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A MILD AND CONVENIENT ONE-POT SYNTHESIS OF 4,6-DIARYL-3-AMINOISOXAZOLO[3,4-*b*]PYRIDINES

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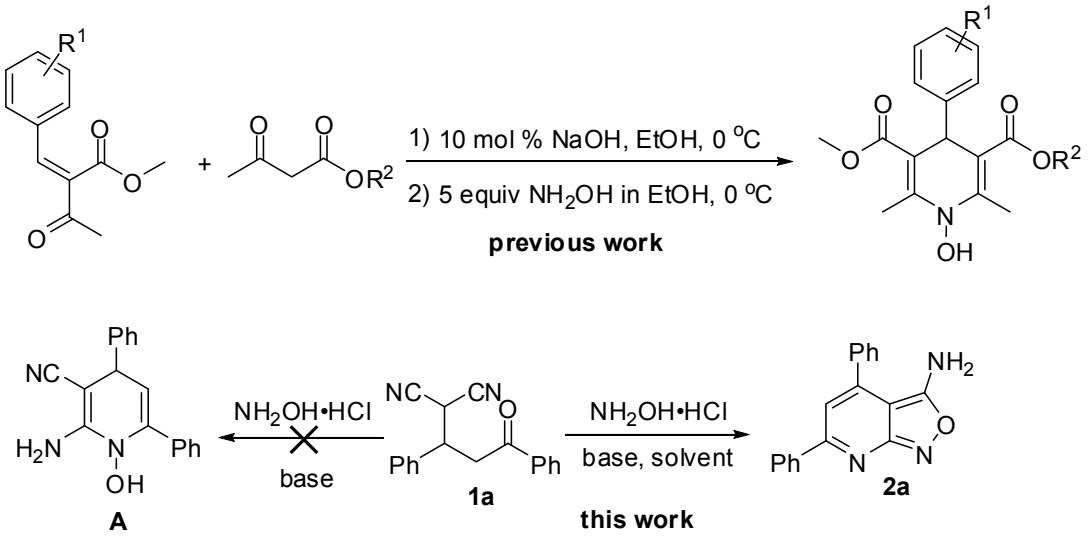
Abstract - We have developed a convenient method for the synthesis of a series of new 4,6-diaryl-3-aminoisoxazolo[3,4-*b*]pyridines through one-pot reaction starting from the easily available chalcones, malononitrile, and hydroxylamine. This class of compounds might have potential pharmacological activities in medicinal chemistry.

Isoxazole-fused pyridine is one of the important heterocyclic units, which has been widely used as a key building block for pharmaceutical agents.[1-4] However, research on the construction of such skeletons with an isoxazole ring fusing to pyridine is seldom reported. Isoxazolopyridine is commonly constructed from either a pyridine[5-7] or an isoxazole precursor.[8,9] Sometimes, isoxazolopyridine can also be obtained by the flash vacuum pyrolysis of 8-acetyltetrazolo[1,5-*a*]pyridine[10] or from the reaction of potassium cyanoacetohydroxamate with 2-arylhydrazono-3-oxobutyrates.[11] Despite several reports on the preparation of isoxazole-pyridines appeared recently,[12-14] there is a continuous demand for the exploitation of new methods to prepare novel isoxazolopyridines. The development of simple routes toward preparing useful organic compounds from readily available reagents and compounds is one of the major tasks in organic synthesis. One-pot operation has proved to be remarkably effective in organic synthesis, while at the same time cutting out several purification steps, minimizing chemical waste generation, and saving time.[15,16] As a continuation of our interest in constructing heterocycles,[17-19] herein, we reported the one-pot synthesis of new isoxazole-fused pyridine derivatives from easily available chalcones, malononitrile, and hydroxylamine hydrochloride.



Scheme 1

Most recently, we reported a one-pot strategy to synthesize the *N*-OH-Hantzsch esters through a tandem Michael addition-condensation process (Scheme 1).[19] In order to broaden the *N*-OH-1,4-dihydropyridines family with different substituents, we attempted to synthesize compound **A** starting from **1a** and hydroxylamine hydrochloride (Table 1). At the onset, the reaction of **1a** with hydroxylamine hydrochloride was performed in the presence of various bases (2 equiv) in EtOH at room temperature (Table 1, entries 1-5). To our disappointment, no desired product **A** was formed. Instead, bicyclic compound **2a** was obtained as the main product and KOH was the relatively efficient base. Up to now, there was rare report on the construction of this kind of isoxazole-fused pyridine structure. So we continued to investigate the reaction in detail. To optimize the reaction, we investigated the influence of different solvents. EtOH was proved to be the most effective solvent, and using other solvents such as THF, DMF, MeCN, acetone or CH_2Cl_2 led to noticeable decrease in the yield of **2a** (Table 1, entries 6-10). Next, the influence of molar ratio of reactants was studied (Table 2, entries 11-15). Changing the molar ratio of $NH_2OH{\cdot}HCl$:KOH from 1:2 to 1:1 resulted in no generation of product, which indicated the cyclization needed a strong base (Table 1, entry 11). Further investigation showed that optimal molar ratio of **1a**:$NH_2OH{\cdot}HCl$:KOH for the formation of **2a** was 1:1.3:2.5 (Table 1, entry 15). The yield of **2a** is not high due to the incomplete conversion and formation of some byproducts. When we modulated the feeding order by adding dropwise a solution of KOH (1.25 mmol) in 10 mL of EtOH to the mixture of **1a** (0.5 mmol) and hydroxylamine hydrochloride in 10 mL of EtOH within 1 h and then continue stirring for another 43 h at room temperature, the yield of **2a** was increased to 50% (Table 1, entry 16). Although 50% yield of **2a** is acceptable, the reaction needed too long time (43 h). Raising the reaction temperature to reflux resulted in a slightly higher yield (58%) within short reaction time (7 h) (Table 1, entry 17).

Table 1. Screening of the reaction conditions[a]

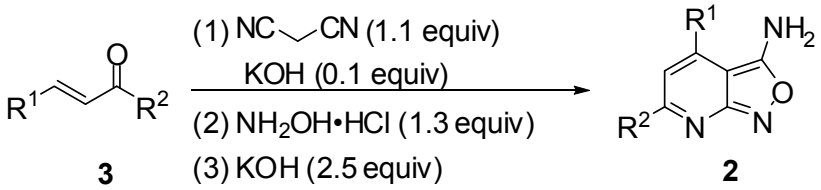
entry	solvent	base	ratio[b]	temperature	time (h)	yield of **2a** (%)[c]
1	EtOH	KOH	1:1:2	rt	43	31
2	EtOH	K_2CO_3	1:1:2	rt	43	trace
3	EtOH	Et_3N	1:1:2	rt	43	0
4	EtOH	piperidine	1:1:2	rt	43	trace
5	EtOH	DBU	1:1:2	rt	43	23
6	THF	KOH	1:1:2	rt	43	trace
7	DMF	KOH	1:1:2	rt	43	5
8	MeCN	KOH	1:1:2	rt	43	8
9	acetone	KOH	1:1:2	rt	43	10
10	CH_2Cl_2	KOH	1:1:2	rt	43	9
11	EtOH	KOH	1:1:1	rt	43	0
12	EtOH	KOH	1:1:1.5	rt	43	11
13	EtOH	KOH	1:1:2.5	rt	43	33
14	EtOH	KOH	1:1:3	rt	43	34
15	EtOH	KOH	1:1.3:2.5	rt	43	40
16[d]	EtOH	KOH	1:1.3:2.5	rt	1+43	50
17[e]	EtOH	KOH	1:1.3:2.5	rt→reflux	1+1+6	58

[a] A mixture of **1a** (0.5 mmol), hydroxylamine hydrochloride, and base was stirred in 20 mL of solvent at room temperature. [b] **1a**: hydroxylamine hydrochloride:base. [c] Isolated yield. [d] The solution of KOH (1.25 mmol) in 10 mL of EtOH was added dropwise into the mixture of **1a** (0.5 mmol) and hydroxylamine hydrochloride in 10 mL of EtOH with 1 h and then the solution was stirred for additional 43 h at room temperature. [e] The same operation as entry 16 except that after addition of the base, the mixture was further stirred for 1 h at room temperature and then refluxed for another 6 h.

In an attempt to make this approach more efficient, a one-pot reaction to prepare **2a** was tested (Table 2). A mixture of chalcone **3a** (0.5 mmol), malononitrile (0.55 mmol) and KOH (0.05 mmol) was stirred in 10 mL of EtOH at room temperature for 1 h. After quantitative conversion to **1a** (detected by TLC), hydroxylamine hydrochloride (46 mg, 0.65 mmol) was added. Subsequently, an ethanol solution of KOH (1.25 mmol, 10 mL) was added dropwise into the reaction mixture within 1 h under stirring. The mixture was continually stirred for 1 h at room temperature and then refluxed for additional 6 h. After purification, the desired 4,6-diphenyl-3-aminoisoxazolo[3,4-*b*]pyridine **2a** was obtained as a white

solid in 54% yield. Under the optimized conditions, the reaction scope was evaluated by using various chalcones **1** (Table 2). The results showed that 3-aminoisoxazolo[3,4-*b*]pyridines **2** with different substituent groups could be generated in moderate yields (40-60%). The electronic effect of the substituent group on the phenyl ring in R^1 had no significant impact on the reaction. However, the electronic effect of substituent group on the phenyl ring in R^2 had great influence on the reaction. When a strong electron-withdrawing group (NO_2) was linked with the phenyl ring in R^2, no product was isolated. Fortunately, heterocycle-substituted bicyclic compounds **2i** and **2j** could also be formed. All the products were characterized by their NMR, IR and MS spectra. The structure of the product **2d** was further established by the X-ray determination (Figure 1, recrystallization from EtOH).

Table 2. One-pot reaction for the preparation of 4,6-diaryl-3-aminoisoxazolo[3,4-*b*]pyridines **2**



entry	substrate	R^1	R^2	time (h)[a]	product	yield (%)
1	**3a**	Ph	Ph	6	**2a**	54
2	**3b**	4-$MeOC_6H_5$	Ph	6	**2b**	52
3	**3c**	4-MeC_6H_5	Ph	6	**2c**	53
4	**3d**	4-ClC_6H_5	Ph	6	**2d**	48
5	**3e**	4-$NO_2C_6H_5$	Ph	5	**2e**	60
6	**3f**	Ph	4-$MeOC_6H_5$	6	**2f**	50
7	**3g**	Ph	4-MeC_6H_5	6	**2g**	48
8	**3h**	Ph	4-ClC_6H_5	6	**2h**	51
9	**3i**	2-furyl	4-MeC_6H_5	8	**2i**	49
10	**3j**	4-$MeOC_6H_5$	2-pyridyl	8	**2j**	25

[a] It refers to the reflux time of the last step.

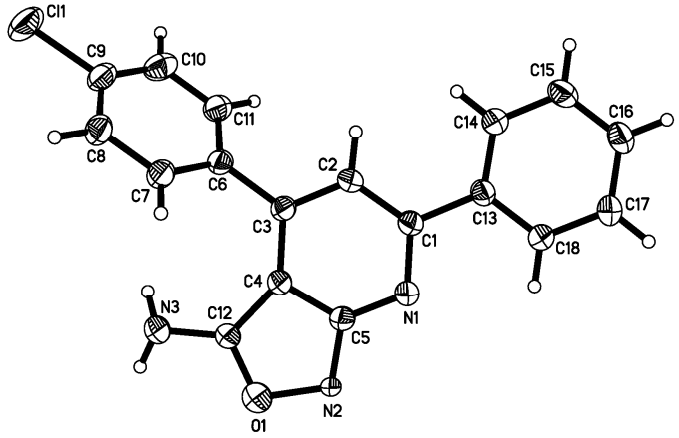
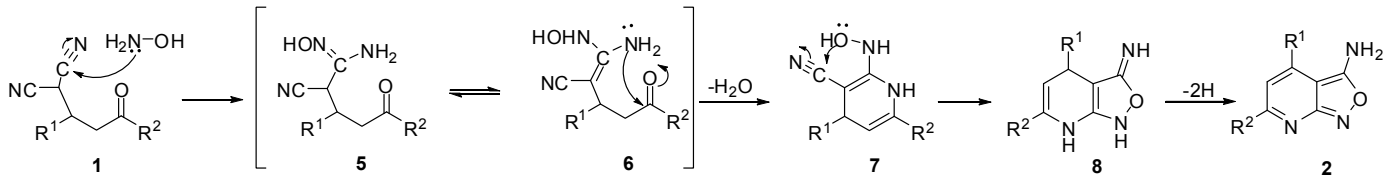


Figure 1. X-Ray crystal structure of **2d**[20]

A mechanism for the formation of **2a-2j** is outlined in Scheme 2. The nucleophilic addition reaction of hydroxylamine with Michael adduct **1** gives the intermediate **5**.[21] Isomerization of **5** to **6**, followed by sequential intramolecular cyclization, and subsequent oxidative dehydrogenation afford compounds **2**.



Scheme 2

In summary, we have developed a facile and convenient method for the synthesis of a series of 4,6-diaryl-3-aminoisoxazolo[3,4-*b*]pyridines. The key factor is to control the third-step cyclization reaction by adding the solution of KOH in dropwise. Particularly, the method shows several attractive characteristics, namely, one-pot, convenient, simple work-up procedure. This kind of skeleton may has potential use in medicinal fields.

EXPERIMENTAL

General Procedure for the Three-Component Reaction of Chalcones 3, Malononitrile and Hydroxylamine Hydrochloride: A mixture of chalcones **3** (0.5 mmol), malononitrile (36.3 mg, 0.55 mmol), and KOH (2.8 mg, 0.05 mmol) was stirred in 10 mL of EtOH at room temperature. Upon completion of the Michael addition reaction (detected by TLC, about 1 h), hydroxylamine hydrochloride (46 mg, 0.65 mmol) was added. Afterwards, a solution of KOH (70.0 mg, 1.25 mmol)

in 10 mL of EtOH was added dropwise into the reaction mixture within 1 h under stirring. The mixture was allowed to stir for 1 h at room temperature and then was refluxed for additional 5-8 h. After completion of the reaction detected by TLC, the mixture was poured into 100 mL of ice-cold water. The precipitate was filtered to give the crude product, which was then dried and purified by column chromatography on silica gel (EtOAc/petroleum ether) to provide the products **2**.

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REFERENCES

1. M. Suzuki, H. Iwasaki, Y. Fujikawa, M. Sakashita, M. Kitahara, and R. Sakoda, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1285.
2. I. Drizin, R. J. Altenbach, S. A. Buckner, K. L. Whiteaker, V. E. Scott, J. F. Darbyshire, V. Jayanti, R. F. Henry, M. J. Coghlan, M. Gopalakrishnan, and W. A. Carroll, *Bioorg. Med. Chem.*, 2004, **12**, 1895.
3. E. J. Hanan, R. V. Fucini, M. J. Romanowski, R. A. Elling, W. Lew, H. E. Purkey, E. C. VanderPorten, and W. Yang, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5186.
4. D. S. Su, J. J. Lim, E. Tinney, B. L. Wan, M. B. Young, K. D. Anderson, D. Rudd, V. Munshi, C. Bahnck, P. J. Felock, M. Q. Lu, M. T. Lai, S. Touch, G. Moyer, D. J. DiStefano, J. A. Flynn, Y. X. Liang, R. Sanchez, R. Perlow-Poehnelt, M. Miller, J. P. Vacca, T. M. Williams, and N. J. Anthony, *J. Med. Chem*., 2009, **52**, 7163.
5. M. D. Taylor, R. J. Himmelsbach, B. E. Kornberg, J. Quin, III, E. Lunney, and A. Michel, *J. Org. Chem*., 1989, **54**, 5585.
6. L. K. Dyall, D. W. Maloney, J. J. Harvey, and B. E. Fulloon, *Aust. J. Chem*., 1996, **49**, 761.
7. F. A. Yassin, *Chem. Heterocycl. Compd*., 2009, **45**, 35.
8. M. F. A. Adamo, E. F. Duffy, D. Donati, and P. Sarti-Fantoni, *Tetrahedron*, 2007, **63**, 2047.
9. F. Al-Omran and A. A. El-Khair, *J. Chem. Res.*, 2009, 433.
10. A. P. Gaywood and H. McNab, *Org. Biomol. Chem.*, 2010, **8**, 5166.
11. E. A. El-Rady and M. A. Barsy, *J. Heterocycl. Chem.*, 2008, **45**, 1233.
12. S.-J. Tu, X.-H. Zhang, Z.-G. Han, X.-D. Cao, S.-S. Wu, S. Yan, W.-J. Hao, G. Zhang, and N. Ma, *J. Comb. Chem.*, 2009, **11**, 428.

13. D. M. Volochnyuk, S. V. Ryabukhin, A. S. Plaskon, Y. V. Dmytriv, O. O. Grygorenko, P. K. Mykhailiuk, D. G. Krotko, A. Pushechnikov, and A. A. Tolmachev, *J. Comb. Chem.,* 2010, **12**, 510.
14. E. Rajanarendar, S. Raju, M. N. Reddy, S. R. Krishna, L. H. Kiran, A. R. N. Reddy, and Y. N. Reddy, *Eur. J. Med. Chem.*, 2012, **50**, 274.
15. B. Jiang, T. Rajale, W. Wever, S.-J. Tu, and G. Li, *Chem. Asian J.*, 2010, **5**, 2318.
16. W. Y. Zhao and F. E. Chen, *Curr. Org. Chem.*, 2012, **9**, 873.
17. C.-B. Miao, M. Zhang, Z.-Y. Tian, H.-T. Xi, X.-Q. Sun, and H.-T. Yang, *J. Org. Chem*., 2011, **76**, 9809.
18. C.-B. Miao, C.-P. Dong, M. Zhang, W.-L. Ren, Q. Meng, X.-Q. Sun, and H.-T. Yang, *J. Org. Chem*., 2013, **78**, 4329.
19. C.-B. Miao, C.-P. Dong, Y.-H. Wang, H.-T. Yang, Q.-Meng, S.-J. Tu, and X.-Q. Sun, *Heterocycles*, 2013, **87**, 853.
20. CCDC reference number CCDC 882522.
21. (a) W. J. Fanshawe, V. J. Bauer, and S. R. Safir, *J. Org. Chem.*, 1965, **30**, 2862; (b) G. Zvilichovsky and M. David, *J. Org. Chem.*, 1983, **48**, 575.