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ARTICLE

Transition-Metal-Free C-N and C-C Formation: Synthesis of Benzo[4,5]imidazo[1,2-*a*]pyridines and 2-Pyridones From Ynones

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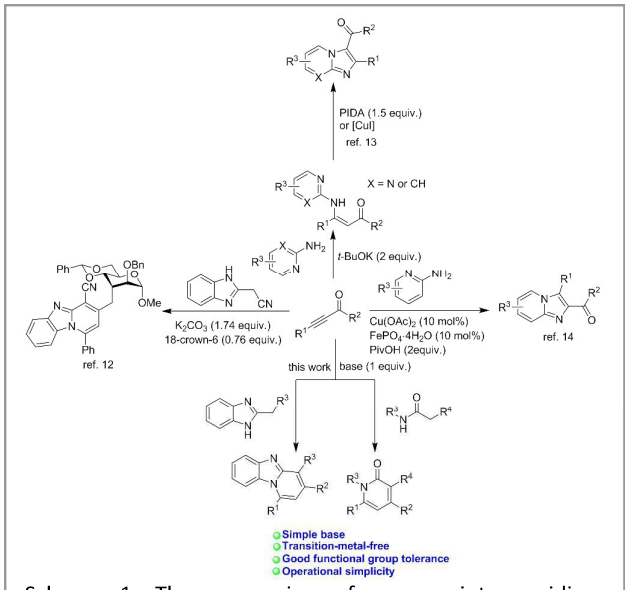
A transition-metal-free and efficient cascade reaction of ynones with 2-methylbenzimidazoles under mild conditions has been revealed. This cascade reaction processed a Michael addition/intramolecular cycloaddition/dehydration and offered the desired benzo[4,5]imidazo[1,2-a]pyridines in moderate to good yields. Furthermore, three benzo[4,5]imidazo[1,2-a]pyridines (**3d**, **3i**, **3q**) exhibited good activities against Hep-G2 (human liver cancer), T-24 (human bladder cancer cell) and SK-OV-3 (human ovarian cancer) cell lines with IC_{50} in the range of 8.05–10.67 μmol/L. To investigate the mechanistic of the effective cell growth inhibition, further studies of compound **3i**, including cell cycle analysis, apoptosis ratio detection, measurement of Ca^{2+} generation, ROS, mitochondrial membrane potential assay and caspase-3/9 activation, were carried out.

Introduction

Ynones, equip with two reaction sites C≡C bond and carbanyl group, have been considered as valuable substrates in organic synthesis.[1] And the transformation of ynones has been widely applied in the construction of high-value linear[2] and cyclization products[3]. Generally, the selective hydrogenations of *α,β*-unsaturated carbonyls promoted by transition-metal catalyst lead to alkyl ketones,[4] propargylic alcohols,[5] and *E*-chalcones[6]. And recently, great interest was focus on the conversion of ynones into pyridine-containing N-heterocycles.[7]

Imidazo[1,2-a]pyridines not only exhibit various pharmaceutical and biological activities[8], but also be used to build blocks for the preparation of a wide range of interesting heteroarene derivatives,[9] that continuously drive us to develop the new synthesis approaches.[10] In 1983, Tsuge and his coworkers reported a cycloaddition of nitrogen-bridged tetravalent sulfur compounds with ynones, the cyclo adducts were easy to undergo desulfurization and 10π cyclization, and offered 4,9c-diazapentaleno-[1,6a,6:ab]-naphthalenes as product[11]. An efficent strategy for the construction of benzo[4,5]imidazo[1,2-a]pyridine is *via* the reaction of ynones with 2-benzimidazolyl-acetonitriles promoted by the combination of potassium carbonate and 18-crown-6.[12] In this reaction, the excess base were required. Recently, significant achievements have been made in the transformation of ynones and heteroaryl amines into imidazo[1,2-a]pyridines. The *N*-pyridyl enaminones from ynones and heteroaryl amines underwent an intramolecular C–H bond cycloamination promoted by hypervalent iodine and led to the imidazo[1,2-*a*]pyridines.[13] Besides, the intermolecular oxidative diamination of alkynones with 2-aminopyridines promoted by the co-catalysis of copper(II) and iron(III) also gave the imidazo[1,2-*a*]pyridines.[14] Although the above methods are useful to construct imidazo[1,2-*a*]pyridines, there are



Scheme 1. The conversion of ynones into pyridine-containing *N*-heterocycles.

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still some drawbacks, such as the limited substrates, the use of transition-metal catalysts or strong oxidants, and multi-step operation.

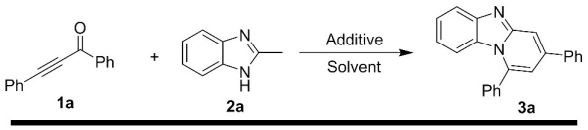
Owing to the rising environmental awareness among nations, the transition-metal-free system has been popular in organic synthesis.[15] Really, the transition-metal-free reaction can dramatically reduce the toxicity and cost, and make the pathways more practical and environmentally friendly.[16] Hence, a high-efficiency and green method for synthesize imidazo[1,2-*a*]pyridines is still highly desired. We are also interested in transition-metal-free system, and have studied the transition-metal-free cascade reaction of ynones to structure.[17]

Results and discussion

Very recently, our group developed a base promoted Michael addition and intramolecular cyclodehydration of diynones with glycine esters or 2-amino-acetophenone hydrochlorides to 3-alkynylpyrrole-2-carboxylates.[18] We envisioned that (1*H*)-*N*-heterocycles should be add to the ynones to form *α,β*-enaminones, which undergo a cyclization to *N*-heterocycles under base conditions. Firstly, We studied the addition of 2-methylbenzimidazoles with ynones under the presence of K_2CO_3 (1 equiv.) in 1,4-Dioxane at 100 °C for 6 h (Table 1, entry 1). Excitingly, 1,3-diphenylbenzo[4,5]imidazo[1,2-a]pyridine **3a** was obtained. This indicates that a transition-metal-free synthesis of benzo[4,5]imidazo[1,2-a]pyridines from ynones and 2-methylbenzimidazoles can be realized. Encouraged by this result, we started to optimize the reaction conditions (Table 1). Originally, a screening of various kinds of additives such as Cs_2CO_3, $KHCO_3$, KOH, NaOH, Et_3N, CH_3Ona, PTSA and $Cu(OTf)_2$, showed that inorganic bases were more effective than organic bases, while the acid or Lewis acid could not promote the reaction, and KOH was the best (Table 1, entries 2-9). When the reaction was carried out in the PhCl, only trace of **3a** was detected (Table 1, entry 10). Other solvents such as Toluene, DMF, and DMSO afforded the desire product in 70%, 73%, 30% yields, respectively (Table 1, entries 11-13). The control experiments indicated that the decrease amount of KOH resulted in the significant loss of **3a**, and the increase loading of KOH didn't obviously affect on this reaction (Table 1, entries 14 and 15). When a higher temperature was employed, not obvious effect on the yield was observed (Table 1, entry 16). But the lower temperature was unfavourable in the reaction, only 60% yield of **3a** was obtained (Table 1, entry 17). Finally, the optimal conditions for this transformation are KOH (1 equiv.) in 1,4-Dioxane at 100 °C for 6 h.

With the optimized reaction conditions in hand, we subsequently investigated the substrate scope of this cascade reaction, and the results are summarized in Table 2. Firstly, various ynones were explored, and the benzo[4,5] imidazo[1,2-*a*]pyridines were obtained in moderate to good yields. When diphenyl ynones were employed, both the electron-donating and electron-withdrawing group in phenyl both generated the corresponding products in good yields (Table 2, **3a**-**3g**). And the structure of **3b** was further confirmed by X-ray crystallographic analysis, which was recrystallized from $CHCl_3$.[19a] The heterocycle ynones were tolerated in this reaction, furyl and thienyl offered **3h** and **3i** in 68% and 65% yield, respectively(Table 2, **3h** and **3i**). Single aliphatic ynones were suitable in this reaction, and gave the products in moderate yields (Table 2, **3j**-**3l**). While, dialkyl ynones were ineffective, only a trace of products was detected (Table 2, **3m**). However, not only the terminal ynones could not work smoothly to produce the desired product, but also 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-one (R1 = TMS) failed to furnish the corresponding product. In the moiety of 2-methylbenzimidazoles, the electron-donating groups, halogen and cyano were tolerant and gave the corresponding products in

Table 1. Optimization of Cascade Cyclization of Ynones into N-heterocycles.[a]



Entry	Additive	Solvent	Yield (%)[b]
1	K_2CO_3	1,4-Dioxane	30
2	Cs_2CO_3	1,4-Dioxane	20
3	$KHCO_3$	1,4-Dioxane	15
4	KOH	1,4-Dioxane	85
5	NaOH	1,4-Dioxane	78
6	Et_3N	1,4-Dioxane	15
7	CH_3ONa	1,4-Dioxane	40
8	PTSA	1,4-Dioxane	0
9	$Cu(OTf)_2$	1,4-Dioxane	0
10	KOH	PhCl	Trace
11	KOH	Toluene	70
12	KOH	DMF	73
13	KOH	DMSO	30
14[c]	KOH	1,4-Dioxane	45
15[d]	KOH	1,4-Dioxane	87
16[e]	KOH	1,4-Dioxane	86
17[f]	KOH	1,4-Dioxane	60

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), additive (1 eq.), solvent (2 mL), at 100 °C, 6 h. [b]Isolated yields. [c]0.5 eq. KOH was used. [d]1.5 eq. KOH was used. [e] At 120 °C. [f] At 80 °C.

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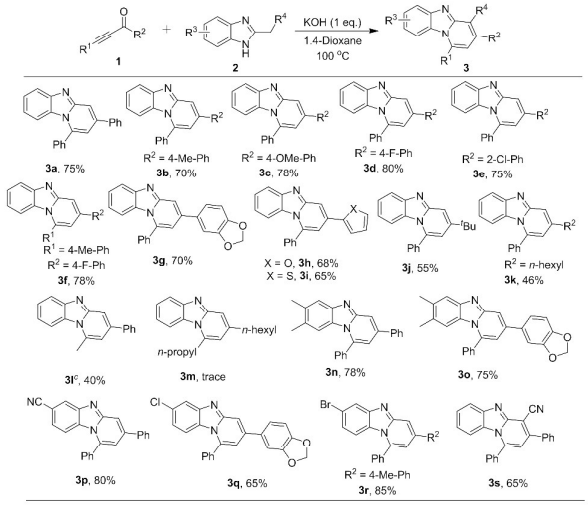
Table 2. Synthesis of Benzo[4,5] imidazo[1,2-*a*]pyridines from Ynones and 2-Methylbenzimidazoles



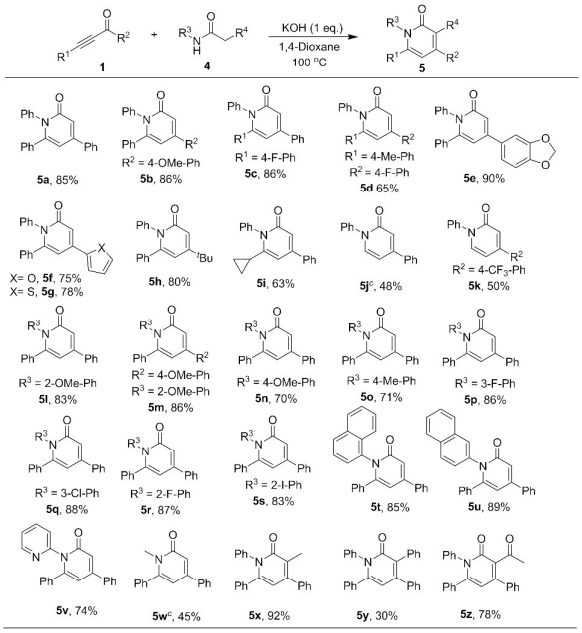
[a]Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), KOH (1 eq.), 1,4-Dioxane (2 mL), 6 h. [b]Isolated yields. [c]2 eq. KOH was used.

high yields (Table 2, **3n**-**3r**). Furthermore, benzo[4,5] imidazo[1,2-a]pyridine **3s** was yielded in 65% when the R^4 was CN (Table 2, **3s**).

We found that amides were also applicable in this cascade reaction, and the results were showed in Table 3. As expected, all kinds of ynones and amides reacted successfully under the standard conditions. Ynones with electron-withdrawing, electron-donating groups and heterocycle groups afforded the corresponding 2-pyridones in appreciable yields (65–90%, Table 3, **5a–5g**). To our delight, the single aliphatic ynones bearing tertiary butyl and cyclopropyl reacted smoothly and afforded the desired products **5h** and **5i** in 80% and 63% yields, respectively (Table 3, **5h** and **5i**). The terminal ynones also worked successfully to generate the 2-pyridones **5j** and **5k** in 48% and 50% yields (Table 3, **5j** and **5k**). Then, various aromatic amides equip with electron-withdrawing groups, electron-donating groups and *N*-heterocycle groups were explored, and provided the cyclization products in moderate to good yields, (Table 3, **5l–5v**). The structure of **5o** was further confirmed by X-ray crystallographic analysis which was recrystallized from $CHCl_3$.[19b] To our delight, the *N*-methylacetamide also worked well in the reaction and resulted to the 2-pyridone **5w** in 45% yield (Table 3, **5w**). Unfortunately, the acetamide failed to produce the corresponding product. While, 30–92% yields of the corresponding products (**5x**-**5z**) were obtained when R^4 was Me, Ph and Ac (Table 3, **5x–5z**).

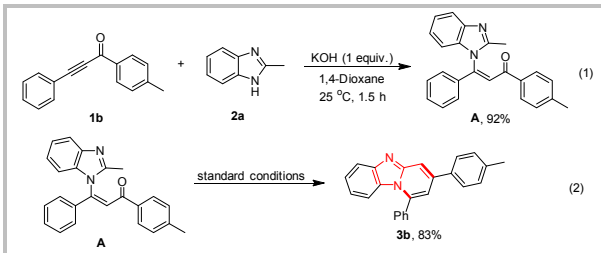
To estimate the plausible mechanism of this transformation, some controlled experiments were performed and the results were showed in Scheme 2. At first, the reaction of **1b** and **2a** in the precence of KOH (1 equiv.) in 1,4-dioxane at 25 °C provided the intermediate **A** in 92% yield (Scheme 2, (1)). Next, the intermediate **A**

Table 3. Synthesis of 2-Pyridones from Ynones and Amides



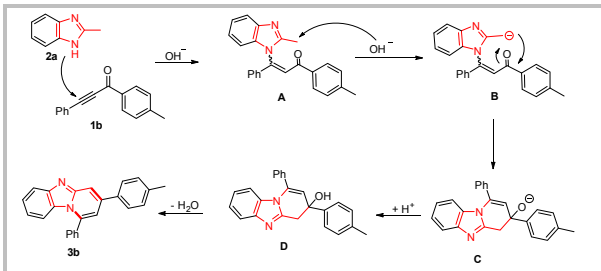
[a]Reaction conditions: **1** (0.6 mmol), **4** (0.5 mmol), KOH (1 eq.), 1,4-Dioxane (2 mL), 6 h. [b]Isolated yields. [c]2 eq. KOH was used.

succeeded to generate the desired product **3b** in 83% yield under the standard conditions (Scheme 2, (2)).



Scheme 2. Controlled experiments.

On the basis of above results and literatures, a plausible mechanism is proposed in Scheme 3. Initially, the Michael addition of **2a** with **1a** generated a *α,β*-enaminone intermediate **A**.[20] Then the intermediate **A** was ready to undergo deprotonation with KOH and form **B**. An intramolecular cycloaddition of **B** produced the cyclization product **C**. Finally, the desired product **3a** was obtained *via* the protonation and dehydration of **C**.[21]



Scheme 3. Plausible reaction mechanism.

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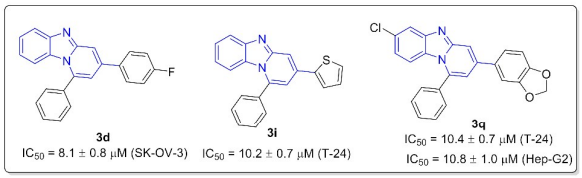

Fig. 1. Anticancer activity of benzo[4,5] imidazo[1,2-*a*]pyridines.

Meanwhile, the in vitro cytotoxicity of **3a–3s**, and **5a–5z** against four human tumor cell lines: human gastric cancer cell line (MGC-803), human bladder cancer cell line (T-24), human ovarian cancer cell line (SK-OV-3), human liver cancer cell line (Hep-G2) and normal liver cell line (WI-38) were determined by methylthiazoltetrazolium (MTT) assay, and the 5-fluorouracil (5-FU) was used as the positive control (Supporting Information Table 1). Fortunately, compounds **3i** (IC_{50} = 10.2 ± 0.7 μM) and **3q** (IC_{50} = 10.4 ± 0.7 μM) exhibited potent inhibitory activity against T-24 cell lines (Fig. 1). Compounds

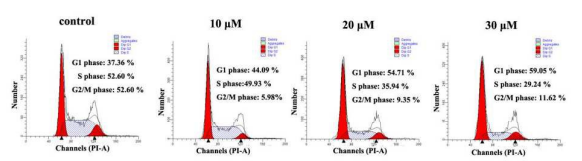

Fig. 2 Cell cycle analysis of T-24 cells treated with **3i**. T-24 cells were treated with different concentrations of **3i** for 24 h to determine the distribution of cell cycle phase.

3d (IC_{50} = 8.1 ± 0.8 μM) and **3q** (IC_{50} = 10.8 ± 1.0 μM) were found to be powerful cytotoxic agents against SK-OV-3 and Hep-G2 cell lines, respectively (Fig. 1). In addition, comparing with the IC_{50} values of cancer and normal cell lines, all compounds have more obvious inhibitory effect on tumor cells than human normal cell line WI-38. Then the compound **3i** was selected for cell cycle analysis and apoptosis analysis in T-24 cells for 24 h.

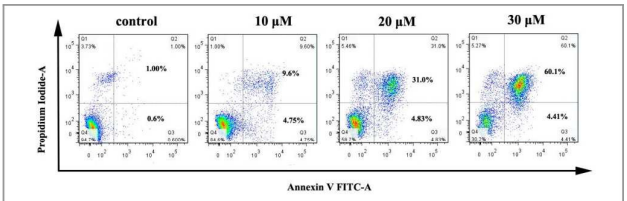

Fig. 3. Apoptosis ratio of T-24 cells treated with **3i** by Annexin V/PI assay.

Primarily, the effect of **3i** on cell cycles was investigated by flow cytometry with propidium iodide stained cells. As shown in Fig. 2, with the increasing concentration of compound **3i**, the percentage of G1 phase cell increased from 37.36% to 59.05%. And compared with the 37.36% in the control group, the percentage of S-phase T-24 cells decreased to 49.93% (10 μM), 35.94% (20 μM), and 29.24% (30 μM), respectively. The results evidently demonstrated that the **3i** could potentially arrest the cell cycle at G1 phase in a concentration-dependent manner.[22]

The apoptosis ration induced by **3i** in T-24 cell line was detected by flow cytometry with propidium iodide and Annexin V stained cells. As shown in Fig. 3, after treated with different concentrations (10, 20 and 30 μM) of **3i**, the apoptosis rate of T-24 cells increased to 14.35%, 35.83% and 64.51% from 1.6%. The results indicated that **3i** might suppress cell proliferation by inducing apotosis. Further mechanistic studies showed that **3i** could elevate intracellular ROS levels and Ca^{2+} levels, decrease the mitochondrial membrane potential, mitochondrial dysfunction and analysis of MMP, activate the expression of Caspase-3/9 (supporting information Fig. 1-4.).

Conclusion

In conclusion, we have developed a transition-metal-free, efficient, and practical procedure for the synthesis of benzo[4,5]imidazo[1,2-a]pyridines and 2-pyridones from ynones and 2-methylbenzimidazoles or acetamides. And this transformation involves C-N and C-C bonds formation. Furthermore, three compounds (**3d**, **3i**, **3q**) showed potent anticancer activities *in vitro*. The further mechanistic studies showed that compound **3i** effectively inhibited cell growth by triggering G1 phase arrest and inducing apoptosis through the mitochondria-mediated pathway.

Experimental

1. **General procedure for the synthesis of 3 and 5**: To a sealed tube was added with ynones **1** (0.6 mmol), acetamides **2** or 2-methylbenzimidazoles **4** (0.5 mmol), KOH (0.5 mmol) and 1,4-Dixoane (2.0 mL). Then the mixture was stirred at 100 °C for 6 h. After completed, the mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the desired product give **3** or **5**.

2. **Biological Assays:** the detailed procedures for other experimental methods are described in SI.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (a) A. S. Karpov, F. Rominger and T. J. J. Müller, *Org. Biomol. Chem*., 2005, **3**, 4382; (b) C. Boersch, E. Merkul, and T. J. J. Müller, *Angew. Chem. Int. Ed*., 2011, **50**, 10448; (c) S. Santra, K. Dhara, P. Ranjan, P. Bera, J. Dash, and S. K. Mandal, *Green Chem*., 2011, **13**, 3238.

2 (a) M. H. Xie, C. Y. Feng, J. T. Zhang, C. Q. Liu, K. Fang, G. Y. Shu, W. S. Zuo, *J. Organomet. Chem.*, 2011, **696**, 3397; (b) A. Dermenci, R. E. Whittaker, Y. Gao, F. A. Cruz, Z.-X. Yu and G. B. Dong, *Chem. Sci*., **2015**, 6, 3201; (c) R. K. Shiroodi, M. Soltani, and V. Gevorgyan, *J. Am. Chem. Soc*., 2014, **136**, 9882; (d) J. Li, L. L. Lin, B. W. Hu, P. F. Zhou, T. Y. Huang, X. H. Liu, and X. M. Feng, *Angew. Chem. Int. Ed*., 2017, **56**, 885.

3 (a) A. V. Vasilyev, S. Walspurger, P. Pale and J. Sommer, *Tetrahedron Lett*., 2004, **45**, 3379; (b) H. Cao, H. F. Jiang, H. W. Huang, *Synthesis*, 2011, **7**, 1019; (c) P. D. Croce and C. L. Rosa, *Heterocycles*, 2001, **10**, 1843; (d) H. Peng, J. Y. Li, F. R. Wang, B. Liu, and B. L. Yin, *J. Org. Chem*., 2016, **81**, 4939; (e) C. D. Pan, B. F. Huang, We. M. Hu, X. M. Feng, and J.-T. Yu, *J. Org. Chem*., 2016, **81**, 2087; (f) M. J. James, R. E. Clubley, K. Y. Palate, T. J. Procter, A. C. Wyton, P. O. Brien, R. J. K. Taylor, and W. P. Unsworth, *Org. Lett*., 2015, **17**, 4372; (g) K. Okamoto, T. Shimbayashi, E. Tamura, and K. Ohe, *Org. Lett*., 2015, **17**, 5843; (h) J. H. Shen, X. D. Wang, X. Lin, Z. H. Yang, G. L. Cheng, and X. L. Cui, *Org. Lett*., 2016, **18**, 1378; (i) J. T. R. Liddon, A. K. Clarke, R. J. K. Taylor, and W. P. Unsworth, *Org. Lett*., 2016, **18**, 6328; (j) T. Sonehara, S. Murakami, S. Yamazaki, and M. Kawatsura, *Org. Lett*., 2017, **19**, 4299; (k) R. Bernini, G. Fabrizi, A. Sferrazza, and S. Cacchi, *Angew. Chem. Int. Ed*., 2009, **48**, 8078; (l) X. B. Yang, S. F. Li, H. X. Liu, Y. Y. Jiang and H. Fu, *RSC Adv*., 2012, **2**, 6549; (m) H. K. Li, P. Cheng, L. Jiang, J.-L. Yang, and L. S. Zu, *Angew. Chem. Int .Ed*., 2017, **56**, 2754; (n) F. E. Celine, C. Thomas, T. Pierre, L. Olivier, and T. Frederic, *Org. Lett*., 2010, **1**, 40; (o) S. Khamarui, Y. Saima, R. M. Laha, S. Ghosh & D. K. Maiti, *Sci. Re*p., 2015, 5, 8636.

4 (a) A. Mori, T. Mizusaki, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa, Y. Monguchi and H. Sajiki, *Tetrahedron*, 2006, **62** 11925; (b) N. M. Patil, T. Sasaki, B. M. Bhanage, *Catal. Lett*., 2014, **144**, 1803; (c) D. B. Bagal, Z. S. Qureshi, K. P. Dhake, S. R. Khan and B. M. Bhanage, *Green Chem*., 2011, **13**, 1490; (d) D. B. Bagal and B. M. Bhanage, *RSC Adv*., 2014, **4**, 32834; (e) T. Kurita, F. Aoki, T. Mizumoto, T. Maejima, H. Esaki, T. Maegawa, Y. Monguchi, and H. Sajiki, *Chem. Eur. J*., 2008, **14**, 3371; (f) S. K. Mahato, R. U. Islam, C. Acharya, M. J. Witcomb, and K. Mallick, *Chem. Cat. Chem*., 2014, **6**, 1419; (g) A. Mori, T. Mizusaki, M. Kawase, T. Maegawa, Y. Monguchi, S. Takao, Y. Takagi, and H. Sajiki, *Adv. Synth. Catal*., 2008, **350**, 406; (h) A. Mori, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa, and H. Sajiki, *Org. Lett*., 2006, **8**, 3279; (i) A. D. Kosal and B. L. Ashfeld, *Org. Lett*., 2010, **12**, 44.

5 S. Enthaler, K. Schröder, S. Inoue, B. Eckhardt, K. Junge, M. Beller, and M. Drieß, *Eur. J. Org. Chem*., 2010, 4893.

6 (a) Z. B. Jian, S. Krupski, K. Škoch, G. Kehr, C. G. Daniliuc, I. Císařová , P. Ště pnička, and G. Erker, *Organometallics*, 2017, **36**, 2940; (b) S. N. Arbuzova, T. E. Glotova, M. Yu. Dvorko, I. A. Ushakov, N. K. Gusarova, and B. A. Trofimov, *Arkivoc*, 2011, **xi**, 183.

7 (a) S. Karabiyikoglu, Y. Kelgokmen, M. Zora, *Tetrahedron*, 2015, **17**, 4324; (b) E. Karadeniz, M. Zora, N. Z. Kılıcaslan, *Tetrahedron*, 2015, **71**, 8943; (c) Y. Kelgokmen and M. Zora, *RSC Adv*., 2016, **6**, 4608; (d) S. N. Karad, W.-K. Chung and R.-S. Liu, *Chem. Sci*., 2015, **6**, 5964; (e) G. L. Cheng, Y. X. Weng, X. F. Yang, and X. L. Cui, *Org. Lett*., 2015, **17**, 3790; (f) A. Modvig, T. L. Andersen, R. H. Taaning, Anders T. Lindhardt, and T. Skrydstrup, *J. Org. Chem*., 2014, **79**, 5861; (g) J. C. Wu, We. B. Xu, Z.-X. Yu, and J. Wang, *J. Am. Chem. Soc*., 2015, **137**, 9489; (h) S. Cacchi, G. Fabrizi, and E. Filisti, *Org. Lett.*, 2008, **10**, 2629; (i) A. Saito, T. Konishi, and Y. Hanzawa, *Org. Lett*., 2010, **12**, 372.

8 (a) H. Takeshita, J. Watanabe, Y. Kimura, K. Kawakami, H. Takahashi, M. Takemuraa, A. Kitamura, K. Someya, R. Nakajima, *Bioorg. Med. Chem. Lett*., 2010, **20**, 3893; (b) M. Sedic, M. Poznic, P. Gehrig, M. Scott, R. Schlapbach, M. Hranjec, K.-Z. Grace, K Pavelic, and S K Pavelic, *Mol. Cancer. Ther*., 2008, **7**, 2121; (c) M. Hranjeca, B. Lucic, I. Ratkaj, S. K. Pavelic, I. Piantanida, K. Pavelic, K.-Z. Grace, *Eur. J. Med. Chem*., 2011, **46**, 2748; (d) M. Hranjec, M. Kralj, I. Piantanida, M. Sedic, L. Sÿuman, K. Pavelic , and K.-Z. Grace, *J. Med. Chem.*, 2007, **50**, 5696; (e) A. J. Ndakala, R. K. Gessner, P. W. Gitari, N. October, K. L. White, A. Hudson, F. Fakorede, D. M. Shackleford, M. l. Kaiser, C. Yeates, S. A. Charman, and K. Chibale, *J. Med. Chem*., 2011, **54**, 4581; (f) M. Hranjec, I. Piantanida, M. Kralj, L. Suman, K. Pavelic, and K.-Z. Grace, *J. Med. Chem*., 2008, **51**, 4899; (g) B. A. Chalmers, S. Saha, T. Nguyen, J. McMurtrie, S. T. Sigurdsson, S. E. Bottle, and K.-S. Masters, *Org. Lett*., 2014, **16**, 5528; (h) S. K. Kotovskaya, Z. M. Baskakova, V. N. Charushin, O. N. Chupakhin, E. F. Belanov, N. I. Bormotov, S. M. Balakhnin, and O. A. Serova, *Pharm. Chem. J*., 2005, **39**, 574.

9 (a) S. Lei, G. J. Chen, Y. Y. Mai, L. B. Chen, H. Y. Cai, J. W. Tan, and H. Cao, *Adv. Synth. Catal.*, 2016, **358**, 67; (b) S. Lei, H. Cao, L. B. Chen, J. Y. Liu, H. Y. Cai, and J. W. Tan, *Adv. Synth. Catal.*, 2015, **357**, 3109; (c) H. Cao, S. Lei, N. Y. Li, L. B. Che, J. Y. Liu, H. Y. Cai, S. X. Qiu, and J. W. Tan, *Chem. Commun*., 2015, **51**, 1823; (d) S. Lei, Y. Y. Mai, C. J. Yan, J. W. Mao, and H. Cao, *Org. Lett*., 2016, **18**, 3582; (e) C. C. Wang, S. Lei, H. Cao, S. X. Qiu, J. Y. Liu, H. Deng, and C. J. Yan, *J. Org. Chem*., 2015, **80**, 12725.

10 (a) S. Rasheed, D. N. Rao, and P. Das, *J. Org. Chem*., 2015, **80**, 9321, (b) Y. M. He, J. B. Huang, D. D. Liang, L. Y. Liu and Q. Zhu, *Chem. Commun*., 2013, **49**, 7352; (c) S. Manna, K. Matcha, and A. P. Antonchick, *Angew. Chem. Int. Ed*., 2014, **53**, 8163; (d) D. D. Liang, Y. M. He, L. Y. Liu, and Q. Zhu, *Org. Lett*., 2013, **15**, 3476; (e) Z. Q. Wu, Q. Huang, X. G. Zhou, L. T. Yu, Z. K. Li, and D. Wu, *Eur. J. Org. Chem*., 2011, 5242; (f) H. G. Wang, Y. Wang, C. L. Peng, J. C. Zhang, and Q. Zhu, *J. Am. Chem. Soc*., 2010, **132**, 13217; (g) G. S. Kumar, S. P. Ragini, A. S. Kumar and H. M. Meshram, *RSC Adv*., 2015, **5**, 51576; (h) D. N. Rao, S. Rasheed, R. A. Vishwakarma and P. Das, *RSC Adv*., 2014, **4**, 25600; (i) L. Dong, J.-R. Huang, C.-H. Qu, Q.-R. Zhang, W. Zhang, B. Han and C. Peng, *Org. Biomol. Chem*., 2013, **11**, 6142.

11 O. Tsugr, S. Kanemasa, and T. Hamamoto, *Chem. Lett*, 1983, 763.

12 I. Otero, H. Feist, D. Michalik, M. Michalik, J. Quincoces, and K. Peseke, *Z. Naturforsch B.*, 2005, **60**, 1175.

13 (a) G. Y. Qian, B. X. Liu, Q. T. Tan, S. W. Zhang, and B. Xu, *Eur. J. Org. Chem*., 2014, 4837; (b) K. R. Reddy, A. S. Reddy, R. Shankar, Rajnikant, and P. Das, *Asian J. Org. Chem.,* 2015, **4**, 573; (c) J. Liu, W. Wei, T. Zhao, X. Y. Liu, J. Wu, W. Q. Yu, and J. B. Chang, *J. Org. Chem*., 2016, **81**, 9326.

14 (a) J. Zeng, Y. J. Tan, M. L. Leow, and X.-W. Liu, *Org. Lett*., 2012, **14**, 4386; (b) H. Cao, X. H. Liu, J. Q. Liao, J. P. Huang, H. F. Qiu, Q. L. Chen, and Y. Y. Chen, *J. Org. Chem*., 2014, **79**, 11209.

15 (a) A. J. Ragauskas, C. K. Williams, B. H. Davison, G. Britovsek, J. Cairney, C. A. Eckert, W. J. F. Jr., J. P. Hallett, D. J. Leak, C. L. Liotta, J. R. Mielenz, R. Murphy, R. Templer, T. Tschaplinski, *Science,* 2006, **311**, 484; (b) Y. M. Wang, B. Liu, K. C. Huang, and Z. H. Zhang, *Ind. Eng. Chem. Res*., 2014, **53**, 1313; (c) K. Yang and Q. L. Song, *Green Chem*., 2016, **18**, 932; (d) G. Q. Lv, H. L. Wang, Y. X. Yang, T. S. Deng, C. M. Chen, Y. L. Zhu and X. L. Hou, *Green Chem.,* 2016, **18**, 2302.

16 (a) A. Ibrar, I. Khan, N. Abbas, U. Farooq and A. Khan, *RSC Adv*., 2016, **6**, 93016; (b) Q. Xiao, L. M. Tian, R. C. Tan, Y. Xia, D. Qiu, Y. Zhang, and J. B. Wang, *Org. Lett*., 2012, **14**, 4230; (c) I. Thome and C. Bolm, *Org. Lett*., 2012, **14**, 1892; (d) W.-M. Shu, K.-L. Zheng, J.-R. Ma, and A.-X. Wu, *Org. Lett*., 2015, **17**, 5216; (e) P. Cyr, C.-R. Alexandre, and S. M. Bronner, *Org. Lett*.,

View Article Online
DOI: 10.1039/C8GC00069G

2016, **18**, 6448; (f) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, **114**, 9219.

17 (a) Y.-L. Xu, Q.-H. Teng, W. Tong, H.-S. Wang, Y.-M. Pan and X.-L. Ma, Molecules, 2017, **22**, 109; (b) Y. He, Y.-Y. Xie, Y.-C. Wang, X.-M. Bin, D.-C. Hu, H.-S. Wang and Y.-M. Pan, *RSC Adv.*, 2016, **6**, 58988; (c) W. Tong, Q.-Y. Li, Y.-L. Xu, H.-S. Wang, Y.-Y. Chen, and Y.-M. Pan, *Adv. Synth. Catal.*, 2017, **359**, 4025.

18 Q.-H. Teng, Y.-L. Xu, Y. Liang, H.-S. Wang, Y.-C. Wang, and Y.-M. Pan, *Adv. Synth. Catal.*, 2016, **358**, 1897.

19 (a) CCDC 1813854 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The single-crystal structure of product **3b** is included in Supporting Information. (b) CCDC 1813403 (**5o**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The single-crystal structure of product **5o** is included in Supporting Information.

20 (a) J. H. Shen, G. L. Cheng and X. L. Cui, *Chem. Commun*., 2013, **49**, 10641; (b) J. S. Peng, G. N. Shang, C. X. Chen, Z. S. Miao, and B. Li, *J. Org. Chem*., 2013, **78**, 1242.

21 (a) H. Aoyama, T. Nishio, Y. Hirabayashi, T. Hasegawa, H. Noda, and N. Sugiyama, *J. Chem. Soc. Perkin Transactions 1,* 1975, **3**, 298; (b) M. Reisser and G. Maas, *J. Org. Chem*., 2004, **69**, 4913; (c) X. Q. Yuan, X. X. Wu, S. P. Dong, G. B. Wu and J. X. Ye, *Org. Biomol. Chem.*, 2016, **14**, 744; (d) W. P. Li, Y. Q. Duan, M. L. Zhang, J. Cheng and C. J. Zhu, *Chem. Commun*., 2016, **52**, 7596.

22 J.-H. Wei, Z.-F. Chen, J.-L. Qin, Y.-C. Liu, Z.-Q. Li, T.-M. Khan, M. Wang, Y.-H. Jiang, W.-Y. Shen and H. Liang, *Dalton Trans*., 2015, **44**, 11408.

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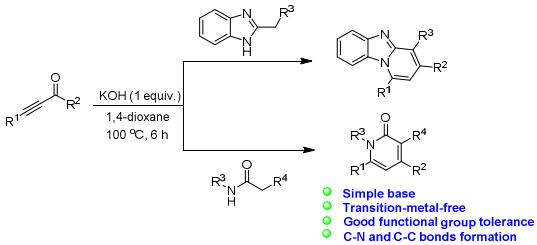
DOI: 10.1039/C8GC00069G



We have developed a facile method for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyridines and 2-pyridones from available ynones and 2-methylbenzimidazoles or acetamides.