有机化学 DOI: 10.6023/cjoc202110015 研究论文
Chinese Journal of Organic Chemistry ARTICLE

温和条件下高效合成咪唑并杂环-肼类衍生物的三组分串联反应

乔辉杰*,[a,b] 杨利婷[a,b] 陈 雅[b] 王嘉琳[b]
孙武轩[b] 董昊博[b] 王云威[b]
([a]中原工学院先进材料研究中心 河南省功能盐材料重点实验室 郑州 450007)
([b]中原工学院材料与化工学院 郑州 450007)

摘要 为了合成咪唑[1,2-*a*]并吡啶-肼类衍生物, 发展了一种以简单易得的甲酰甲基溴化物、2-氨基吡啶衍生物和偶氮二甲酸酯为原料的三分子串联反应的方法. 该串联反应先生成咪唑[1,2-*a*]并吡啶, 然后紧接着连续发生 C(3)—H 键肼基化反应, 而不像传统的一步接一步反应的方法. 该方法具有操作简单、反应条件温和(无需过渡金属且反应温度低等)以及底物适用性广的特点. 实验结果表明, 带有给电子取代基的甲酰甲基溴化物和 2-氨基吡啶衍生物有利于反应的进行, 并以优秀的产率获得目标产物.

关键词 三组分反应; 串联反应; 咪唑并杂环化合物; C(3)—H 肼基化反应

An Efficient Three-Component Tandem Approach for the Synthesis of Imidazoheterocycle-Hydrazine Derivatives under Mild Conditions

Qiao, Huijie*,[a,b] Yang, Liting[a,b] Chen, Ya[b] Wang, Jialin[b]
Sun, Wuxuan[b] Dong, Haobo[b] Wang, Yunwei[b]
([a] *Henan Key Laboratory of Functional Salt Materials, Center for Advanced Materials Research, Zhongyuan University of Technology, Zhengzhou 450007*)
([b] *School of Materials and Chemical Engineering, Zhongyuan University of Technology, Zhengzhou 450007*)

Abstract An three-component tandem reaction for the synthesis of imidazo[1,2-*a*]pyridine-hydrazines was accomplished with the easily available formyl methyl bromides, pyridin-2-amines and azodiformates. This tandem reaction process includes the generation of imidazo[1,2-*a*]pyridines followed by C(3)—H hydrazination in a sequential way, instead of the classical step-by-step methods. The approach features simple operation, mild conditions (transition-metal-free and low reaction temperature) as well as good tolerance of substrates. Note that formyl methyl bromides and pyridin-2-amines bearing electron-donating groups are benefit for this reaction, affording target products in excellent yields.

Keywords three-component reaction; tandem reaction; imidazoheterocycle; C(3)—H hydrazination

1 Introduction

Imidazoheterocycles have wide applications in optoelectronics and pharmaceuticals due to their unique biological and pharmacological properties,[1] such as anti-tumor,[2] anti-inflammatory,[3] anti-ulcer,[4] anti-microbial,[5] anti-fungal,[6] anti-viral[7] and so on. Among them, imidazo[1,2-*a*]pyridine derivatives could also serve as the key structures of many excellent natural products and marketed drugs, including alpidem, divalpon, DS-1, necopidem, olprinone, saripidem, zolpidem and zolimidine[8]. Therefore, developing the economical and environment-friendly routes to functionalized imidazo[1,2-*a*]-pyridine derivatives is of great significance, which has attracted increasing attentions of the chemists and medicinal chemists.

During the past decades, multitudinous efforts have been devoted to exploit the methodologies for direct C—H functionalization of imidazo[1,2-*a*]pyridines, achieving greet progress in the transformations from C—H to C—C and C—heteroatom bonds[9-15]. Among the rest, there are only few protocols for the C(3)—H hydrazinations of im-

* Corresponding author. E-mail: 598405179@qq.com
Received October 12, 2021; revised November 14, 2021; published online December 8, 2021.
Project supported by the Natural Science Foundation of Henan Province (Nos. 202300410515, 212300410318).
河南省自然科学基金(Nos. 202300410515, 212300410318)资助项目.

idazoheterocycles. For example, the pioneering work of C(3)—H hydrazination of imidazo[1,2-*a*]pyridines belongs to Li and co-workers,[16] who developed a procedure of metal-free regioselective hydrazination of imidazo[1,2-*a*]-pyridine with diethyl azodicarboxylate in 2015 (Scheme 1, a). Then, Tang's group[17] developed an iron-catalyzed hydrazination of imidazoheterocycles at C(3) position, which could produce diverse imidazoheterocycle-hydrazines (Scheme 1, b). Generally, these methods are useful and efficient, but both of them need to employ purified imidazoheterocycles as the reactants, which add another procedure to generate and separate the imidazoheterocycles. Besides, both of them are operated at high temperature, which is difficult to conduct due to the necessary of water coolant and closed system. Meanwhile, employ organic solvents at high temperature could virtually increase the dangerousness of the experiment.

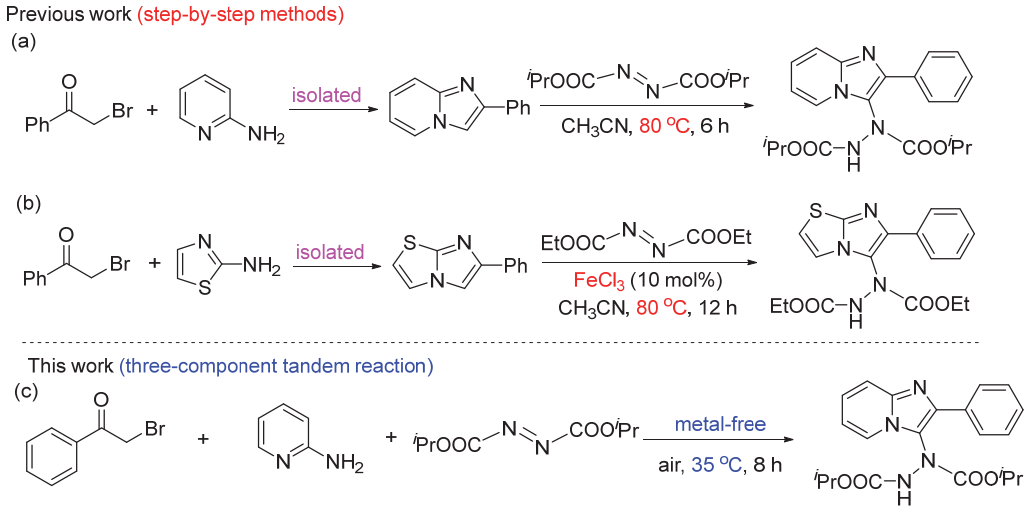
Recently, multicomponent tandem reactions were emerged possibly as the efficient, powerful and atom-economical methodologies in organic synthesis.[18] These strategies exhibited multitudinous advantages, such as saving operation time (without time-consuming multiple processes, preclusion of the isolation of intermediates), improving the overall yields and so on. In particular, the multicomponent tandem reactions had been realized in the formation of polyfunctionalized heterocyclic molecules.[19] Though there have been some reports about the preparation of C(3)-functionalized imidazo[1,2-*a*]pyridines in three-component tandem approaches,[20] yet the generation of imidazo[1,2-*a*]pyridine-hydrazines by sequential multi-component tandem reaction is still unknown.

The research interest of our group is focused on the discovery of new reaction patterns for construction of C—C and C—heteroatom bonds under easy and simple reaction conditions.[21] Herein, we envisioned developing a three-component tandem reaction for the synthesis of imidazo-[1,2-*a*]pyridine-hydrazines under mild conditions by employing formyl methyl bromides, pyridin-2-amines and azodiformates as the reactants (Scheme 1, c).

2 Results and discussion

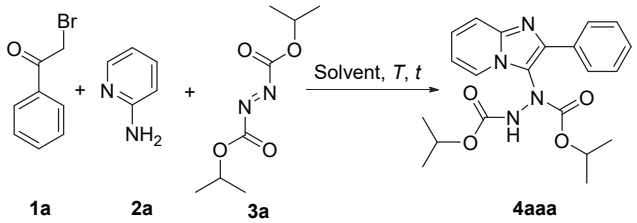
The reaction of 2-bromo-1-phenylethan-1-one (**1a**), pyridin-2-amine (**2a**) with diisopropyl (*E*)-diazene-1,2-dicarboxylate (**3a**) in CH_3CN was chosen as the model reaction (Table 1), and the target product **4aaa** was obtained in 82% yield (Table 1, Entry 1). The molecular structure of **4aaa** was unambiguously confirmed by single crystal X-ray diffraction study (CCDC 2103347). Then, other solvents including CH_3CN/H_2O (V ∶ V=1 ∶ 1), H_2O, EtOH, tetrahydrofuran (THF), 1,4-dioxane, *o*-xylene, *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), petroleum ether, ethyl acetate, 1,2-dichloroethane (1,2-DCE) and dichloromethane (DCM) were also examined, but none of them could match the efficacy of DCM, affording the desired product **4aaa** in 84% yield (Table 1, Entries 1～12 vs Entry 13). When the reaction temperature was altered from 30 ℃ to 35 ℃, a better result was observed and the coupling product was afforded in 91% (Table 1, Entry 14). Encouraged by this result, we attempted to increase the temperature to 40 ℃, but the result showed no significantly improvement (Table 1, Entry 15). In addition, increasing the reaction time to 9 h or decreasing to 7 h led to the hydrazination product in no better yields (Table 1, Entries 16, 17 vs. Entry 14).

With the optimized reaction conditions in hand, the applicability of formyl methyl bromides was explored, and the results are summarized in Table 2. Arylformyl methyl bromides bearing electronic neutral, electron-donating, or electron-withdrawing groups on the benzene ring are all well tolerated in this hydrazination reaction, and the target products could be afforded in 36%～95% yields (**4aaa**～**4haa**). Comparatively, electronic neutral substituents (**1a**, **1b**) and electron-donating substituents (**1c**, **1d**, R^1=Me, OMe) resulted in higher yields than those of the electron-withdrawing substituents (**1e**～**1h**, R^1=, F, Cl, Br and CF_3). According to the above, electron-withdrawing groups on the benzene ring could reduce the reactivity of



Scheme 1 Protocols for the preparation of imidazoheterocycle-hydrazines

Table 1 Screening optimal conditions[a]



1a **2a** **3a** **4aaa**

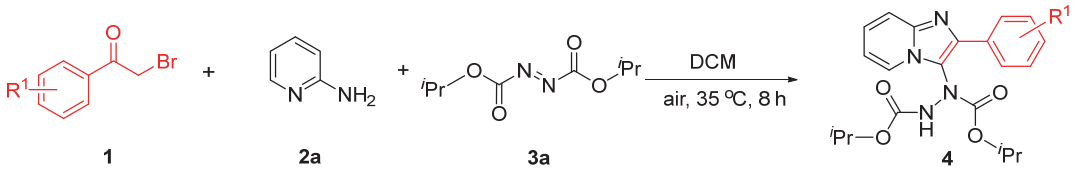
Entry	Solvent	T/℃	t/h	Yield[b]/%
1	CH_3CN	30	8	82
2	CH_3CN/H_2O (V∶V=1∶1)	30	8	71
3	H_2O	30	8	66
4	EtOH	30	8	15
5	THF	30	8	52
6	1,4-Dioxane	30	8	55
7	*o*-Xylene	30	8	45
8	DMF	30	8	10
9	DMSO	30	8	16
10	Petroleum ether	30	8	37
11	Ethyl acetate	30	8	58
12	1,2-DCE	30	8	80
13	DCM	30	8	84
14	DCM	**35**	**8**	**91**
15	DCM	40	8	90
16	DCM	35	9	91
17	DCM	35	7	86

[a] Reaction conditions: **1a** (0.2 mmol, 39.6 mg), **2a** (0.4 mmol, 37.7 mg), **3a** (0.6 mmol, 119 μL), solvent (1 mL), under air. [b] Isolated yield.

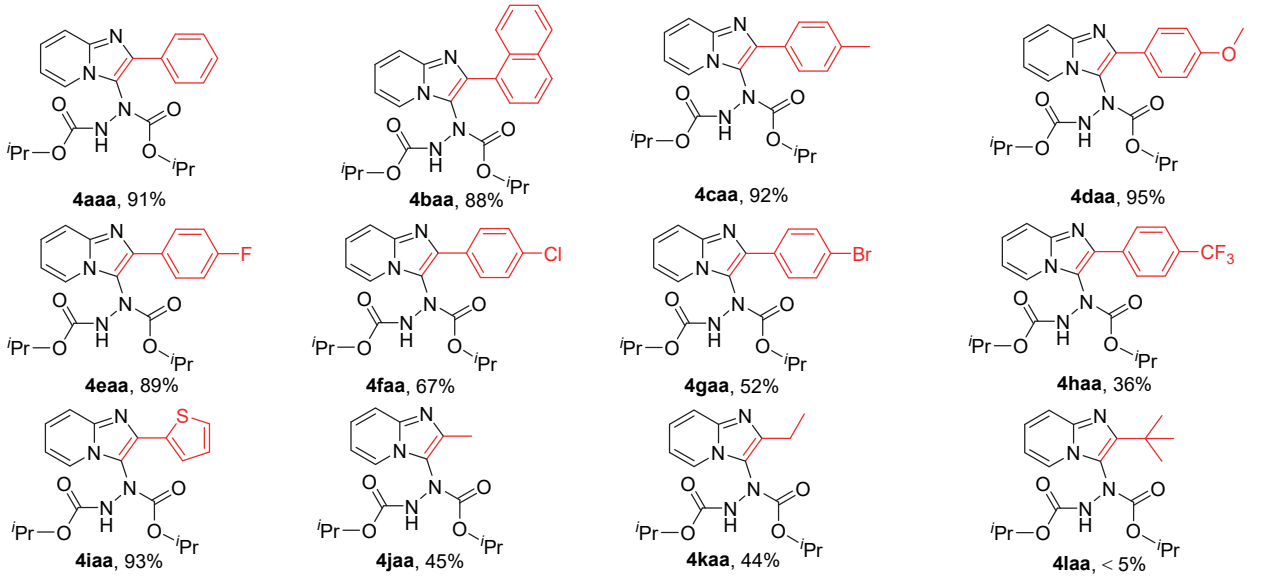
this hydrazination reaction. To our delight, a heterocyclic formyl methyl bromide, such as 2-bromo-1-(thiophen-2-yl)ethan-1-one, could also participate in this coupling, producing the desired product (**4iaa**) in 93% yield. Besides, bromoaliketones (*e.g.* 1-bromopropan-2-one, 1-bromobutan-2-one) could be applicable to this reaction system, affording the target products in moderate yields (**4jaa** ～ **4kaa**). However, employing 1-bromo-4,4-dimethylpentan-2-one as the reactant resulted in undetectable destination product, which might be affected by the steric hindrance of *tert*-butyl group (**4laa**).

Then, a variety of substituted 2-amino heterocyclic compounds were examined under the standard reaction conditions (Table 3). Similar to Table 2, electronic neutral and electron-donating groups on the pyridine ring are benefit for this hydrazination reaction, generating the desired products in good to excellent yields (**4aaa**～**4ada**). However, electron-withdrawing groups on the pyridine ring could result in the sharp decline of yields (**4aea**～**4aja**). In particular, only trace amount of the coupling product was observed when the C(4) position of pyridin-2-amine was blocked by a CF_3 group (**4aja**). Compared with Table 2, the electronic effect was more obvious on the pyridine ring of pyridin-2-amine than on the benzene ring of arylformyl methyl bromides. Besides, benzo[*d*]thiazol-2-amine and thiazol-2-amine could also be well tolerated in this reaction, affording the desired product in moderate yields of 46% and 41%, respectively (**4aka**～**4ala**).

Table 2 Substrate scope of arylformyl methyl bromides[a,b]

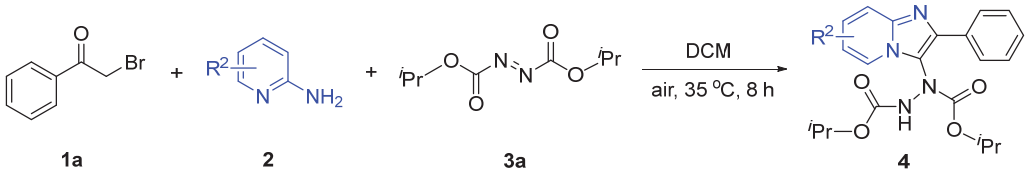


1 **2a** **3a** **4**

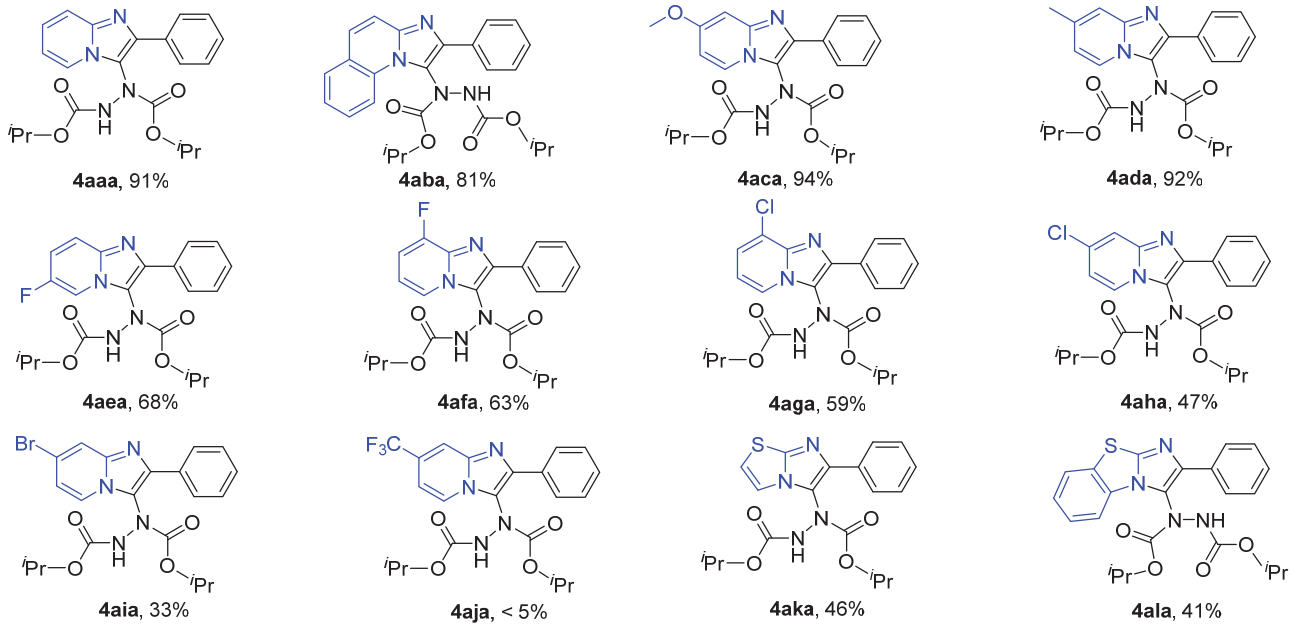


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol, 37.7 mg), **3a** (0.6 mmol, 119 μL), DCM (1 mL), under air at 35 ℃ for 8 h. [b] Isolated yield.

Table 3 Substrate scope of 2-amino heterocyclic compounds[a,b]



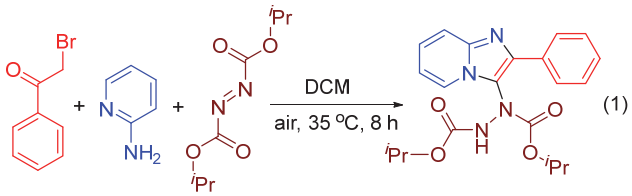
1a 2 3a 4



[a] Reaction conditions: **1a** (0.2 mmol, 39.6 mg), **2a** (0.4 mmol), **3a** (0.6 mmol, 119 μL), DCM (1 mL), under air at 35 ℃ for 8 h. [b] Isolated yield.

To further investigate the scope in this hydrazination the standard reaction conditions, a small range of azodiformates were examined under the standard reaction conditions (Table 4). Both alkyl azodiformates and benzyl azodicarboxylates were well applicable to this reaction system in excellent yields (**4aaa**～**4aab**, **4aad**～**4aaf**) except for di-*tert*-butyl azodicarboxylate (**3c**), and the low yield of **4aac** might be affected by the steric hindrance of *tert*-butyl group. By contrast, substrates bearing chloric substituent (**4aad** and **4aaf**, 93% and 95% yields, respectively) resulted in the coupling products in slightly higher yields than the corresponding unsubstitutional substrates (**4aab** and **4aae**, 90% and 92% yields, respectively). However, implying azodicarbonamide, azodiisobutyronitrile and azobenzene as the hydrazination reagents resulted in almost no transformation on account of the low reactivity (**4aag**～**4aai**).

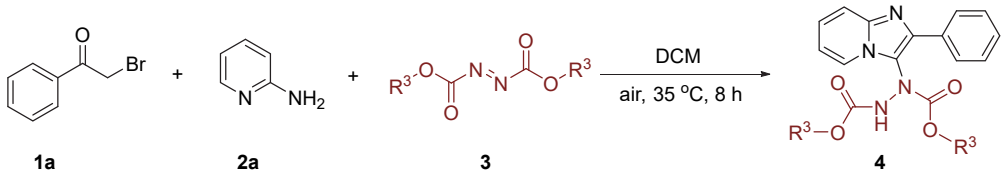
To demonstrate the potential application value of this protocol in organic synthesis, a gram-scale reaction of **1a**, **2a** with **3a** was executed (Eq. 1). This reaction could afford the target product **4aaa** in an isolated yield of 89%.



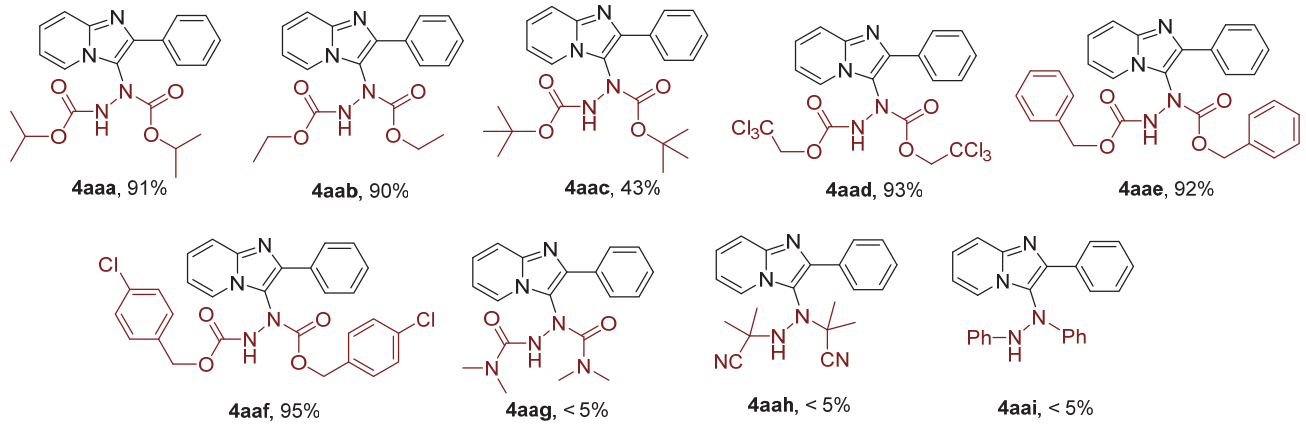
1a 0.792 g **2a** 0.756 g **3a** 2.426 g **4aaa** 1.411 g (89% yield) (1)

Next, we performed some condition control experiments to understand the probable reaction mechanism of this tandem reaction (Scheme 2). The addition of radical inhibitor 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-diisopropyl-4-methylphenol (BHT) could not suppress the reaction, indicating that this reaction might involve an ionic mechanism (Scheme 2, a). Performing the reaction under nitrogen atmosphere instead of air resulted in a similar yield of **4aaa**, which demonstrating that oxygen might have no effect on this tandem hydrazination reaction (Scheme 2, b). When we got rid of **1a** or **2a** in the standard conditions respectively, no coupling products were detected (Scheme 2, c and d). Removing **3a** in the standard conditions could obtain the 2-phenylimidazo[1,2-*a*]-pyridine (**5**) in an isolated yield of 98% (Scheme 2, e). Using **5** as the reactant instead of **1a** and **2a** in the standard conditions could also acquire the desired product **4aaa** in an excellent yield (Scheme 2, f). These observations indicated that this tandem hydrazination reaction began with **1a** and **2a** to generate the intermediate product 2-phenylimidazo-[1,2-*a*]pyridine, and then the C(3)—H hydrazination reaction of 2-phenylimidazo[1,2-*a*]pyridine with diisopropyl azodiformate took place.

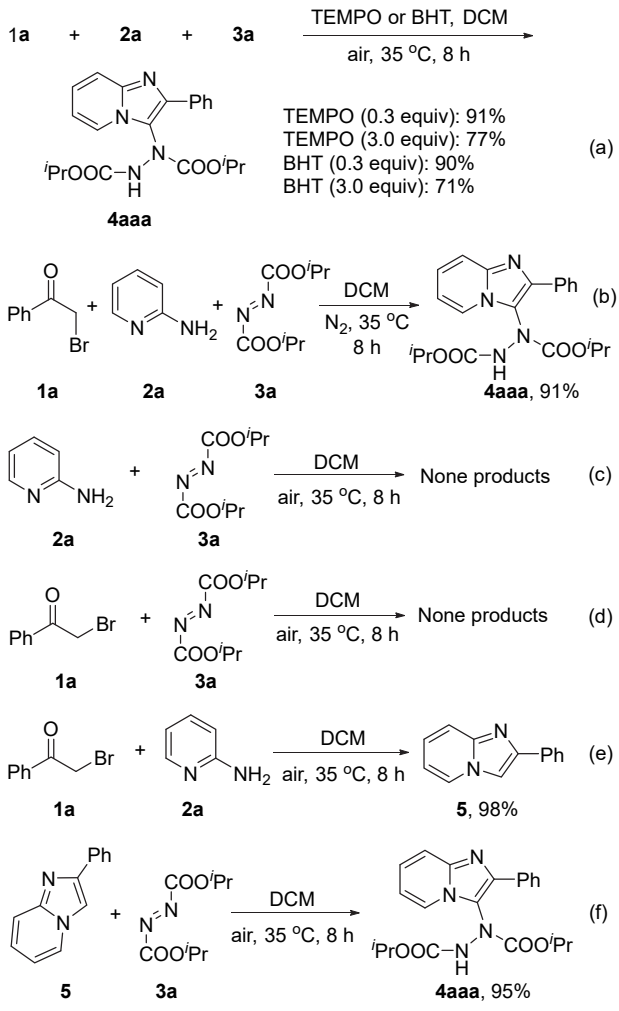
Table 4 Substrate scope of azodiformates[a,b]



1a 2a 3 4

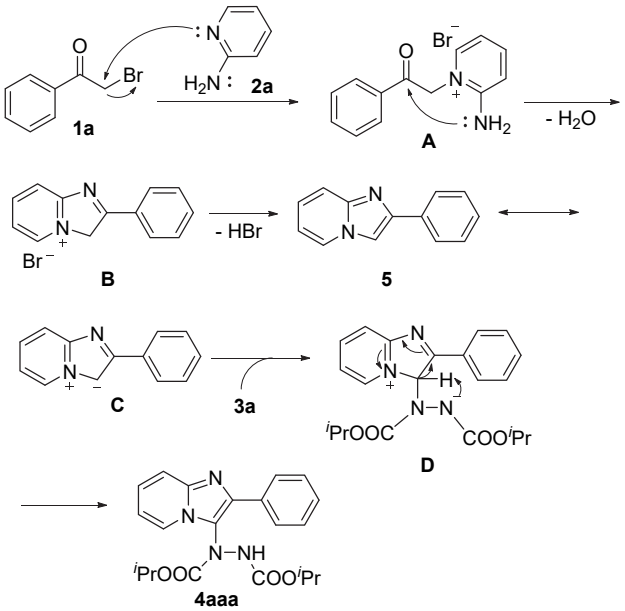


[a] Reaction conditions: **1a** (0.2 mmol, 39.6 mg), **2a** (0.4 mmol, 37.7 mg), **3a** (0.6 mmol), DCM (1 mL), under air at 35 °C for 8 h. [b] Isolated yield.



Scheme 2 Control experiments

Although the mechanism involved here remains unclear at present, a plausible mechanism of the reaction was proposed on the above-mentioned results and previous reports (Scheme 3)[16-17,22-23]. First, **2a** nucleophilicaly attacks **1a**, generating the pyridinium intermediate **A**. Then, **A** undergoes an intramolecular ring-forming condensation reaction to produce intermediate **B**, which releases a molecule of HBr to afford the intermediate **5**. Note that **5** could undergo an interconversion process to afford the intermediate **C**. Subsequently, the carbanion of **C** could attack the N=N bond of **3a** through a *pseudo*-Michael reaction, forming an intermediate **D**. Finally, proton translocation



Scheme 3 Plausible mechanism

and restoring conjugation of **D** provides the desired product **4aaa**.

3 Conclusions

In summary, a three-component tandem reaction for the preparation of imidazo[1,2-*a*]pyridine-hydrazines by using formyl methyl bromides, pyridin-2-amines and azodiformates as the reactants instead of the general two-step procedure was developed. The advantages of the present method include low reaction temperature, transition-metal-free, simple and efficient reaction system as well as good tolerance of substrates. Moreover, we indicate that formyl methyl bromides and pyridin-2-amines bearing electron-withdrawing groups are not conducive to this reaction. Finally, a gram-scale tandem hydrazination reaction is also successfully realized, which demonstrates its potential synthetic value.

4 Experimental section

4.1 General considerations

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-400 spectrometer or Bruker DPX-600 spectrometer with $CDCl_3$ as the solvent and TMS as an internal standard. Melting points were measured using a WC-1 microscopic apparatus and uncorrected. High resolution mass spectra were ensured on a MALDI-FTMS Agilent 1290-6540 Q-Tof high resolution liquid chromatography mass spectrometer. Single crystal X-ray diffraction study was tested on a Bruker D8 VENTURE X-ray single crystal diffractometer. All solvents were used directly without further purification. Dichloromethane, ethyl acetate and hexane were used for column chromatography. The commercials were obtained from commercial sources and used as received without further purification unless otherwise noted.

4.2 Typical procedure for the products

4.2.1 Typical procedure for product 4

A 10 mL reaction tube was equipped with a magnetic stir bar and charged with formyl methyl bromides **1** (0.2 mmol), pyridin-2-amines **2** (0.4 mmol, 2 equiv.), azodiformates **3** (0.6 mmol, 3 equiv) and DCM (1 mL). The resulting mixture was stirred under air at 35 ℃ for 8 h. Upon completion, the solvent was removed under reduced pressure. Then the residue was purified by column chromatography on silica gel (200～300 mesh) using hexane-EtOAc as an eluent to afford the pure product **4**.

Diisopropyl 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)-hydrazine-1,2-dicarboxylate (**4aaa**): White solid, 91% yield. m.p. 165～167 ℃ (lit.[24] 167～169 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 7.77 (d, J=8.0 Hz, 2H), 7.60 (d, J=9.0 Hz, 1H), 7.42～7.30 (m, 4H), 7.26～7.23 (m, 1H), 6.86 (t, J=5.9 Hz, 1H), 5.10～4.94 (m, 2H), 1.26～0.99 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 154.8, 143.0, 139.4, 133.0, 128.9, 128.3, 126.9, 125.8, 124.7, 118.7, 117.3, 112.4, 72.1, 70.6, 22.0, 21.8, 21.7, 21.6.

Diisopropyl 1-(2-(naphthalen-1-yl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4baa**): Orange solid, 88% yield. m.p. 138～139 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 8.31 (s, 1H), 7.94～7.85 (m, 4H), 7.66 (d, J=8.9 Hz, 1H), 7.53～7.49 (m, 2H), 7.30 (t, J=7.4 Hz, 1H), 7.09～7.00 (m, 1H), 6.91 (t, J=5.8 Hz, 1H), 5.18～4.96 (m, 2H), 1.29～1.06 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.4, 154.8, 143.2, 139.2, 133.6, 133.1, 130.3, 128.8, 128.4, 127.7, 126.5, 126.2, 126.0, 124.7, 124.2, 119.0, 117.3, 112.5, 72.3, 70.7, 22.0, 21.8, 21.7; HRMS (ESI$^+$) calcd for $C_{25}H_{27}N_4O_4$ $[M+H]^+$ 447.2027, found 447.2029.

Diisopropyl 1-(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)-hydrazine-1,2-dicarboxylate (**4caa**): Orange solid, 92% yield. m.p. 157～158 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.67 (s, 1H), 7.68 (d, J=7.6 Hz, 2H), 7.60 (d, J=8.9 Hz, 1H), 7.26～7.25 (m, 3H), 7.08～7.00 (m, 1H), 6.87 (t, J=6.4 Hz, 1H), 5.13～4.95 (m, 2H), 2.39 (s, 3H), 1.29～1.03 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.4, 154.8, 143.0, 139.4, 138.3, 130.1, 129.7, 126.6, 125.7, 124.5, 118.3, 117.2, 112.3, 72.1, 70.6, 21.9, 21.8, 21.7, 21.6, 21.3; HRMS (ESI$^+$) calcd for $C_{22}H_{27}N_4O_4$ $[M+H]^+$ 411.2027, found 411.2025.

Diisopropyl 1-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4daa**): Orange solid, 95% yield. m.p. 144～146 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 7.71 (d, J=8.7 Hz, 2H), 7.58 (d, J=9.0 Hz, 1H), 7.26～7.22 (m, 2H), 6.95 (d, J=8.8 Hz, 2H), 6.85 (t, J=6.7 Hz, 1H), 5.10～4.94 (m, 2H), 3.83 (s, 3H), 1.27～1.01 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 156.4, 154.8, 142.9, 139.3, 128.0, 125.6, 125.5, 124.5, 117.8, 117.0, 114.3, 112.2, 72.1, 70.5, 55.2, 21.9, 21.8, 21.7, 21.6; HRMS (ESI$^+$) calcd for $C_{22}H_{27}N_4O_5$ $[M+H]^+$ 427.1976, found 427.1979.

Diisopropyl 1-(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4eaa**): White solid, 89% yield. m.p. 175～177 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 7.77～7.75 (m, 2H), 7.60 (d, J=8.9 Hz, 1H), 7.29～7.26 (m, 1H), 7.20～7.10 (m, 3H), 6.89 (t, J=6.3 Hz, 1H), 5.12～4.95 (m, 2H), 1.28～1.01 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.8 (d, J=248.6 Hz), 156.5, 154.7, 143.0, 138.6, 129.2, 128.7, 126.0, 124.7, 118.4, 117.2, 115.9 (d, J=21.6 Hz), 112.5, 72.3, 70.7, 21.9, 21.8, 21.7, 21.6; HRMS (ESI$^+$) calcd for $C_{21}H_{24}FN_4O_4$ $[M+H]^+$ 415.1776, found 415.1777.

Diisopropyl 1-(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4faa**): White solid, 67% yield. m.p. 171～173 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 7.73 (d, J=8.4 Hz, 2H), 7.61 (d, J=8.9 Hz, 1H), 7.41 (d, J=8.5 Hz, 2H), 7.29～7.27 (m, 1H), 7.12～7.01 (m, 1H), 6.90 (t, J=6.4 Hz, 1H), 5.12～4.95 (m, 2H), 1.29～1.02 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.5, 154.6, 143.1, 138.3, 134.3, 131.5, 129.2, 128.1, 126.1, 124.7, 118.7, 117.3, 112.6, 72.3, 70.8, 21.9, 21.8, 21.7, 21.6; HRMS (ESI$^+$) calcd for $C_{21}H_{24}ClN_4O_4$ $[M+H]^+$ 431.1481, found 431.1480.

Diisopropyl 1-(2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4gaa**): White solid, 52% yield. m.p. 168～171 ℃ (lit.[24] 170～172 ℃); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.68 (s, 1H), 7.65 (d, J=7.8 Hz, 2H), 7.59 (d, J=8.9 Hz, 1H), 7.53 (d, J=8.3 Hz, 2H), 7.43～7.18 (m, 2H), 6.88 (s, 1H), 5.10～4.95 (m, 2H), 1.26～1.00 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$$\delta$): 156.5, 154.6, 143.0, 138.2, 132.0, 131.8, 128.3, 126.0, 124.7, 122.4, 118.7, 117.2, 112.5, 72.2, 70.6, 21.9, 21.8, 21.6, 21.6.

Diisopropyl 1-(2-(4-(trifluoromethyl)phenyl)imidazo-[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4haa**): White solid, 36% yield. m.p. 174～175 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.71 (s, 1H), 7.92 (d, J=8.0 Hz, 2H), 7.69 (d, J=8.2 Hz, 2H), 7.63 (d, J=8.9 Hz, 1H), 7.31 (t, J=7.5 Hz, 1H), 7.16～7.03 (m, 1H), 6.92 (t, J=6.0 Hz, 1H), 5.13～4.97 (m, 2H), 1.30～1.02 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6, 154.5, 143.2, 137.9, 136.5, 130.1 (q, J=31.3 Hz), 127.0, 126.3, 125.9, 124.8, 124.1 (q, J=268.2 Hz), 119.3, 117.5, 112.8, 72.4, 70.9, 21.9, 21.8, 21.7, 21.6; HRMS (ESI$^+$) calcd for $C_{22}H_{24}F_3N_4O_4$ [M+H]$^+$ 465.1774, found 465.1778.

Diisopropyl 1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-hydrazine-1,2-dicarboxylate (**4iaa**): White solid, 45% yield. m.p. 68～70 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 8.26～8.14 (m, 1H), 7.47 (d, J=8.8 Hz, 1H), 7.16 (t, J=7.6 Hz, 1H), 6.78 (t, J=5.7 Hz, 1H), 4.98～4.96 (m, 2H), 2.34 (s, 3H), 1.30～1.09 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 154.9, 142.5, 138.7, 124.9, 123.9, 119.4, 116.6, 111.9, 71.7, 70.2, 21.9, 21.8, 21.7, 12.7; HRMS (ESI$^+$) calcd for $C_{16}H_{22}N_4O_4$ [M＋H]$^+$ 335.1714, found 335.1715.

Diisopropyl 1-(2-ethylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4jaa**): White solid, 44% yield. m.p. 65～66 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (s, 1H), 7.87 (s, 1H), 7.50 (d, J=8.9 Hz, 1H), 7.16 (t, J=7.5 Hz, 1H), 6.78 (t, J=6.1 Hz, 1H), 4.98～4.95 (m, 2H), 2.69 (q, J=7.4 Hz, 3H), 1.30～1.09 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 154.9, 144.0, 142.7, 124.9, 124.0, 118.6, 116.7, 111.9, 71.7, 70.3, 21.9, 21.8, 21.7, 20.4, 13.2; HRMS (ESI$^+$) calcd for $C_{17}H_{24}N_4O_4$ [M+H]$^+$ 349.1870, found 349.1872.

Diisopropyl 1-(2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4jaa**): Brown solid, 91% yield. m.p. 118～120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (s, 1H), 7.59～7.53 (m, 4H), 7.35 (d, J=4.7 Hz, 1H), 7.28～7.24 (m, 2H), 7.13～7.11 (m, 1H), 6.87 (t, J=6.5 Hz, 1H), 5.11～4.93 (m, 2H), 1.31～1.01 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.5, 154.6, 143.2, 135.3, 135.0, 128.0, 126.1, 125.8, 125.0, 124.6, 117.5, 117.0, 112.5, 72.3, 70.7, 21.9, 21.8, 21.6, 21.6; HRMS (ESI$^+$) calcd for $C_{19}H_{23}N_4O_4S$ [M＋H]$^+$ 403.1435, found 403.1437.

Diisopropyl 1-(2-phenylimidazo[1,2-*a*]quinolin-1-yl)-hydrazine-1,2-dicarboxylate (**4aba**): Orange solid, 81% yield. m.p. 117～118 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.04 (s, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.75 (d, J=7.2 Hz, 2H), 7.68 (t, J=7.4 Hz, 1H), 7.60～7.56 (m, 2H), 7.52～7.47 (m, 3H), 7.41 (t, J=7.4 Hz, 1H), 6.87～6.73 (m, 1H), 5.23～4.91 (m, 2H), 1.26～0.97 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.5, 155.2, 142.4, 133.5, 133.1, 129.3, 128.8, 128.7, 128.4, 127.9, 127.0, 125.0, 124.3, 123.0, 117.2, 72.7, 70.3, 21.9, 21.9, 21.8, 21.6; HRMS (ESI$^+$) calcd for $C_{25}H_{27}N_4O_4$ [M＋H]$^+$ 447.2027, found 447.2031.

Diisopropyl 1-(7-methoxy-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aca**): White solid, 94% yield. m.p. 136～137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.75 (d, J=7.5 Hz, 2H), 7.42 (t, J=7.4 Hz, 2H), 7.35～7.31 (m, 1H), 7.14～7.05 (m, 1H), 6.89 (d, J=2.0 Hz, 1H), 6.59 (dd, J=7.2, 1.7 Hz, 1H), 5.10～4.94 (m, 2H), 3.87 (s, 3H), 1.28～1.02 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9, 156.4, 154.8, 144.6, 138.7, 133.0, 128.9, 128.1, 126.5, 125.2, 117.8, 107.3, 94.6, 72.1, 70.6, 55.5, 21.9, 21.8, 21.7, 21.6; HRMS (ESI$^+$) calcd for $C_{22}H_{27}N_4O_5$ [M＋H]$^+$ 427.1976, found 427.1974.

Diisopropyl 1-(7-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4ada**): Orange solid, 92% yield. m.p. 147～149 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.56 (s, 1H), 7.76 (d, J=7.3 Hz, 2H), 7.43 (t, J=7.6 Hz, 2H), 7.35～7.33 (m, 2H), 7.11～7.06 (m, 1H), 6.71 (d, J=6.5 Hz, 1H), 5.11～4.96 (m, 2H), 2.41 (s, 3H), 1.28～1.02 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.4, 154.8, 143.5, 139.0, 136.8, 133.1, 128.9, 128.2, 126.7, 123.8, 118.2, 115.7, 115.0, 72.1, 70.6, 21.9, 21.8, 21.7, 21.6, 21.4; HRMS (ESI$^+$) calcd for $C_{22}H_{27}N_4O_4$ [M＋H]$^+$ 411.2027, found 411.2028.

Diisopropyl 1-(6-fluoro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aea**): White solid, 68% yield. m.p. 171～172 ℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 7.74 (d, J=7.5 Hz, 2H), 7.59～7.56 (m, 1H), 7.42 (t, J=7.4 Hz, 2H), 7.34 (t, J=7.3 Hz, 1H), 7.28 (s, 1H), 7.18 (t, J=8.0 Hz, 1H), 5.12～4.95 (m, 2H), 1.28～0.99 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6, 154.5, 153.2 (d, J=237.2 Hz), 140.6 (d, J=31.2 Hz), 132.6, 128.9, 128.5, 126.7, 126.0, 119.9, 117.8 (d, J=15.2 Hz), 117.7, 111.7 (d, J=45.4 Hz), 72.4, 70.7, 21.9, 21.8, 21.7, 21.5; HRMS (ESI$^+$) calcd for $C_{21}H_{24}FN_4O_4$ [M+H]$^+$ 415.1776, found 415.1779.

Diisopropyl 1-(8-fluoro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4afa**): White solid, 63% yield. m.p. 168～169 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.54 (s, 1H), 7.80 (d, J=7.5 Hz, 2H), 7.43 (t, J=7.4 Hz, 2H), 7.36 (t, J=7.1 Hz, 1H), 7.17 (s, 1H), 6.97 (t, J=8.9 Hz, 1H), 6.79 (d, J=4.1 Hz, 1H), 5.11～4.94 (m, 2H), 1.27～1.00 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.5, 154.5, 151.2 (d, J=253.3 Hz), 139.8, 135.5 (d, J=29.3 Hz), 132.4, 128.9, 128.6, 126.9, 121.0, 119.9, 112.3, 108.3 (d, J=16.0 Hz), 72.3, 70.7, 21.9, 21.8, 21.6, 21.5; HRMS (ESI$^+$) calcd for $C_{21}H_{24}FN_4O_4$ [M+H]$^+$ 415.1776, found 415.1772.

Diisopropyl 1-(8-chloro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aga**): Orange solid,

59% yield. m.p. 179～181 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.79 (s, 1H), 7.75 (d, J=7.4 Hz, 2H), 7.55 (t, J=9.2 Hz, 1H), 7.42 (t, J=7.4 Hz, 2H), 7.35 (t, J=7.3 Hz, 1H), 7.23～7.15 (m, 2H), 5.12～5.00 (m, 2H), 1.33～0.99 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.5, 154.4, 141.3, 140.3, 132.5, 129.0, 128.6, 127.2,126.8, 122.7, 120.8, 119.0, 117.7, 72.4, 70.7, 21.9, 21.8, 21.7, 21.5; HRMS (ESI$^+$) calcd for $C_{21}H_{24}ClN_4O_4$ $[M+H]^+$ 431.1481, found 431.1479.

Diisopropyl 1-(7-chloro-2-phenylimidazo[1,2-a]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aha**): White solid, 47% yield. m.p. 168～169 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.67 (s, 1H), 7.75 (d, J=7.3 Hz, 2H), 7.61 (s, 1H), 7.46～7.43 (m, 2H), 7.39～7.37 (m, 1H), 7.13～7.08 (m, 1H), 6.87 (t, J=6.5 Hz, 1H), 5.12～4.96 (m, 2H), 1.30～1.02 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6, 154.5, 142.8, 140.1, 132.6, 129.0, 128.6, 127.1, 126.8, 125.1, 118.9, 116.1, 114.1, 72.4, 70.8, 21.9, 21.8, 21.7, 21.5; HRMS (ESI$^+$) calcd for $C_{21}H_{24}ClN_4O_4$ $[M+H]^+$ 431.1481, found 431.1483.

Diisopropyl 1-(7-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aia**): White solid, 33% yield. m.p. 172～173 ℃; 1H NMR (600 MHz, $CDCl_3$) δ: 8.61 (s, 1H), 7.79～7.74 (m, 3H), 7.44～7.43 (m, 2H), 7.36 (s, 1H), 7.18～7.08 (m, 1H), 6.98 (d, J=6.3 Hz, 1H), 5.12～4.96 (m, 2H), 1.30～1.01 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6, 154.5, 143.1, 140.1, 132.4, 129.0, 128.6, 127.1, 126.8, 125.1, 120.0, 119.5, 116.3, 72.4, 70.8, 21.9, 21.8, 21.7, 21.5; HRMS (ESI$^+$) calcd for $C_{21}H_{24}BrN_4O_4$ $[M+H]^+$ 475.0975, found 475.0977.

Diisopropyl 1-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)hydrazine-1,2-dicarboxylate (**4aka**): Obtained as a white solid in 56% yield. m.p. 165～166 ℃ (lit.[17] 168～170 ℃); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.89 (s, 1H), 7.70 (d, J=7.2 Hz, 2H), 7.40 (t, J=7.6 Hz, 2H), 7.30 (t, J=7.4 Hz, 1H), 7.14～7.08 (m, 1H), 6.80 (s, 1H), 5.09～4.96 (m, 2H), 1.30～1.04 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.5, 154.7, 148.1, 140.8, 133.2, 128.8, 127.8, 126.2, 120.3, 119.3, 112.1, 72.2, 70.7, 22.0, 21.8, 21.7, 21.6.

Diisopropyl 1-(2-phenylbenzo[*d*]imidazo[2,1-b]thiazol-3-yl)hydrazine-1,2-dicarboxylate (**4ala**): Light yellow solid, 51% yield. m.p. 175～177 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.32 (s, 1H), 7.68 (d, J=7.4 Hz, 3H), 7.50～7.45 (m, 3H), 7.37～7.34 (m, 2H), 6.98 (s, 1H), 5.12～4.92 (m, 2H), 1.33～1.04 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.4, 154.9, 146.5, 140.1, 133.0, 132.5, 129.8, 129.2, 128.0, 126.1, 124.9, 123.6, 122.4, 115.5, 72.6, 70.4, 21.9, 21.8, 21.7; HRMS (ESI$^+$) calcd for $C_{23}H_{25}N_4O_4S$ $[M+H]^+$ 453.1591, found 453.1587.

Diethyl 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aab**): Obtained as an orange solid in 90% yield. m.p. 140～141 ℃ (lit.[17] 141.7～142.3 ℃); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 7.78 (d, J=7.5 Hz, 2H), 7.62 (d, J=8.9 Hz, 1H), 7.44 (t, J=7.5 Hz, 2H), 7.36 (t, J=7.4 Hz, 1H), 7.29～7.26 (m, 1H), 6.89 (t, J=6.5 Hz, 1H), 6.59 (s, 1H), 4.21～4.18 (m, 4H), 1.27～1.11 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.8, 155.2, 143.1, 139.4, 132.8, 129.0, 128.4, 126.8, 125.9, 124.6, 118.4, 117.3, 112.5, 64.0, 62.2, 14.4, 14.3.

Di-*tert*-butyl 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)-hydrazine-1,2-dicarboxylate (**4aac**): Orange solid, 43% yield. m.p. 181～182 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.73 (s, 1H), 7.79 (d, J=7.3 Hz, 2H), 7.59 (d, J=8.8 Hz, 1H), 7.45 (t, J=7.5 Hz, 2H), 7.36 (t, J=7.0 Hz, 1H), 7.26～7.24 (m, 1H), 6.93～6.59 (m, 2H), 1.45～1.24 (m, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.7, 153.7, 142.8, 138.8, 133.2, 129.0, 128.2, 126.7, 125.6, 124.7, 119.3, 117.2, 112.3, 83.4, 82.1, 28.1, 27.8; HRMS (ESI$^+$) calcd for $C_{23}H_{29}N_4O_4$ $[M+H]^+$ 425.2183, found 425.2185.

Bis(2,2,2-trichloroethyl) 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aad**): White solid, 93% yield. m.p. 191～192 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.75～8.30 (m, 2H), 7.77～7.73 (m, 2H), 7.62 (d, J=9.0 Hz, 1H), 7.34～7.27 (m, 4H), 6.90 (t, J=6.5 Hz, 1H), 4.99～4.62 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.2, 153.6, 143.3, 140.5, 132.2, 128.9, 128.6, 127.1, 126.4, 124.6, 117.5, 117.3, 112.8, 94.4, 94.0, 76.0, 75.3; HRMS (ESI$^+$) calcd for $C_{19}H_{15}C_{l6}N_4O_4$ $[M+H]^+$ 572.9219, found 572.9216.

Dibenzyl 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aae**): Orange solid, 92% yield. m.p. 159～160 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.66 (s, 1H), 7.68 (d, J=6.8 Hz, 2H), 7.61 (d, J=8.7 Hz, 1H), 7.46～6.85 (m, 16H), 5.37～5.02 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.6, 155.1, 143.1, 139.7, 135.0, 134.8, 132.5, 128.9, 128.6, 128.5, 128.2, 126.7, 126.0, 124.6, 118.1, 117.3, 112.6, 69.4, 68.3; HRMS (ESI$^+$) calcd for $C_{29}H_{25}N_4O_4$ $[M+H]^+$ 493.1870, found 493.1872.

Bis(4-chlorobenzyl) 1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (**4aaf**): Orange solid, 95% yield. m.p. 171～173 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.63 (s, 1H), 7.66～7.59 (m, 4H), 7.31～6.97 (m, 12H), 6.85 (s, 1H), 5.29～4.96 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.5, 155.0, 143.1, 139.7, 134.4, 133.5, 133.3, 132.4, 129.5, 128.9, 128.8, 128.7, 128.5, 126.8, 126.1, 124.5, 117.8, 117.3, 112.7, 68.5, 67.3; HRMS (ESI$^+$) calcd for $C_{29}H_{23}Cl_2N_4O_4$ $[M+H]^+$ 561.1091, found 561.1094.

4.2.2 Typical procedure for the gram scale reaction

A 100 mL reaction tube was equipped with a magnetic stir bar and charged with 2-bromo-1-phenylethan-1-one (**1a**, 4 mmol, 0.792 g), pyridin-2-amine (**2a**, 8 mmol, 0.756 g), diisopropyl (*E*)-diazene-1,2-dicarboxylate (**3a**, 12 mmol, 2.426 g) and DCM (20 mL). The resulting mixture was stirred under air at 35 ℃ for 8 h. Upon completion, the solvent was removed under reduced pressure. Then the residue was purified by column chromatography on silica gel (20～300 mesh) using hexane-EtOAc as an eluent to afford the pure product **4aaa** (1.411 g, 89% yield).

Supporting Information Crystallography of product **4aaa**, ^{1}H NMR and ^{13}C NMR spectra of the products. The Supporting Information is available free of charge via the

Internet at http://sioc-journal.cn.

References

[1] (a) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888.
(b) Dyminska, L. *Bioorg. Med. Chem.* **2015**, *23*, 6087.

[2] (a) Kamal, A.; Reddy, J. S.; Ramaiah, M. J.; Dastagiri, D.; Bharathi, E. V.; Sagar, M. V. P.; Pushpavalli, S. N. C. V. L.; Ray, P.; Pal-Bhadra, M. *Med. Chem. Commun.* **2010**, *1*, 355.
(b) Kim, O.; Jeong, Y.; Lee, H.; Hong, S. S.; Hong, S. *J. Med. Chem.* **2011**, *54*, 2455.
(c) El-Sayed, W. M.; Hussin, W. A.; Al-Faiyz, Y. S.; Ismail, M. A. *Eur. J. Pharmacol.* **2013**, *715*, 212.

[3] Lacerda, R. B.; de Lima, C. K. F.; da Silva, L. L.; Romeiro, N. C.; Miranda, A. L.; Barreiro, E. J.; Fraga, C. A. *Bioorg. Med. Chem.* **2009**, *17*, 74.

[4] Kaminski, J. J.; Doweyko, A. M. *J. Med. Chem.* **1997**, *40*, 427.

[5] (a) AlTel, T. H.; Al-Qawasmeh, R. A.; Zaarour, R. *Eur. J. Med. Chem.* **2011**, *46*, 1874.
(b) Shukla, N. M.; Salunke, D. B.; Yoo, E.; Mutz, C. A.; Balakrishna, R.; David, S. A. *Bioorg. Med. Chem.* **2012**, *20*, 5850.

[6] Rival, Y.; Grassy, G.; Taudon, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, *26*, 13.

[7] (a) Lhassani, M.; Chavignon, O.; Chezal, J. M.; Teulade, J. C.; Chapat, J. P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271.
(b) Gudmundsson, K. S.; Williams, J. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2003**, *46*, 1449.
(c) Gudmundsson, K. S.; Johns, B. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2735.
(d) Véron, J. B.; Allouchi, H.; Enguehard-Gueiffier, C.; Snoeck, R.; Andrei, G.; De Clercq, E.; Gueiffier, A. *Bioorg. Med. Chem.* **2008**, *16*, 9536.

[8] (a) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1965**, *8*, 305.
(b) Belohlavek, D.; Malfertheiner, P. *Scand. J. Gastroenterol. Suppl.* **1979**, *54*, 44.
(c) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol.* **1990**, *46*, 61.
(d) Uemura, Y.; Tanaka, S.; Ida, S.; Yuzuriha, T. *J. Pharm. Pharmacol.* **1993**, *45*, 1077.
(e) Pellón, R.; Ruíz, A.; Lamas, E.; Rodríguez, C. *Behav. Pharmacol.* **2007**, *18*, 81.
(f) Wafford, K. A.; van Niel, M. B.; Ma, Q. P.; Horridge, E.; Herd, M. B.; Peden, D. R.; Belelli, D.; Lambert, J. J. *Neuropharmacology* **2009**, *56*, 182.
(g) Du, B.; Shan, A.; Zhang, Y.; Zhong, X.; Chen, D.; Cai, K. *Am. J. Med. Sci.* **2014**, *347*, 178.

[9] For selected examples of C-C bond formation: (a) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979.
(b) Fu, H. Y.; Chen, L.; Doucet, H. J. *J. Org. Chem.* **2012**, *77*, 4473.
(c) Choy, P. Y.; Luk, K. C.; Wu, Y. N.; So, C. M.; Wang, L. L.; Kwong, F. Y. *J. Org. Chem.* **2015**, *80*, 1457.
(d) Cao, H.; Lei, S.; Li, N. Y.; Chen, L. B.; Liu, J. Y.; Cai, H. Y.; Qiu, S. X.; Tan, J. W. *Chem. Commun.* **2015**, *51*, 1823.
(e) Monir, K.; Bagdi, A. K.; Ghosh, M.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 1332.
(f) Liu, Q. X.; He, B. Y.; Qian, P. C.; Shao, L. X. *Org. Biomol. Chem.* **2017**, *15*, 1151.
(g) Xue, C.; Han, J.; Zhao, M.; Wang, L. *Org. Lett.* **2019**, *21*, 4402.
(h) Li, X.; Wang, S.; Zang, J.; Liu, M.; Jiang, G.; Ji, F. *Org. Biomol. Chem.* **2020**, *18*, 9100.
(i) Gernet, A.; Sevrain, N.; Volle, J.-N.; Ayad, T.; Pirat, J.-L.; Virieux, D. *J. Org. Chem.* **2020**, *85*, 14730.

[10] For selected examples of C—N bond formation: (a) Mondal, S.; Samanta, S.; Jana, S.; Hajra, A. *J. Org. Chem.* **2017**, *82*, 4504.
(b) Samanta, S.; Ravi, C.; Rao, S. N.; Joshi, A.; Adimurthy, S. *Org. Biomol. Chem.* **2017**, *15*, 9590.
(c) Liu, K.; Wu, J.; Deng, Y.; Song, C.; Song, W.; Lei, A. *ChemElectroChem* **2019**, *6*, 4173.
(d) Saba, S.; Dos Santos, C. R.; Zavarise, B. R.; Naujorks, A. A. S.; Franco, M. S.; Schneider, A. R.; Scheide, M. R.; Affeldt, R. F.; Rafique, J.; Braga, A. L. *Chem.-Eur. J.* **2020**, *26*, 4461.

[11] For selected examples of C—O bond formation: (a) Kibriya, G.; Samanta, S.; Jana, S.; Mondal, S.; Hajra, A. *J. Org. Chem.* **2017**, *82*, 13722.
(b) Yadav, R. K.; Kumar, Y.; Chaudhary, S. *ChemistrySelect* **2020**, *5*, 9235.
(c) Mo, Z.-Y.; Wang, X.-Y.; Zhang, Y.-Z.; Yang, L.; Tang, H.-T.; Pan, Y.-M. *Org. Biomol. Chem.* **2020**, *18*, 3832.
(d) Xu, X.; Chen, D.; Wang, Z. *Chin. J. Org. Chem.* **2019**, *39*, 3338 (in Chinese).
(徐鑫明, 陈德茂, 王祖利, 有机化学, **2019**, *39*, 3338.)

[12] For selected examples of C—S bond formation: (a) Matheis, C.; Wagner, V.; Goossen, L. J. *Chem.-Eur. J.* **2016**, *22*, 79.
(b) Siddaraju, Y.; Prabhu, K. R. *J. Org. Chem.* **2016**, *81*, 7838.
(c) Iida, H.; Demizu, R.; Ohkado, R. *J. Org. Chem.* **2018**, *83*, 12291.
(d) Rahaman, R.; Das, S.; Barman, P. *Green Chem.* **2018**, *20*, 141.
(e) Wen, J.; Niu, C.; Yan, K.; Cheng, X.; Gong, R.; Li, M.; Guo, Y.; Yang, J.; Wang, H. *Green Chem.* **2020**, *22*, 1129.
(f) Han, L.; Huang, M.; Li, Y.; Zhang, J.; Zhu, Y.; Kim, J. K.; Wu, Y. *Org. Chem. Front.* **2021**, *8*, 3110.
(g) Singh, D.; Chowdhury, S. R.; Pramanik, S.; Maity, S. *Tetrahedron* **2021**, *88*, 132125.
(h) Zeng, F.-L.; Zhu, H.-L.; Chen, X.-L.; Qu, L.-B.; Yu, B. *Green Chem.* **2021**, *23*, 3677.

[13] For selected examples of C—P bond formation: (a) Yadav, M.; Dara, S.; Saikam, V.; Kumar, M.; Aithagani, S. K.; Paul, S.; Vishwakarma, R. A.; Singh, P. P. *Eur. J. Org. Chem.* **2015**, *2015*, 6526.
(b) Yuan, Y.; Qiao, J.; Cao, Y.; Tang, J.; Wang, M.; Ke, G.; Lu, Y.; Liu, X.; Lei, A. *Chem. Commun.* **2019**, *55*, 4230.
(c) Tashrifi, Z.; Mohammadi-Khanaposhtani, M.; Larijani, B.; Mahdavi, M. *Eur. J. Org. Chem.* **2020**, *2020*, 269.
(d) Bagdi, A. K.; Hajra, A. *Org. Biomol. Chem.* **2020**, *18*, 2611.
(e) Gao, F.; Sun, K.; Chen, X.-L.; Shi, T.; Li, X.-Y.; Qu, L.-B.; Zhao, Y.-F.; Yu, B. *J. Org. Chem.* **2020**, *85*, 14744.

[14] For selected examples of C-X bond formation: (a) Liu, P.; Gao, Y.; Gu, W.; Shen, Z.; Sun, P. *J. Org. Chem.* **2015**, *80*, 11559.
(b) Semwal, R.; Ravi, C.; Kumar, R.; Meena, R.; Adimurthy, S. *J. Org. Chem.* **2019**, *84*, 792.
(c) Neto, J. S. S.; Balaguez, R. A.; Franco, M. S.; de SaMachado, V. C.; Saba, S.; Rafique, J.; Galetto, F. Z.; Braga, A. L. *Green Chem.* **2020**, *22*, 3410.
(d) Kalari, S.; Balasubramanian, S.; Rode, H. B. *Tetrahedron Lett.* **2021**, *71*, 153028.

[15] For selected examples of C—Se bond formation: (a) Rafique, J.; Saba, S.; Franco, M. S.; Bettanin, L.; Schneider, A. R.; Silva, L. T.; Braga, A. L. *Chem.-Eur. J.* **2018**, *24*, 4173.
(b) Guo, T.; Wei, X.-N.; Liu, Y.; Zhang, P.-K.; Zhao, Y.-H. *Org. Chem. Front.* **2019**, *6*, 1414.
(c) Kim, Y. J.; Kim, D. Y. *Tetrahedron Lett.* **2019**, *60*, 739.
(d) Zhu, Y.-S.; Xue, Y.; Liu, W.; Zhu, X.; Hao, X.-Q.; Song, M.-P. *J. Org. Chem.* **2020**, *85*, 9106.

[16] Wang, Y.; Frett, B.; McConnell, N.; Li, H.-Y. *Org. Biomol. Chem.* **2015**, *13*, 2958.

[17] Jiao, J.; Xu, L.; Zheng, W.; Xiong, P.; Hu, M.-L.; Tang, R.-Y. *Synthesis* **2017**, *49*, 1839.

[18] (a) Volla, C. M.; Atodiresei, I.; Rueping, M. *Chem. Rev*. **2014**, *114*, 2390.
(b) Chen, D.-F.; Han, Z.-Y.; Zhou, X.-L.; Gong, L.-Z. *Acc. Chem. Res*. **2014**, *47*, 2365.
(c) Zhu, S.; Zhao, X.; Li, H.; Chu, L. *Chem. Soc. Rev.* **2021**, *50*,

10836.
(d) Flores-Reyes, J. C.; Islas-Jácome, A.; González-Zamora, E. *Org. Chem. Front.* **2021**, *8*, 5460.
(e) Pan, J.; Wu, J.; Wu, F. *Chin. J. Org. Chem.* **2021**, *41*, 983 (in Chinese).
(潘军, 吴晶晶, 吴范宏, 有机化学, **2021**, *41*, 983.)
[19] (a) D'Souza, D. M.; Mueller, T. J. J. *Chem. Soc. Rev*. **2007**, *36*, 1095.
(b) Xiao, Y.; Lin, J.-B.; Zhao, Y.-N.; Liu, J.-Y.; Xu, P.-F. *Org. Lett.* **2016**, *18*, 6276.
(c) Fan, W.; Ma, S. *Angew. Chem.*, *Int. Ed*. **2014**, *53*, 14542.
(d) Yang, Q.; Yan, X.-T.; Feng, C.-T.; Chen, D.-X.; Yan, Z.-Z.; Xu, K. *Org. Chem. Front.* **2021**, *8*, 6384.
(e) Wang, X.; Chen, P.; Zhi, S.; Hu, H.; Kan, Y.; Tang, G.; Zhang, Z. *Chin. J. Org. Chem.* **2021**, *41*, 1241 (in Chinese).
(王翔, 陈平, 支三军, 胡华友, 阚玉和, 唐果东, 张载超, 有机化学, **2021**, *41*, 1241.)
(f) Ma, W.; Han, Y.; Sun, J.; Yan, C. *Chin. J. Org. Chem.* **2021**, *41*, 3180 (in Chinese).
(马蔚青, 韩莹, 孙晶, 颜朝国, 有机化学, **2021**, *41*, 3180.)
[20] (a) Ge, W.; Zhu, X.; Wei, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 6015.
(b) Mohan, D. C.; Rao, S. N.; Ravi, C.; Adimurthy, S. *Asian J. Org. Chem.* **2014**, *3*, 609.
(c) Kundu, S.; Basu, B. *RSC Adv.* **2015**, *5*, 50178.
(d) Reddy, R. J.; Shankar, A.; Kumari, A. H. *Asian J. Org. Chem.* **2019**, *8*, 2269.
[21] (a) Qiao, H.; Sun, S.; Yang, F.; Zhu, Y.; Zhu, W.; Dong, Y.; Wu, Y.; Kong, X.; Jiang, L.; Wu, Y. *Org. Lett.* **2015**, *17*, 6086.
(b) Qiao, H.; Sun, S.; Yang, F.; Zhu, Y.; Kang, J.; Wu, Y.; Wu, Y. *Adv. Synth. Catal.* **2017**, *359*, 1976.
(c) Qiao, H.; Sun, S.; Zhang, Y.; Zhu, H.; Yu, X.; Yang, F.; Wu, Y.; Li, Z.; Wu, Y. *Org. Chem. Front.* **2017**, *4*, 1981.
(d) Qiao, H.; Sun, S.; Kang, J.; Yang, F.; Wu, Y.; Wu, Y. *Chin. J. Org. Chem.* **2018**, *38*, 86 (in Chinese).
(乔辉杰, 孙素颜, 康建勋, 杨帆, 吴豫生, 吴养洁, 有机化学, **2018**, *38*, 86.)
[22] Jian, W.-Q.; Wang, H.-B.; Du, K.-S.; Zhong, W.-Q.; Huang, J.-M. *ChemElectroChem* **2019**, *6*, 2733.
[23] Vieira, B. M.; Padilha, N.; Nascimento, N. M.; Perin, G.; Alves, D.; Schumacher, R. F.; Lenardão, E. J. *ARKIVOC* **2019**, *ii*, 6.
[24] Kandimalla, S. R.; Sabitha, G. *RSC Adv.* **2016**, *6*, 67086.

(Zhao, C.)

