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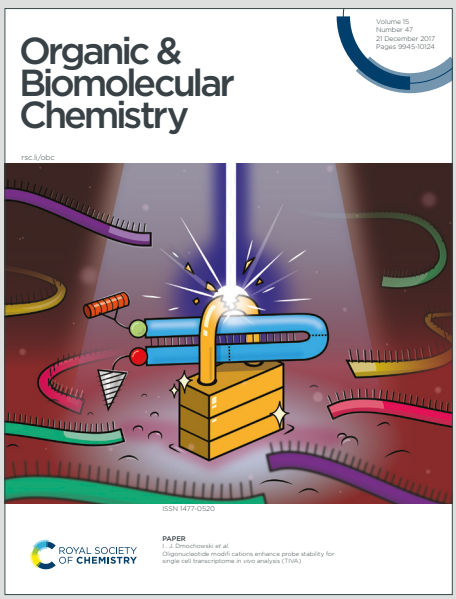

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ARTICLE

Substituent-controlled Chemoselective Synthesis of Multi-substituted Pyridones via One-pot Three-component Cascade Reaction†

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An efficient and concise one-pot strategy for the synthesis of multisubstituted pyridones via one-pot three-component cascade reaction catalyzed by Cs_2CO_3 under solvent-free conditions has been developed. The substituent-controlled chemoselective cycloaddition process involved steps including a Michael addition/ethanol elimination/intermolecular cyclization sequence by utilizing anilines, diethyl acetylenedicarboxylate, and diethyl ethoxymethylenemalonate. In doing so, various 2-pyridone and 4-pyridone species (41 examples) could be obtained in good to excellent yields.

Introduction

The pyridone core as a unique heterocyclic unit can be commonly found in a variety of natural products and biologically active molecules. In particular, pyridone-containing derivatives often exhibit diverse biological activities such as antifungal, antibacterial, insecticidal activities, antiviral, anti-inflammatory, and anti-HIV activities etc. (Figure 1, a).[1] For the past few decades, the pyridone keleton has attracted much attention in the scientific community and a range of different synthetic routes have been studied to obtain these molecules.[2] Until now, synthetic strategies for the construction of pyridone often involved routes such as the following: traditional Guareschi-Thorpe reactions (Route 1),[3] 1,4-addition of malonic esters with alkynyl imines (Route 2) or 1,4-addition of 2-(phenylsulfinyl)acetamide to α,β-unsaturated ketones followed by cyclization/sulfoxide elimination (Route 3),[4] intramolecular cyclization of *N*-(2-furanylmethyl)alkynamides (Route 4),[5] and our recent work involving a four-component cascade reaction (Route 5).[6] However, despite these considerable advances, the aforementioned methods frequently require transition-metal catalysis (e. g. Pd, Cu)[5], strong bases (e. g. NaH)[4a] and toxic as well as hazardous reagents[3]. Exploring new, effective, and practical protocols to access pyridones and their derivatives remains a critical, albeit unmet, synthetic challenge.[7]

The one-pot multicomponent cascade reaction represents one of the most powerful approaches for the preparation of heterocyclic compounds and can be used to access multiple bonds-formation and avoid multi-steps purification procedures.[8] Recently, our group has developed a variety of efficient and convenient strategies to construct functional organic molecules,[9] including one-pot multicomponent cascade reactions (MCRs).[6,10] Based on enaminones studied in Wan's work,[11] we envisioned that this compound class may also react with diethyl ethoxymethylenemalonateas or diethyl acetylenedicarboxylate to result in the formation of multiple bonds in one-pot. Herein, we report a substituent-controlled, one-pot three-component procedure for the construction of multi-substituted pyridones by utilizing aniline, diethyl acetylenedicarboxylate and diethyl ethoxymethylenemalonate as catalyzed by an inorganic base under solvent-free conditions.

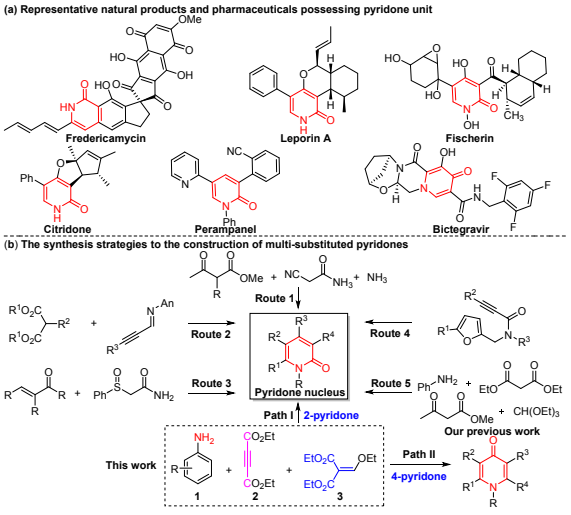

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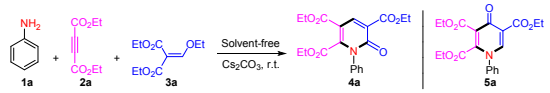
Figure 1. Representative biologically active molecules and synthetic strategies

Results and discussion

Initially, we carried out our study by investigating the model reaction involving aniline **1a** (1.0 mmol), diethyl acetylenedicarboxylate **2a** (1.0 mmol), and diethyl ethoxymethylenemalonate **3a** (1.0 mmol) catalyzed by Cs_2CO_3 under solvent-free conditions at room temperature. Importantly, the reaction proceeded smoothly, providing 2-pyridone **4a** in 70% yield. However, 4-pyridone **5a** could not be detected (Table 1, entry 1). The relative configuration of compound **4a** was determined by X-ray crystal analysis as shown in Table 2 (CCDC 1965346). Following these promising results, other base-catalysts, including strong inorganic bases (KOH, NaOH) were screened and product **4a** could be obtained in 20-35% yields (Table 1, entries 2-6). Notably, the reaction could not be carried out in the absence of any base catalyst (Table 1, entry 7). In addition, a series of solvents were screened, and solvent-free conditions proved to be the most suitable (Table 1, entries 8-13). Subsequently, different raw material ratios were investigated. Compounds **1a** and **2a** (**1a**:**2a**:**3a** = 1.2:1.2:1.0) used in excess proved to be beneficial for the reaction progress (Table 1, entries 14-16). Additionally, an increase in temperature adversely affected the product yields (Table 1, entry 17). Encouraged by these experimental results, we further examined the reactions with different catalyst loadings (Table 1, entries 18-22). When the catalyst loading was decreased from 50 to 10 mol%, the yield of the product decreased obviously. Remarkably, 4-pyridone **5a** could not be detected in all cases. Ultimately, the optimal reaction conditions were as follows: aniline **1a** (1.2 mmol), diethyl acetylenedicarboxylate **2a** (1.2mmol), diethyl ethoxymethylenemalonate **3a** (1.0 mmol) catalyzed by Cs_2CO_3 (50 mol%) under solvent-free conditions at room temperature (Table 1, entry 16).

Table 1. Optimization of the reaction conditions[a]

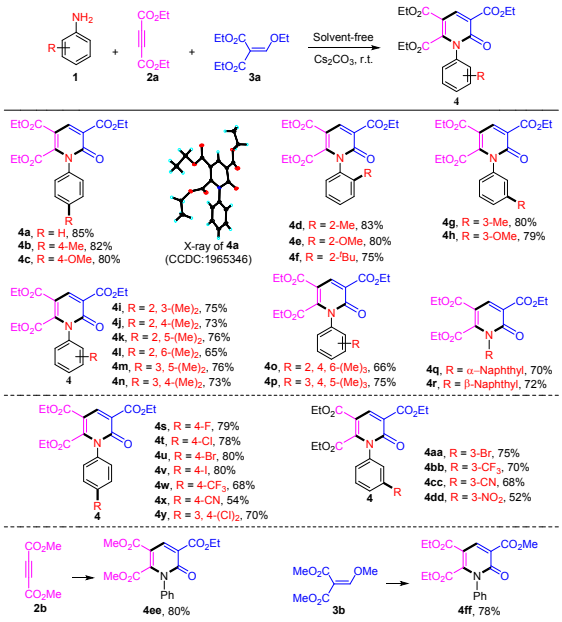


Entry	Catalyst	Solvent	t/h	yield%[b]
1	Cs_2CO_3	-	5	70
2	K_2CO_3	-	5	20
3	KOH	-	5	40
4	NaOH	-	5	35
5	Et_3N	-	5	-
6	DABCO	-	5	-
7	-	-	5	-
8	Cs_2CO_3	CH_3CN	5	32
9	Cs_2CO_3	EtOH	5	34
10	Cs_2CO_3	THF	5	-
11	Cs_2CO_3	Toluene	5	-
12	Cs_2CO_3	$CHCl_3$	5	-
13	Cs_2CO_3	H_2O	5	-
14[c]	Cs_2CO_3	-	5	76
15[d]	Cs_2CO_3	-	4	82
16[e]	**Cs_2CO_3**	-	**4**	**85**
17[f]	Cs_2CO_3	-	4	58
18[g]	Cs_2CO_3	-	5	80
19[h]	Cs_2CO_3	-	5	83
20[i]	Cs_2CO_3	-	5	75
21[j]	Cs_2CO_3	-	5	40
22[k]	Cs_2CO_3	-	5	trace

[a]The reaction was performed: **1a**, **2a** and **3a** in one-pot, catalyst (50 mol%). [b]Isolated yield based on **3a**. [c]The molar ratio of **1a**:**2a**:**3a** = 1.1:1.1:1.0. [d]The molar ratio of **1a**:**2a**:**3a** = 1.1:1.2:1.0. [e]The molar ratio of **1a**:**2a**:**3a** = 1.2:1.2:1.0. [f]The reaction temperature was 40 °C. [g]Cs_2CO_3 loading (60 mol%). [h]Cs_2CO_3 loading (40 mol%). [i]Cs_2CO_3 loading (30 mol%). [j]Cs_2CO_3 loading (20 mol%). [k]Cs_2CO_3 loading (10 mol%).

With the optimized reaction conditions in hand, we then shifted our focus to the investigation of the scope and generality of this one-pot, three-component cascade transformation. As shown in Table 2, various substituted anilines were screened. For anilines, electron-donating substituents (Me, OMe, ^{t}Bu) in *para*-, *ortho*-, or *meta*-positions of the aromatic ring were demonstrated to provide the corresponding 2-pyridones in yields ranging between 75 and 83% (**4b**-**4h**). A range of disubstituted anilines were tested and delivered compounds **4i**-**4n** in yields ranging between 65 and 76%, respectively. Notably, trisubstituted anilines with sterically hindered groups also proved to be suitable substrates for this reaction type (**4o**-**4p**). In addition, α-naphthyl- and β-naphthylamines were compatible with this cascade transformation type (**4q**-**4r**). Subsequently, electron-withdrawing (F, Cl, Br, I, CN, CF_3) groups in *para*-position of the aromatic aniline ring were investigated, resulting in the desired products **4s**-**4y** obtained in yields of 54–80%. An electron-withdrawing group in *meta*-position of the anilines could provide the corresponding 2-pyridones **4aa**-**4dd** in good yields. Additionally, dimethyl acetylenedicarboxylate **2b** as well as dimethyl 2-(methoxymethylene)malonate **3b** as the substrates in this transformation could also provide the corresponding 2-pyridone species **4ee** and **4ff** with satisfactory yields, respectively.

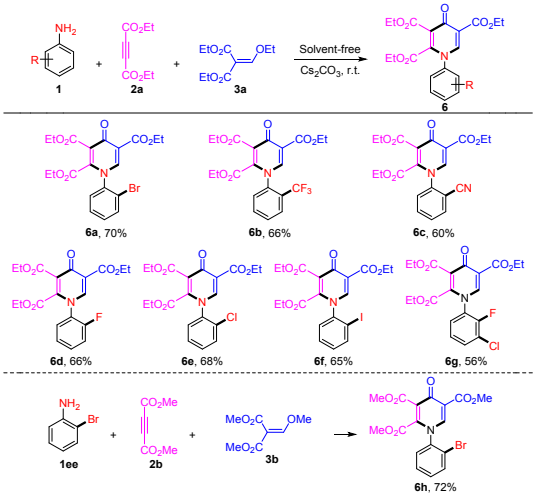
Table 2. Substrate scope[a]



[a]All reactions were performed with **1**, **2** and **3** in one-pot, Cs_2CO_3 (50 mol%), isolated yield based on **3**, the molar ratio of **1**:**2**:**3** = 1.2:1.2:1.0.

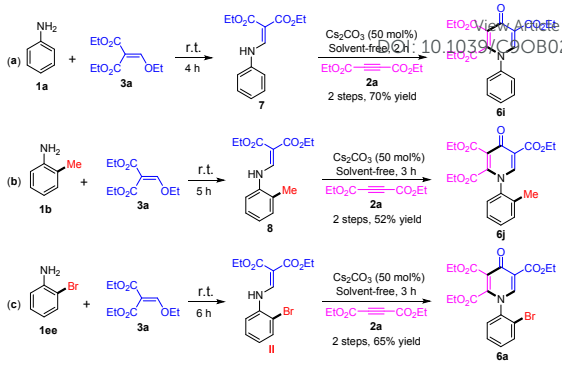
Interestingly, electron-withdrawing substituents (F, Cl, Br, I, CF_3, CN) in *ortho*-position of the aniline ring could produce the corresponding 4-pyridone species with good yields of 56-70% (**6a**-**6f**). Moreover, aniline bearing dielectron-withdrawing substituents (2-F-3-Cl) could provide the desired product **6g** with good yield. Dimethyl acetylenedicarboxylate **2b** and dimethyl 2-(methoxymethylene)malonate **3b** as substrates were reacted with 2-bromo aniline and underwent this cascade reaction, producing the 4-pyridone **6h** with 72% yield (Table 3). However, 2-nitroaniline could not be used to produce the corresponding 4-pyridone, only intermediate **IV** was obtained (details in Supporting Information).

Table 3. Substrate scope[a]



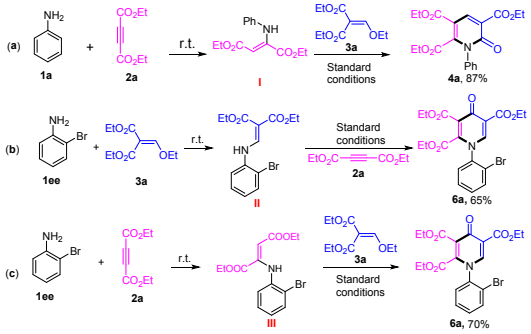
[a]All reactions were performed with **1, 2 and 3** in one-pot, Cs_2CO_3 (50 mol%), isolated yield based on **3**, the molar ratio of **1**:**2**:**3** = 1.2:1.2:1.0.

To further investigate this one-pot three-component cascade reaction process to form 4-pyridones, the reagent addition order was investigated (Scheme 1, a, b, c). Initially, the substitution reaction of aniline **1** (**1a**, **1b**, **1ee**) with compound **3a** led to the formation of intermediates **7**, **8**, and **II** under solvent-free conditions at room temperature for 4-6 h. Then, the intermediates **7**, **8**, **II** were individually reacted with compound **2a** via aza-Michael addition/ethanol elimination/intermolecular cyclization sequence, providing the 4-pyridones **6a**, **6i**, **6j** with good yields, respectively. In addition, the corresponding 2-pyridones could not be detected. Notably, the overall efficiency of this one-pot cascade reaction was demonstrated to be improved over that of a two-step reaction process.



Scheme 1. The reagents addition order was investigated of the cascade reaction

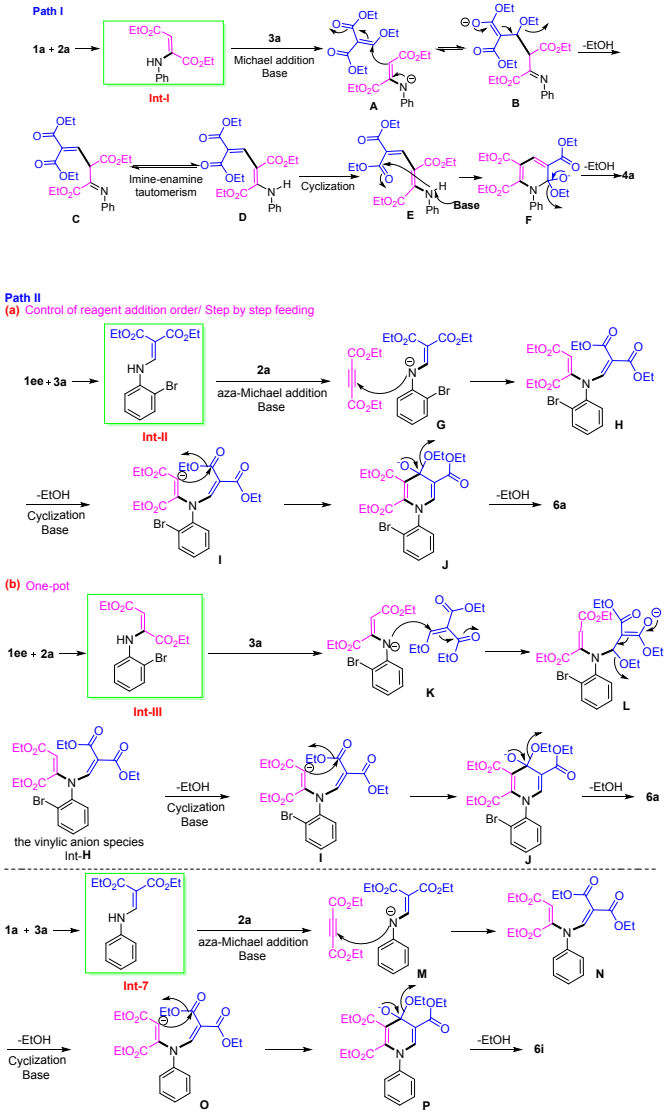
Several control experiments were conducted to investigate the two different cyclization routes (Scheme 2). Firstly, enamine **I** was prepared from reaction of compound **1a** with **2a**, which was then reacted with compound **3a** under standard conditions, providing the expected 2-pyridone **4a** in 87% yield (Scheme 2, a). In addition, the intermediate enamine **II** could be obtained via substitution reaction of 2-bromo aniline **1ee** with compound **3a**. Ultimately, 4-pyridone **6a** was formed via reaction of intermediate **II** with compound **2a** (Scheme 2, b). Another control experiment was carried out between 2-bromo aniline **1ee** and compound **2a**. Then, intermediate **III** was reacted with compound **3a** to provide compound **6a** with almost identical yield (Scheme 2, c).



Scheme 2. Control experiments to investigate the cyclization process

Based on the aforementioned experimental results and related literatures,[11b,12] a plausible reaction mechanism involving a substituent-controlled one-pot cascade process could be depicted as shown in Scheme 3. For 2-pyridone **4a**, initially, Int-**I** was generated after reaction of compound **1a** with **2a**, which then underwent Michael reaction with compound **3a**. Then, an alcohol elimination process took place to provide intermediate **D** (tautomer of **C**). Finally, product **4a** formed after cyclization/ethanol elimination reaction (Scheme 3, Path **I**). In addition, there are two possible routes for the formation of 4-pyridone **6a**. For one of the possible routes, Int-**II** was formed via substitution reaction of 2-bromo aniline **1ee** with compound **3a**, which then underwent aza-Michael reaction with compound **2a** to generate the vinylic anion species corresponding to intermediate **H**. Ultimately, the 4-pyridone **6a** was constructed after intramolecular attack to the ester carbonyl group and subsequent ethanol elimination reaction (Scheme 3, Path **II, a**). For another possible route, Int-**III** was generated after reaction of compound **1ee** with **2a**, which then underwent aza-Michael reaction with compound **3a** to generate the intermediate **H**. Finally, the 4-pyridone **6a** was formed after

intramolecular attack to the ester carbonyl group and subsequent ethanol elimination reaction (Scheme 3, Path **II, b**). For the 4-pyridone **6i**, the path is similar to a Path **II** (**a**) (Scheme 3).



Scheme 3. The proposed mechanism

Conclusions

In summary, we have successfully developed an efficient and practical one-pot three-component cascade reaction catalyzed by Cs_2CO_3 under solvent-free conditions. The transformation involved steps including Michael addition/ethanol elimination/ intermolecular cyclization utilizing anilines, diethyl acetylenedicarboxylate and diethyl ethoxymethylenemalonate. This chemoselective, one-pot, three-component cascade reaction process was controlled by substitution of anilines, providing the multisubstituted 2-pyridones and 4-pyridones in good to excellent yields. Further studies on the applicability of the multisubstituted pyridones obtained through this process for the preparation of new potent bioactive molecules are currently ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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Notes and reference

1 For selected recent reports, see: (a) J. Diesel, A. M. Finogenova and N. Cramer, *J. Am. Chem. Soc*., 2018, **140**, 4489; (b) V. Nagaraju, D. Purnachander, N. S. V. M. R. Mangina, S. Suresh, B. Sridhar and G. V. Karunakar, *Org. Biomol. Chem*., 2015, **13**, 3011; (c) H. J. Jessen and K. Gademann, *Nat. Prod. Rep*., 2010, **27**, 1168; (d) R. M. Wilson and S. J. Danishefsky, *Acc. Chem. Res*., 2006, **39**, 539; (e) C. Tohda, T. Kuboyama and K. Komatsu, *Neurosignals*, 2005, **14**, 34; (f) P. S. Dragovich, T. J. Prins, R. Zhou, E. L. Brown, F. C. Maldonado, S. A. Fuhrman, L. S. Zalman, T. Tuntland, C. A. Lee, A. K. Patick, D. A. Matthews, T. F. Hendrickson, M. B. Kosa, B. Liu, M. R. Batugo, J. P. Gleeson, S. K. Sakata, L. Chen, M. C. Guzman, J. W. Meador, R. A. Ferre and S. T. Worland, *J. Med. Chem*., 2002, **45**, 1607; (g) E. Lo Presti, R. Boggia, A. Feltrin, G. Menozzi, P. Dorigo and L. Mosti, *Farmaco*, 1999, **54**, 465; (h) A. G. E. Amr and M. M. Abdulla, *Bioorg. Med. Chem*., 2006, **14**, 4341; (i) M. T. Cocco, C. Congiu and V. Onnis, *Eur. J. Med. Chem*., 2000, **35**, 545; (j) J. J. Kaminski, A. M. Doweyko, *J. Med. Chem*., 1997, **40**, 427.

2 (a) J. Kim, H. Kim and S. B. Park, *J. Am. Chem. Soc*., 2014, **136**, 14629; (b) M. Torres, S. Gil and M. Parra, *Curr. Org. Chem*., 2005, **9**, 1757; (c) K. Hirano and and M. Miura, *Chem. Sci*., 2018, **9**, 22; (d) A. M. Prendergast and G. P. McGlacken, *Eur. J. Org. Chem*., 2018, **44**, 6068.

3 H. Baron, F. G. P. Remfry and J. F. Thorpe, *J. Chem. Soc. Trans*., 1904, **85**, 1726.

4 (a) I. Hachiya, K. Ogura and M. Shimizu, *Org. Lett*., 2002, **4**, 2755; (b) M. Fujii, T. Nishimura, T. Koshiba, S. Yokoshima and T. Fukuyama, *Org. Lett*., 2013, **15**, 232.

5 Y. Yang, C. Fei, K. Wang, B. Liu, D. Jiang and B. Yin, *Org. Lett*., 2018, **20**, 2273.

6 H. R. Bai, R. R. Sun, S. T. Liu, L. J. Yang, X. B. Chen and C. Huang, *J. Org. Chem*., 2018, **83**, 12535.

7 N. Poomathi, P. T. Perumal and S. Ramakrishna, *Green Chem*., 2017, **19**, 2524.

8 (a) B. Li, B. Zhang, X. Zhang and X. Fan, *J. Org. Chem*., 2016, **81**, 9530; (b) S. Rajkumar, K. Shankland, J. M. Goodman and J. A. Cobb, *Org. Lett*., 2013, **15**, 1386; (c) L. Fan, J. Liu, L. Bai, Y. Wang and X. Luan, *Angew. Chem. Int. Ed*., 2017, **56**, 14257; (d) H. Jiang, R. Mai, H. Cao, Q. Zhu and X. Liu, *Org. Biomol. Chem*., 2009, **7**, 4943; (e) J. P. Wan, Y. Lin, Q. Huang and Y. Liu, *J. Org. Chem*., 2014, **79**, 7232; (f) X. Feng, Q. Wang, W. Lin, G. L. Dou, Z. B. Huang and D. Q. Shi, *Org. Lett*., 2013, **15**, 2542; (g) C. L. Ji, Y. Pan, F. Z. Geng, W. J. Hao, S. J. Tu and B. Jiang, *Org. Chem. Front*., 2019, **6**, 474.

9 (a) T. Liu, J. Liu, S. Xia, J. Meng, X. Shen, X. Zhu, W. Chen, C. Sun and F. Cheng, *ACS Omega*, 2018, **3**, 1409; (b) T. Liu, J. Liu, X. Shen, J. Xu, B. Nian, N. He, S. Zeng and F. Cheng, *Synthesis*, 2019, **51**, 1365; (c) T. Liu, Y. Zhang, R. Yu and F. Cheng, *Synthesis*, 2020, **52**, 253; (d) T. Liu, Y. Li, F. Cheng, X. Shen, J. Liu and J. Lin, *Green Chem*., 2019, **21**, 3536.

10 (a) H. R. Bai, F. J. Liu, X. J. Wang, P. Wang and C. Huang, *ACS*

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DOI: 10.1039/C9OB02456E

Omega, 2018, **3**, 11233; (b) H. R. Bai, R. R. Sun, X. B. Chen, L. J. Yang and C. Huang, *ChemistrySelect*, 2018, **3**, 4635; (c) R. R. Sun, J. H. Guo, C. Yang, L. J. Yang and C. Huang, *Curr. Org. Synth.*, 2018, **15**, 237; (d) H. M. Fu, H. B. Wang, L. J. Yang, W. R. Yang and C. Huang, *Heterocycles*, 2018, **96**, 311; (e) X. B. Chen, X. Q. Wang, J. N. Song, Q. L. Yang, C. Huang and W. Liu, *Org. Biomol. Chem.*, 2017, **15**, 3611; (f) C. Huang, J. H. Guo, H. M. Fu, M. L. Yuan and L. J. Yang, *Tetrahedron Lett.*, 2015, **56**, 3777; (g) C. Huang, Y. Q. Yin, J. H. Guo, J. Wang, B. M. Fan and L. J. Yang, *RSC Adv.*, 2014, **4**, 10188.

11 (a) J. P. Wan, Y. Jing, C. Hu and S. Sheng, *J. Org. Chem.*, 2016, **81**, 6826; (b) J. P. Wan, Y. Lin, Y. Jing, M. Xu, Y. Liu, *Tetrahedron*, 2014, **70**, 7874.

12 (a) B. Jiang, Q. Ye, W. Fan, S. L. Wang, S. J. Tu and G. Li, *Chem. Comm.*, 2014, **50**, 6108; (b) X. Zhang, X. Xu, G. Chen and W. Yi, *Org. Lett.*, 2016, **18**, 4864; (c) Y. Li, X. Cao, Y. Liu and J. P. Wan, *Org. Biomol. Chem.*, 2017, **15**, 9585; (d) X. Xu, Y. Yang, X. Zhang and W. Yi, *Org. Lett.*, 2018, **20**, 566; (e) G. Zhu, Z. Yi, J. Zhou, Z. Chen, P. Guo, Y. Huang, J. Chen, H. Song and W. Yi, *ACS Omega*, 2018, **3**, 13494; (f) D. Ba, Y. Chen, W. Lv, S. Wen and G. Cheng, *Org. Lett.*, 2019, **21**, 8603; (g) Q. Luo, R. Huang, Q. Xiao, Y. Yao, J. Lin and S. J. Yan, *J. Org. Chem.*, 2019, **84**, 1999.

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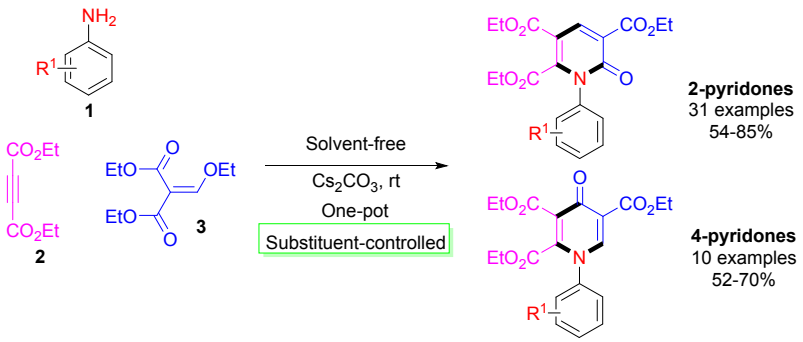

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