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A domino reaction for the synthesis of pyrrolo[2,1-*a*]isoquinolines from 2-aryl-pyrrolidines and alkynes promoted by a four-component catalytic system under aerobic conditions†

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Pyrrolo[2,1-*a*]isoquinoline derivatives were synthesized from 2-aryl-pyrrolidines and alkynes *via* an oxidative dehydrogenation/cyclization coupling/dehydrogenative aromatization domino process. This reaction was promoted by a four-component catalytic system which included $[RuCl_2(p\text{-cymene})]_2$, CuCl, copper acetate monohydrate and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under aerobic conditions.

In recent decades, domino reactions have received widespread attention and have been applied in the construction of complex organic molecules, such as materials, drugs, and other molecules.[1] The advantages of domino reactions include the ability to construct complex molecules from easily available raw materials without the need to separate intermediates, which saves time and cost greatly. Recently, a large number of review articles on domino reactions have been published.[2] However, developing more efficient and green domino reactions remains one of the challenges currently faced by organic chemists.

Pyrrolo[2,1-*a*]isoquinoline is a skeleton of diverse natural alkaloids whose biological activities were discovered by Mikhailovskii and Shklyaev in 1997.[3] These biological activities include antitumor, antiviral, anticancer, anti-HIV, antibacterial, antidepressant *etc.*[3,4] Furthermore, their excellent optoelectronic performance has also attracted the attention of material scientists in recent years (Fig. 1).[5]

Therefore, the development of new synthetic methods for pyrrolo[2,1-*a*]isoquinoline is still a hot topic in organic chemistry.[6] In most cases, 2-aryl-indoles were used as the starting materials to synthesize pyrrolo[2,1-*a*]isoquinolines. However, 2-aryl-pyrroles were rarely reported as a starting material due to lack of availability.[7] As we known, pyrroles could be synthesized from pyrrolines through oxidative dehydrogenative aromatization reaction.[8] Therefore, the development of a domino reaction which using the easily available 2-aryl-pyrrolidines[9] as starting materials instead of 2-aryl-pyrroles to synthesize pyrrolo[2,1-*a*]isoquinolines would be very attractive.

Herein, a domino reaction for the synthesis of pyrrolo[2,1-*a*]isoquinolines from 2-aryl-pyrrolidines and alkynes under aerobic oxidation conditions was reported (Scheme 1).

In order to optimize the reaction conditions, we chose 5-phenylpyrrolidine-2,3,4-tricarboxylate (**1a**) and diphenylacetylene (**2a**) as the starting materials. The best isolated yield (86%) was achieved under the standard reaction conditions: **1a** (0.20 mmol), **2a** (0.26 mmol), CuCl (10 mol%), TEMPO (30 mol%), copper acetate monohydrate (10 mol%), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) and 1,4-dioxane (1.0 mL) as the solvent under O_2 atmosphere (balloon) at 100 °C for 18 h (Table 1, entry 8). Using other solvent instead of 1,4-dioxane significantly reduce the

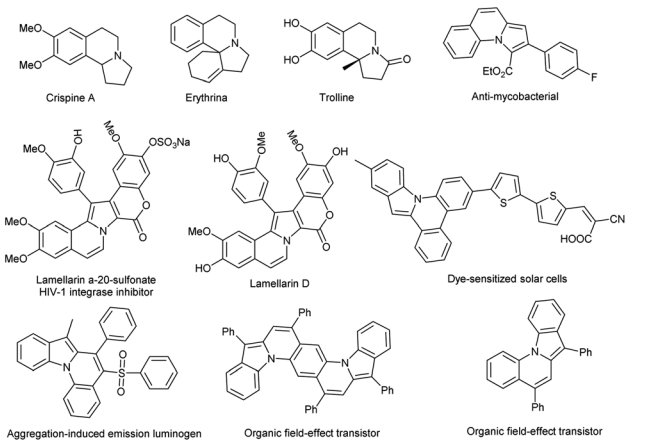

Fig. 1 Natural alkaloids, drugs and materials with pyrrolo[2,1-*a*]isoquinoline skeleton.

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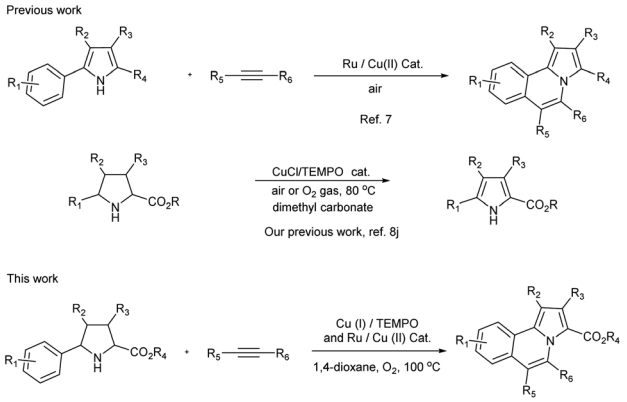
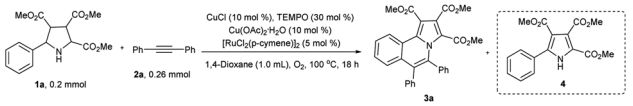


Scheme 1 The difference of this work with previous work.

Table 1 Evaluation of reaction conditions

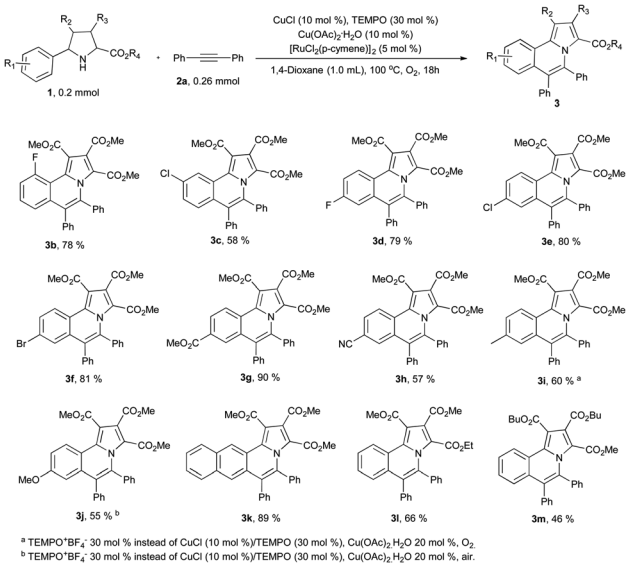


Entry	Variation from the standard condition	Yield[a] (%)
1	Other solvent instead of 1,4-dioxane	59–68
2	With 20 mol% $Cu(OAc)_2 \cdot H_2O$ without CuCl	74
3	With 20 mol% CuCl without $Cu(OAc)_2 \cdot H_2O$	(54[b])
4	Without $[RuCl_2(p\text{-cymene})]_2$	(90[b])
5	Without TEMPO	8 + (33[b])
6	With 20 mol% TEMPO	24[c]
7	Replace O_2 with air	22 + (24[b])
8	No	86

[a] Isolated yield of **3a**. [b] Isolated yield of **4**. [c] 36 h.

reaction yields (entry 1, see details in ESI†). Using 20% copper acetate monohydrate as the catalyst without any CuCl added reduce the yield of **3a** to 74% (entry 2). Surprisingly, when using 20% CuCl as the catalyst and without any copper acetate monohydrate added, **4** was isolated in 54% yield and no any **3a** was formed (entry 3). Also no **3a** was formed and **4** was isolated in 90% yield when no any $[RuCl_2(p\text{-cymene})]_2$ was added (entry 4). **3a** and **4** were isolated in 8% yield and 33% yield without TEMPO (entry 5). Reducing the amount of TEMPO from 30% to 20% and prolonging the reaction time to 36 h would greatly reduce the yield of **3a** to 24% (entry 6). **3a** and **4** were isolated in 22% and 24% yields respectively when the reaction was running under air instead of oxygen gas (entry 7).

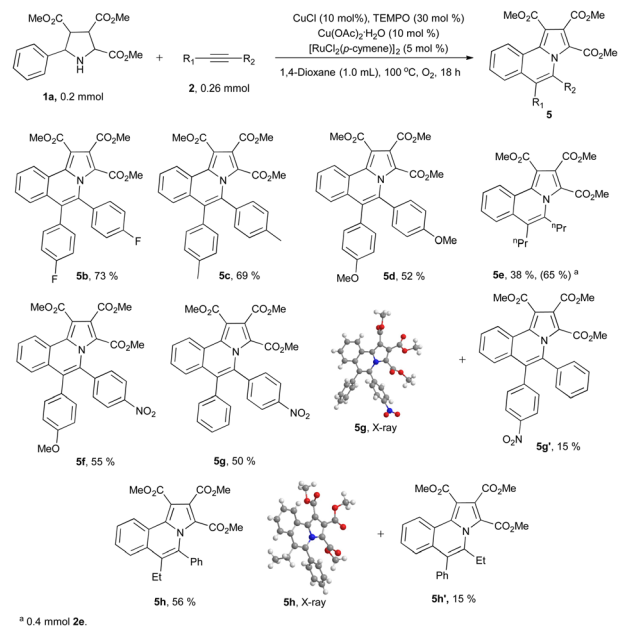
With the optimized conditions in hand, we firstly studied the scope of pyrrolidines (Scheme 2). When pyrrolidines substituted with electron-withdrawing groups on the phenyl ring were used as the starting materials, the corresponding products (**3b–3h**) were isolated in moderate to excellent yields (57–90%). Only a single isomer **3c** was isolated in 58% yield due to steric effect when there was substituent in the *meta* position of the phenyl ring. However, when electron donating groups were bearing in the phenyl ring of pyrrolidines, the



Scheme 2 The substrate scopes of pyrrolidines.

corresponding products were isolated in extremely low yields under the optimized conditions. Further optimization of the reaction conditions revealed that using $TEMPO^+BF_4^-$ (30%) as the catalyst to replace the CuCl and TEMPO and increasing the amount of copper acetate monohydrate to 20 mol%, **3i** was isolated in 60% yield under O_2 atmosphere and **3j** was isolated in 55% yield under air. Only one isomer **3k** was isolated in excellent yield (89%) when 2-naphthyl was bearing at the pyrrolidine. **3l** and **3m** also were isolated in 66% and 46% yields under standard reaction conditions respectively.

We next explored the substrate scopes of alkynes (Scheme 3). Diphenylacetylene derivatives with electron withdrawing or



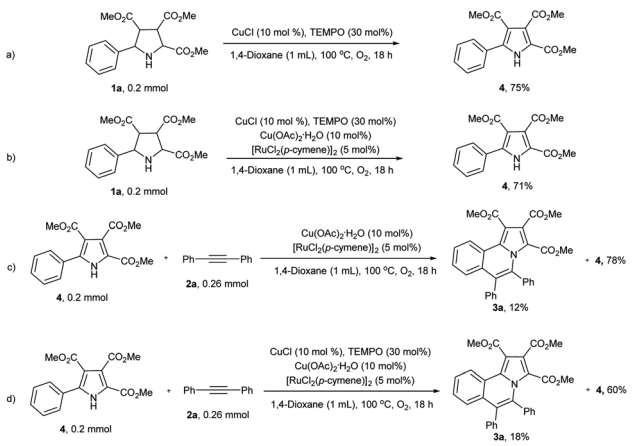
Scheme 3 The scope and region-selectivity of alkyne.

electron donating groups on the phenyl group could produce designed products (**5b–5d**) smoothly under standard reaction conditions. 4-Octyne (**2e**) also works well and the corresponding product **5e** is isolated in 38% yield. When the amount of **2e** is increased from 1.3 equivalent to 2.0 equivalent, the isolated yield of **5e** also increased to 65%. Asymmetric alkynes show moderate region-selectivity (around 55% *vs.* 15%). The more electron deficient side of asymmetric alkyne tends to react with the nitrogen of pyrrolidine (**5g** *vs.* **5g′** and **5h** *vs.* **5h′**). The structure of **5g**[10] and **5h**[11] were confirmed by X-ray.

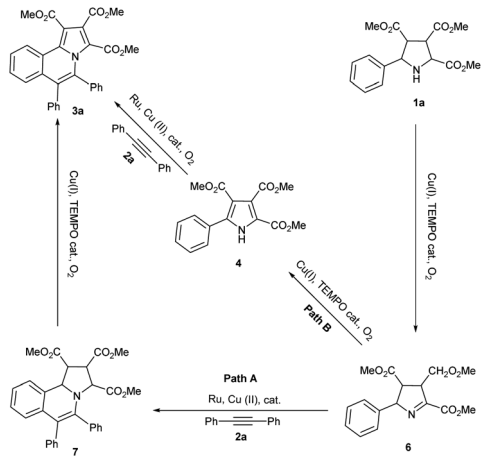
To reveal the reaction mechanism, a series of control experiments were conducted. When the alkyne was absence, pyrrolidines **1a** was reacted under the standard reaction conditions and yield the corresponding pyrrole **4** in 71% yield (Scheme 4b). Which was similar to the yield (75%) in the absence of copper acetate monohydrate and $[RuCl_2(p\text{-cymene})]_2$ (Scheme 4a). To our surprise, when pyrrole **4** reacted with diphenylacetylene (**2a**) under standard reaction conditions, **3a** was only isolated in 18% yield and 60% of **4** was remain untouched (Scheme 4d). The yield of **3a** even lower (12%) in the absence of CuCl and TEMPO (Scheme 4c).

Based on the above results and our previous results, the mechanism of this domino reaction was proposed (Scheme 5). Under the catalytic system of Cu(I)/TEMPO/O_2, pyrrolidine **1a** was oxidized to the intermediate **6** *via* oxidative dehydrogenation firstly.[12] Then **6** could transformed to the final product pyrrolo[2,1-*a*]isoquinoline **3a** through two pathways. The major pathway is **6** reacted with alkyne **2a** to produce intermediate **7** which was catalyzed by Ru and Cu(II). Then **7** was transformed to **3a** through oxidative dehydrogenative aromatization which was catalyzed by Cu(I) and TEMPO with O_2 as the terminal oxidant (path A).[13] The minor pathway is that pyrrole **4** was formed firstly catalyzed by Cu(I) and TEMPO under oxygen gas. Then **4** reacted with alkyne **2a** to form the final product **3a** *via* Ru and Cu(II) catalyzed aerobic oxidative coupling reaction.[7]

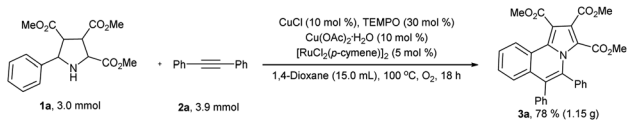
In order to demonstrate the practicality of the reaction, we successfully increased the reaction scale to gram-scale (Scheme 6). Under the standard reaction conditions, 1.15 grams of **3a** was isolated in reasonable yield (78%) which was slightly lower than the yield of small scale reaction.



Scheme 4 The results of control experiments (a)–(d).



Scheme 5 Plausible mechanism.



Scheme 6 The result of gram scale reaction.

In summary, we have reported on the first of a domino reaction for the synthesis of pyrrolo[2,1-*a*]isoquinolines from 2-aryl-pyrrolidines and alkynes. This process was promoted by a four-component catalytic system which included $[RuCl_2(p\text{-cymene})]_2$, CuCl, copper acetate monohydrate and TEMPO. Control experiments show all four catalysts were important for this reaction and pyrrole was not the key intermediate. Using oxygen gas as a solo oxidant made this transformation green. In short, this method of synthesizing pyrrolo[2,1-*a*]isoquinolines is green, simple, and practical, which may provide assistance for the application of such compounds in fields of biomedicine and materials.

Author contributions

Z. Luo and H. Hu conceived the project and performed the investigation on the scope. Z. Luo and Z. Yang optimized the reaction and prepared the experimental parts and first draft of the manuscript. H. Hu supervised the project, H. Hu, C. Wang and Y. Wang edited the manuscript and proofread the experimental part.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) *Domino Reactions: Concepts for Efficient Organic Synthesis*, ed. L. F. Tietze, Wiley-VCH Verlag GmbH & Co. KGaA, 2014; (*b*) L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006.

2 For recent reviews: (*a*) H. Pellissier, *Adv. Synth. Catal.*, 2023, **365**, 620; (*b*) A. Pounder, E. Neufeld, P. Myler and W. Tam, *Beilstein J. Org. Chem.*, 2023, **19**, 487; (*c*) F. Doraghi, F. Mohaghegh, O. H. Qareaghaj, B. Larijani and M. Mahdavi, *RSC Adv.*, 2023, **13**, 13947.

3 A. G. Mikhailovskii and V. S. Shklyaev, *Chem. Heterocycl. Compd.*, 1997, **33**, 243.

4 (*a*) Q. Zhang, G. Tu, Y. Zhao and T. Cheng, *Tetrahedron*, 2002, **58**, 6795; (*b*) R. Wang, X. Yang, C. Ma, S. Cai, J. Li and Y. Shoyama, *Heterocycles*, 2004, **63**, 1443; (*c*) B. Su, C. Cai, M. Deng, D. Liang, L. Wang and Q. Wang, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2881; (*d*) C. Ballot, J. Kluza, A. Martoriati, U. Nyman, P. Formstecher, B. Joseph, C. Bailly and P. Marchetti, *Mol. Cancer Ther.*, 2009, **8**, 3307; (*e*) M. V. R. Reddy, M. R. Rao, D. Rhodes, M. S. T. Hansen, K. Rubins, F. D. Bushman, Y. Venkateswarlu and D. J. Faulkner, *J. Med. Chem.*, 1999, **42**, 1901; (*f*) S. Muthusaravanan, S. Perumal, P. Yogeeswari and D. Sriram, *Tetrahedron Lett.*, 2010, **51**, 6439; (*g*) B. E. Maryanoff, J. L. Vaught, R. P. Shank, D. F. McComsey, M. J. Costanzo and S. O. Nortey, *J. Med. Chem.*, 1990, **33**, 2793.

5 (*a*) C. Baik, D. Kim, M. Kang, K. Song, S. O. Kang and J. Ko, *Tetrahedron*, 2009, **65**, 5302; (*b*) K. Sun, Y. Zhang, X. Chen, H. Su, Q. Peng, B. Yu, L. Qu and K. Li, *ACS Appl. Bio Mater.*, 2020, **3**, 505; (*c*) E. Ahmed, A. L. Briseno, Y. Xia and S. A. Jenekhe, *J. Am. Chem. Soc.*, 2008, **130**, 1118; (*d*) L. Zhu, E.-G. Kim, Y. Yi, E. Ahmed, S. A. Jenekhe, V. Coropceanu and J.-L. Brédas, *J. Phys. Chem. C*, 2010, **114**, 20401; (*e*) H. H. Choi, H. Najafov, N. Kharlamov, D. V. Kuznetsov, S. I. Didenko, K. Cho, A. L. Briseno and V. Podzorov, *ACS Appl. Mater. Interfaces*, 2017, **9**, 34153.

6 (*a*) S. Kumarab and A. K. Singh, *Chem. Commun.*, 2022, **58**, 11268; (*b*) R. Michikita, Y. Usuki and T. Satoh, *Eur. J. Org Chem.*, 2022, e202200550; (*c*) D. Das and A. R. Das, *J. Org. Chem.*, 2022, **87**, 11443; (*d*) R. Heckershoff, G. May, J. Däumer, L. Eberle, P. Krämer, F. Rominger, M. Rudolph, F. F. Mulks and A. S. K. Hashmi, *Chem. – Eur. J.*, 2022, **28**, e202201816; (*e*) S. Kumarab and A. K. Singh, *Chem. Commun.*, 2022, **58**, 11268; (*f*) S. Thavaselvan and K. Parthasarathy, *Org. Lett.*, 2020, **22**, 3810; (*g*) Y. Liu, Z. Yang, R. Chauvin, W. Fu, Z. Yao, L. Wang and X. Cui, *Org. Lett.*, 2020, **22**, 5140; (*h*) A. Obata, A. Sasagawa, K. Yamazaki, Y. Ano and N. Chatani, *Chem. Sci.*, 2019, **10**, 3242; (*i*) K. Morimoto, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 2068.

7 (*a*) L. Ackermann, L. Wang and A. V. Lygin, *Chem. Sci.*, 2012, **3**, 177; (*b*) X. Tang, L. Huang, C. Qi, W. Wu and H. Jiang, *Chem. Commun.*, 2013, **49**, 9597.

8 (*a*) A. Arrieta, D. Otaegui, A. Zubia, F. P. Cossío, A. Díaz-Ortiz, A. de la Hoz, M. A. Herrero, P. Prieto, C. Foces-Foces, J. L. Pizarro and M. I. Arriortua, *J. Org. Chem.*, 2007, **72**, 4313; (*b*) T. Das, P. Saha and V. K. Singh, *Org. Lett.*, 2015, **17**, 5088; (*c*) H. Liu, H. Tao, H. Cong and C. Wang, *J. Org. Chem.*, 2016, **81**, 3752; (*d*) H. Liu, K. Liu, Z. Xue, Z. He and C. Wang, *Org. Lett.*, 2015, **17**, 5440; (*e*) S. N. Murthy and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2011, **52**, 4481; (*f*) I. Fejes, L. Toke, G. Blasko, M. Nyerges and C. S. Pak, *Tetrahedron*, 2000, **56**, 8545; (*g*) B. Oussaid, B. Garrigues and M. Soufiaoui, *Can. J. Chem.*, 1994, **72**, 2483; (*h*) M. Baumann, I. R. Baxendale, A. Kirschning, S. V. Ley and J. Wegner, *Heterocycles*, 2011, **82**, 1297; (*i*) Y. Liu, H. Hu, X. Wang, S. Zhi, Y. Kan and C. Wang, *J. Org. Chem.*, 2017, **82**, 4194; (*j*) Z. Luo, Y. Liu, C. Wang, D. Fang, J. Zhou and H. Hu, *Green Chem.*, 2019, **21**, 4609.

9 (*a*) A. Cayuelas, O. Larranaga, C. Najera, J. M. Sansano, A. de Cozar and F. P. Cossio, *Tetrahedron*, 2016, **72**, 6043; (*b*) E. M. Arpa, M. Gonzalez-Esguevillas, A. Pascual-Escudero, J. Adrio and J. C. Carretero, *J. Org. Chem.*, 2016, **81**, 6128; (*c*) H. Xu, C. Golz, C. Strohmann, A. P. Antonchick and H. Waldmann, *Angew. Chem., Int. Ed.*, 2016, **55**, 7761; (*d*) X. Bai, L. Li, Z. Xu, Z. Zheng, C. Xia, Y. Cui and L. Xu, *Chem. – Eur. J.*, 2016, **22**, 10399; (*e*) Z. Zhang, B. Xu, S. Xu, H. Wu and J. Zhang, *Angew. Chem., Int. Ed.*, 2016, **55**, 6324.

10 CCDC no. 2299581.

11 CCDC no. 2299583.

12 H. Richter and O. G. Mancheño, *Eur. J. Org Chem.*, 2010, 4460.

13 (*a*) J. Xu, H. Hu, Y. Liu, X. Wang, Y. Kan and C. Wang, *Eur. J. Org Chem.*, 2017, 257; (*b*) F. Shi, Y. Zhang, Z. Lu, X. Zhu, W. Kan, X. Wang and H. Hu, *Synthesis*, 2016, **48**, 413; (*c*) W. Wang, J. Han, J. Sun and Y. Liu, *J. Org. Chem.*, 2017, **82**, 2835.