. Lee, W. C. Wu, P. S. Dangate, L. C. Shen, W. S. Chung, C. M. Sun, *ACS Comb. Sci.* **2015**, *17*, 623; h) K. S. Kumar, P. M. Kumar, K. A. Kumar, M. Sreenivasulu, A. A. Jafar, D. Rambabu, G. R. Krishna, C. M. Reddy, R. Kapavarapu, K. Shivakumar, K. K. Priya, K. V. Parsa, M. Pal, *Chem. Commun.* **2011**, *47*, 5010; i) H. Divišová, H. Havlišová, P. Borek, P. Pazdera, *Molecules* **2000**, *5*, 1166; j) N. P. Peet, S. Sunder, W. H. Braun, *J. Org. Chem.* **1976**, *41*, 2729.

[11] For selected recent reviews, see: a) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* **2013**, *42*, 5257; b) S. Lang, *Chem. Soc. Rev.* **2013**, *42*, 4867; c) V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin, V. Y. Kukushkin, *Chem. Rev.* **2015**, *115*, 2698; d) B. Zhang, A. Studer, *Chem. Soc. Rev.* **2015**, *44*, 3505; e) B. Song, B. Xu, *Chem. Soc. Rev.* **2017**, *46*, 1103; f) S. Chakrabarty, S. Choudhary, A. Doshi, F.-Q. Liu, R. Mohan, M. P. Ravindra, D. Shah, X. Yang, F. F. Fleming, *Adv. Synth. Catal.* **2014**, *356*, 2135; g) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2013**, *52*, 7084; *Angew. Chem.*

2013, *125*, 7222; h) *Isocyanide Chemistry Applications in Synthesis and Materials Science*; V. Nenajdenko, Ed.; Wiley-VCH: Weinheim, **2012**; i) A. V. Lygin, A. de Meijere, *Angew. Chem. Int. Ed.* **2010**, *49*, 9094; *Angew. Chem.* **2010**, *122*, 9280.

[12] a) Z. Hu, J. Dong, Y. Men, Z. Lin, J. Cai, X. Xu, *Angew. Chem. Int. Ed.* **2017**, *56*, 1805; *Angew. Chem.* **2017**, *129*, 1831; b) Z. Hu, M. Zhang, Q. Zhou, X. Xu, B. Tang, *Org. Chem. Front.* **2020**, *7*, 507; c) J. W. Collet, E. A. van der Nol, T. R. Roose, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *J. Org. Chem.* **2020**, *85*, 7378; d) A. Clemenceau, Q. Wang, J. Zhu, *Org. Lett.* **2017**, *19*, 4872; e) Y. Gao, Z. Hu, J. Dong, J. Liu, X. Xu, *Org. Lett.* **2017**, *19*, 5292; f) J. Cai, Z. Hu, Y. Li, J. Liu, X. Xu, *Adv. Synth. Catal.* **2018**, *360*, 3595; g) L. J. Zhang, W. Yang, Z. Hu, X. M. Zhang, X. Xu, *Adv. Synth. Catal.* **2020**, *362*, 2379; h) B. Neue, R. Reiermann, R. Fröhlich, B. Wibbeling, K. Bergander, E.-U. Würthwein, *Eur. J. Org. Chem.* **2013**, 4944; i) K. Kobayashi, H. Hashimoto, M. Matsumoto, H. Inouchi, *Tetrahedron* **2014**, *70*, 6398; j) R. S. Borisov, A. I. Polyakov, L. A. Medvedeva, V. N. Khrustalev, N. I. Guranova, L. G. Voskressensky, *Org. Lett.* **2010**, *12*, 3894; k) K. Kobayashi, Y. Okamura, H. Konishi, *Synthesis* **2009**, 1494; l) K. Kobayashi, K. Yoneda, K. Miyamoto, O. Morikawa, H. Konishi, *Tetrahedron* **2004**, *60*, 11639; m) Z. Hu, L. Zhang, J. Li, W. Yang, Q. Wei, X. Xu, *J. Org. Chem.* **2019**, *84*, 1563.

[13] a) A. V. Lygin, A. de Meijere, *Org. Lett.* **2009**, *11*, 389; b) Y. Oe, T. Miyamoto, Y. Ito, T. Ohta, *Chem. Lett.* **2017**, *46*, 1763; c) P. Patil, M. Ahmadian-Moghaddam, A. Dömling, *Green Chem.* **2020**, *22*, 6902.

[14] X.-H. Meng, M. Yang, J.-Y. Peng, Y.-L. Zhao, *Adv. Synth. Catal.* **2021**, *363*, 244.

[15] For selected recent examples, see: a) Y.-X. Liang, M. Yang, B.-W. He, Y.-L. Zhao, *Org. Lett.* **2020**, *22*, 7640; b) Z. Wang, X.-H. Meng, P. Liu, W.-Y. Hu, Y.-L. Zhao, *Org. Chem. Front.* **2020**, *7*, 126; c) M. Yang, X.-H. Meng, Z. Wang, Y. Gong, Y.-L. Zhao, *Org. Chem. Front.* **2020**, *7*, 3493; d) L. Zhang, T. Liu, Y. M. Wang, J. Chen, Y.-L. Zhao, *Org. Lett.* **2019**, *21*, 2973; e) Y.-X. Liang, X.-H. Meng, M. Yang, H. Mehfooz, Y.-L. Zhao, *Chem. Commun.* **2019**, *55*, 12519; f) X.-B. Bu, Z. Wang, X.-D. Wang, X.-H. Meng, Y.-L. Zhao, *Adv. Synth. Catal.* **2018**, *360*, 2945; g) L. Zhang, J.-J. Chen, S.-S. Liu, Y.-X. Liang, Y.-L. Zhao, *Adv. Synth. Catal.* **2018**, *360*, 2172.

[16] CCDC 2035223 (**3 ao**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[17] For selected examples, see: a) Y. Wang, L. Jiang, L. Li, J. Dai, D. Xiong, Z. Shao, *Angew. Chem. Int. Ed.* **2016**, *55*, 15142; *Angew. Chem.* **2016**, *128*, 15366; b) L. Albrecht, L. K. Ransborg, V. Lauridsen, M. Overgaard, T. Zweifel, K. A. Jorgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 12496; *Angew. Chem.* **2011**, *123*, 12704; c) D. E. Carrera, *Chem. Commun.* **2017**, *53*, 11185; d) L. Y. Chen, H. He, W. H. Chan, A. W. Lee, *J. Org. Chem.* **2011**, *76*, 7141; e) Y. Qian, G. Ma, A. Lv, H. L. Zhu, J. Zhao, V. H. Rawal, *Chem. Commun.* **2010**, *46*, 3004.

[18] For selected reviews: a) Z. Xu, Q. Wang, J. Zhu, *Chem. Soc. Rev.* **2018**, *47*, 7882; b) A. A. Festa, L. G. Voskressensky, E. V. V. der Eycken, *Chem. Soc. Rev.* **2019**, *48*, 4401; c) K. Nagaraju, D. Ma, *Chem. Soc. Rev.* **2018**, *47*, 8018; d) S. Lancianesi, A. Palmieri, M. Petrini, *Chem. Rev.* **2014**, *114*, 7108; e) E. Stempel, T. Gaich, *Acc. Chem. Res.* **2016**, *49*, 2390; f) G. Bartoli, R. Dalpozzo, M. Nardi, *Chem. Soc. Rev.* **2014**, *43*, 4728; g) M. A. Corsello, J. Kim, N. K. Garg, *Chem. Sci.* **2017**, *8*, 5836; h) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489.

