Accepted Manuscript

NBS-mediated practical cyclization of *N*-acyl amidines to 1,2,4-oxadiazoles *via* oxidative N–O bond formation

Ertong Li, Manman Wang, Zhen Wang, Wenquan Yu, Junbiao Chang

PII: S0040-4020(18)30869-X

DOI: 10.1016/j.tet.2018.07.036

Reference: TET 29696

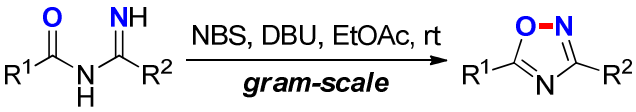
To appear in: *Tetrahedron*

Received Date: 24 May 2018

Revised Date: 5 July 2018

Accepted Date: 17 July 2018

Please cite this article as: Li E, Wang M, Wang Z, Yu W, Chang J, NBS-mediated practical cyclization of *N*-acyl amidines to 1,2,4-oxadiazoles *via* oxidative N–O bond formation, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.07.036.



25 examples, 91-99% yield

NBS-Mediated Practical Cyclization of *N*-Acyl Amidines to 1,2,4-Oxadiazoles *via* Oxidative N−O Bond Formation

Ertong Li, Manman Wang, Zhen Wang, Wenquan Yu,* and Junbiao Chang*

College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan Province 450001, China

Abstract: A reaction involving an efficient NBS-mediated oxidative N−O bond formation has been established for the synthesis of 1,2,4-oxadiazoles from readily accessible *N*-acyl amidines. The features of this synthetic method include simplicity of operation, mild reaction conditions, short reaction times, high yields, and eco-friendliness. The reaction also works well with crude *N*-acyl amidines obtained by amidation of simple benzoic acids and amidines to produce biologically relevant 1,2,4-oxadiazoles in a scalable fashion.

Keywords: NBS; N−O bond formation; 1,2,4-oxadiazole; *N*-acyl amidine; ethyl acetate

▪ Introduction

1,2,4-Oxadiazole is an important heterocyclic scaffold in many important biological and pharmaceutical compounds.[1] Ataluren (**3**, Figure 1) for example, is an orally available drug in Europe for the treatment of Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene. As a Nrf2 activator, 1,2,4-oxadiazole derivative **4** exhibits good efficacy in LPS-challenged mouse model.[2] Compound **5** has been identified as a metabotropic glutamate subtype 5 (mGlu5) receptor antagonist.[3] Phidianidines A and B are two 1,2,4-oxadiazole-containing marine natural products with potent antiproliferative activity.[4] 1,2,4-Oxadiazoles are also useful synthons for construction of other heterocyclic systems and have extensive applications in material science as components of polymers, liquid crystals, and luminescent materials.[1]

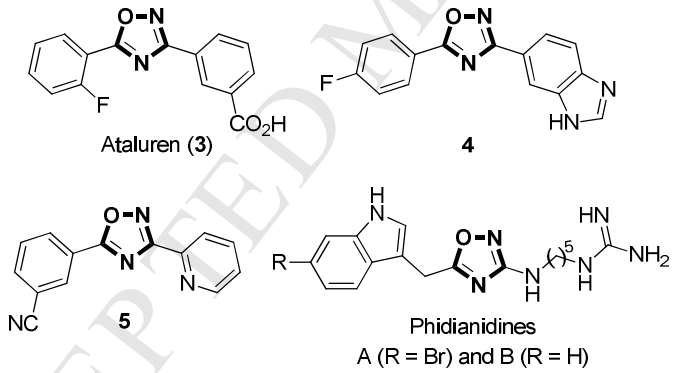


Figure 1. Representative bioactive 1,2,4-oxadiazole-containing molecules.

The classical method for the construction of 1,2,4-oxadiazole frameworks involves cyclodehydration of *O*-acylamidoximes or amidoximes with various carboxylic acid derivatives.[5] 1,2,4-Oxadiazoles can also be synthesized *via* oxidative pathways from amides with nitriles,[6] *N*-benzyl amidoximes,[7] aldoximes with nitriles,[8] and amidines with methylarenes.[9] *N*-acyl amidines, also useful precursors in the synthesis of 1,2,4-oxadiazoles can be readily prepared by amidation of amidines with benzoic

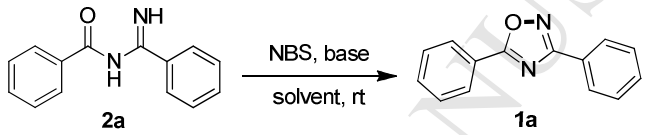
acids. Previously, oxidative cyclization of such substrates to form 1,2,4-oxadiazoles was only achieved using hypochlorites.[10] Recently, Hajela *et al.* reported a non-oxidative annulation reaction of *N*-acyl amidines with hydroxylamine in acetic acid,[11] and later disclosed an I_2-mediated oxidative cyclization method.[12] There are still certain limitations associated with existing methods including harsh reaction conditions, limited substrate scope or scalability, and use of hazard materials. Therefore, it is important to develop practical and environmentally benign approaches to the synthesis of 1,2,4-oxadiazole derivatives under mild reaction conditions. Herein we describe an NBS-promoted oxidative cyclization reaction of *N*-acyl amidines with ethyl acetate as solvent, leading to 1,2,4-oxadiazoles.

▪ Results and Discussion

N-Bromosuccinimide (NBS) is a commercially available and inexpensive oxidant and brominating reagent which enjoys a wide range of applications in organic synthesis.[13] As an oxidant, NBS has been successfully employed in various annulation reactions involving C–C,[14] C–O,[15] C–N[16] and C–S[17] bond formation. Yet, to the best of our knowledge, applications of this reagent in heteroatom-heteroatom bond formation have not been reported. Continuing our interest in heteroatom-heteroatom bond construction,[18] we investigated the use of NBS-mediated oxidative N−O bond formation reactions in 1,2,4-oxadiazole synthesis. The necessary *N*-acyl amidine substrate (**2a**) was readily obtained by the amidation of benzamidine with benzoic acid.[11] In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base, NBS-mediated cyclization of substrate **2a** was complete within 10 min at room temperature in most solvents (Table 1, entries 3−7), affording the expected product **1a** in excellent yields. This transformation requires a longer reaction time in EtOH (entry

1) and toluene (entry 8) and resulted in decreased yields of **1a** when the solvent was DMF (entry 2) or toluene (entry 8). In view of the environmental impact of solvents,[19] EtOAc was chosen for further optimization. Replacement of DBU with inorganic bases (entries 9–10) affected both the conversion rate and the yield of the product. No desired product was formed when NEt_3 was used as the base (entry 11) or no base was used (entry 12). Complete consumption of substrate **2a** required at least 1.2 equiv of NBS (entry 5) and the yield was not affected by additional oxidant, NBS (entry 14).

Table 1. Optimization of reaction conditions for the synthesis of 1,2,4-oxadiazole **1a**.[a]



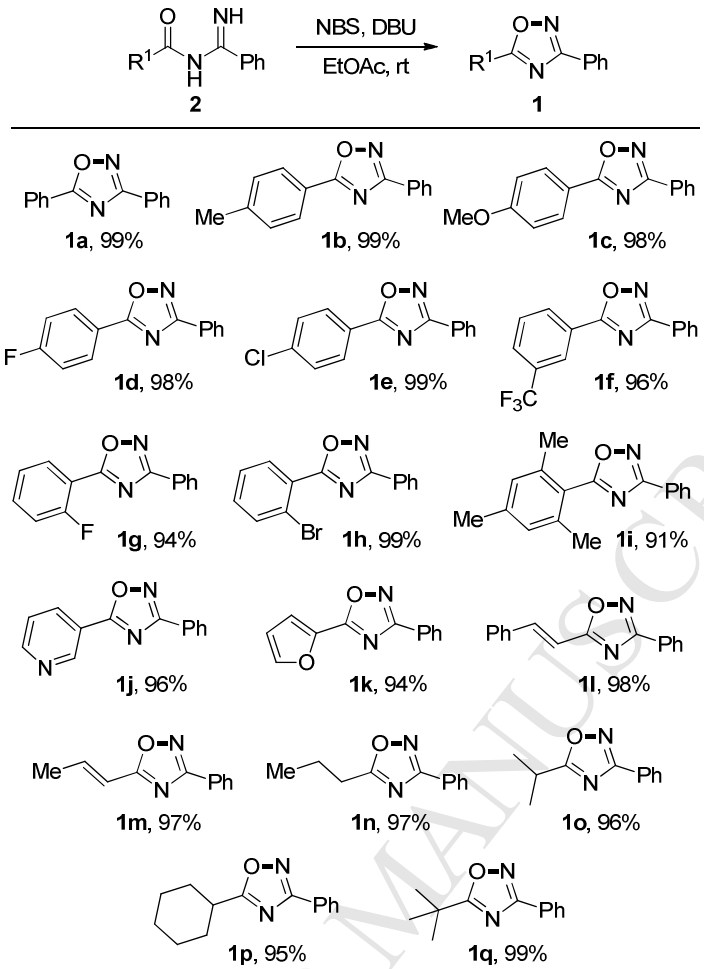
2a **1a**

Entry	NBS	Base	Solvent	Time	Yield[b]
1	1.2 eq	DBU	EtOH	3 h	96%
2	1.2 eq	DBU	DMF	10 min	90%
3	1.2 eq	DBU	DMSO	10 min	95%
4	1.2 eq	DBU	MeCN	10 min	96%
5	**1.2 eq**	**DBU**	**EtOAc**	**10 min**	**99%**
6	1.2 eq	DBU	1,4-dioxane	10 min	97%
7	1.2 eq	DBU	CH_2Cl_2	10 min	95%
8	1.2 eq	DBU	toluene	12 h	73%
9	1.2 eq	K_2CO_3	EtOAc	5 h	85%
10	1.2 eq	Cs_2CO_3	EtOAc	5 h	94%
11	1.2 eq	NEt_3	EtOAc	5 h	trace
12	1.2 eq	–	EtOAc	5 h	0%

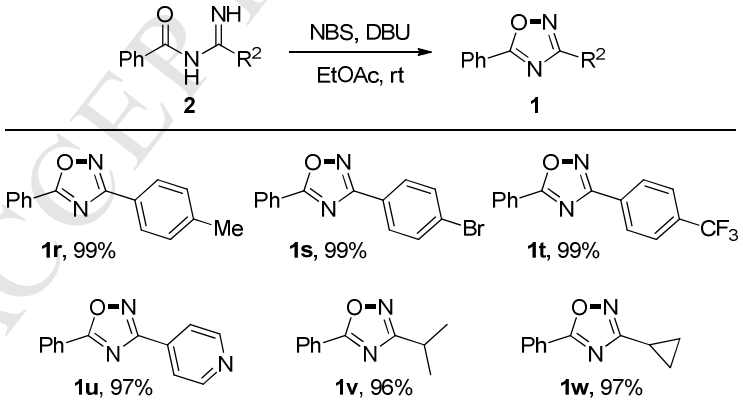
13	1.0 eq	DBU	EtOAc	0.5 h	82%
14	1.4 eq	DBU	EtOAc	10 min	99%

[a]Reaction conditions: 1) **2a** (0.5 mmol), NBS (0.6 mmol), DBU (0.6 mmol), solvent (5 mL), rt. [b]Isolated yields.

With the optimal reaction conditions in hand, we explored the substrate scope and generality of this synthetic method. As shown in Scheme 1, the reaction tolerates both electron-donating and electron-withdrawing groups at the *ortho*-, *meta*- or *para*-positions of the *N*-aroyl ring of substrates to produce 3,5-diaryl-1,2,4-oxadiazoles (**1b**−**i**) in excellent yields. The 2-pyridyl (**1j**) and 2-furyl (**1k**) substituted products could also be synthesized from corresponding precursors in good yields. *N*-acyl benzamidines bearing alkenyl (**1l**−**m**) or alkyl substituents (**1n**−**q**) were also viable substrates. Noticeably, *ortho*-substitution on the benzoyl moiety, R^1 (**1g**−**i**) and a bulky *tert*-butyl group (**1q**) had no effect on either the conversion rate or the yield. Substrates bearing substituted phenyl (**1r**–**t**), 2-pyridyl (**1u**) or aliphatic groups (**1v**–**w**) at the R^2 position were all readily cyclized to form the desired 1,2,4-oxadiazole (Scheme 2).



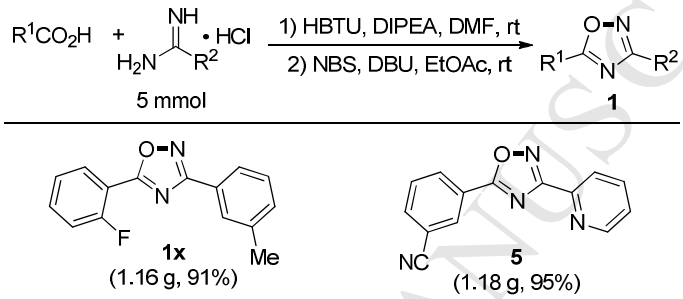
Scheme 1. Substrate scope of the R^1 group.



Scheme 2. Substrate scope of the R^2 group.

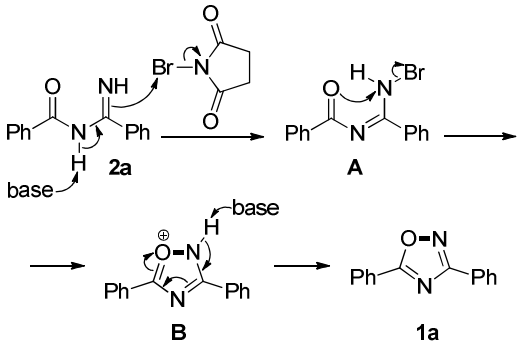
To assess the practicality of this reaction, we probed the feasibility of direct 1,2,4-oxadiazole synthesis from simple benzoic acids and amidines without

purification of the *N*-acyl amidine intermediates. The crude *N*-acyl amidines obtained from the first step amidation were subjected directly to the NBS-mediated oxidative cyclization conditions, and yielded 2-fluorophenyl-1,2,4-oxadiazole **1x** and the mGlu5 receptor antagonist **5**[3] efficiently on a gram scale (Scheme 3). The former product (**1x**) is an important intermediate in the synthesis of the Duchenne muscular dystrophy drug Ataluren (**3**).[11]



Scheme 3. Gram-scale synthesis of biologically interesting 1,2,4-oxadiazoles (**1x**, **5**) omitting purification of the *N*-acyl amidine intermediates.

A tentative mechanism for this NBS-mediated cyclization of *N*-acyl amidines to 1,2,4-oxadiazoles is proposed in Scheme 4. In the formation of **1a** for example, bromination of substrate **2a** by NBS under basic conditions generates a plausible *N*-bromo species **A**.[20] The carbonyl oxygen atom then attacks the bromo-substituted nitrogen in compound **A** to form an intermediate (**B**) containing a new N−O bond. Finally, the subsequent proton elimination by base produces the 1,2,4-oxadiazole skeleton (**1a**). Owing to the halogen bond interaction between imines and NBS,[21] DBU is preferable as the base (cf. entries 5, 9−11 in Table 1) in this transformation.



Scheme 4. Proposed mechanism for the formation of 1,2,4-oxadiazole **1a**.

▪ Conclusion

We have developed a first NBS-promoted oxidative N−O bond formation reaction in the presence of DBU as base for 1,2,4-oxadiazole synthesis. This practical and eco-friendly approach provides a facile and efficient access to 1,2,4-oxadiazole derivatives from the corresponding *N*-acyl amidine precursors under mild reaction conditions and with short reaction times. Moreover, sequential synthesis of biologically interesting products from simple benzoic acids and amidines without purification of *N*-acyl amidine intermediates can be conveniently carried out on a gram scale.

▪ Experimental Section

General Information. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz (100 MHz for ^{13}C NMR) spectrometer. Chemical shift values are given in ppm (parts per million) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets. The coupling constants (*J*) are reported in Hertz (Hz). Melting points were determined on a micromelting point apparatus and are uncorrected. High-resolution mass spectra

(HRMS) were obtained on a Q-TOF Mass Spectrometer equipped with an electrospray ion source (ESI) and operated in the positive mode. Flash column chromatography was performed over 200–300 mesh silica gel, and the eluent was a mixture of EtOAc and petroleum ether (PE).

General procedure A for preparation of *N*-acyl amidine substrates 2.[11] A mixture of a carboxylic acid (2 mmol), the corresponding amidine salt (2 mmol), HBTU (834 mg, 2.2 mmol) and DIPEA (1.03 g, 8 mmol) in DMF (8 mL) was stirred at room temperature for 3 h. It was then quenched with H_2O (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with H_2O (10 mL) and brine (10 mL) successively, dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to give the substrate **2**.

General procedure B for synthesis of 1,2,4-oxadiazoles 1. A solution of the *N*-acyl amidine **2** (0.5 mmol) in EtOAc (5 mL) was treated with NBS (0.6 mmol) and DBU (0.6 mmol) in sequence and then stirred at room temperature for 10 min when TLC indicated the conversion was completed. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, concentrated, and then purified through silica gel column chromatography to afford the product **1**.

3,5-Diphenyl-1,2,4-oxadiazole (1a). Eluent: EtOAc/PE 10:90; yield: 111 mg, 99%; white solid, mp 107-109 °C (lit.[5j] mp 106-108 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.17 (m, 4H), 7.63-7.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 169.0, 132.8, 131.2, 129.1, 128.9, 128.2, 127.6, 127.0, 124.4; HRMS (m/z) $[M + H]^+$ calcd for $C_{14}H_{11}N_2O$, 223.0866, found 223.0872.

3-Phenyl-5-(p-tolyl)-1,2,4-oxadiazole (1b). Eluent: EtOAc/PE 10:90; yield: 118 mg, 99%; white solid, mp 115-117 °C (lit.[5f] mp 114-116 °C); ^{1}H NMR (400 MHz, $CDCl_3$):

δ 8.19-8.16 (m, 2H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.52-7.49 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 168.9, 143.5, 131.1, 129.8, 128.8, 128.1, 127.5, 127.1, 121.6, 21.8; HRMS (m/z) $[M + H]^+$ calcd for $C_{15}H_{13}N_2O$, 237.1022, found 237.1020.

5-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazole (1c). Eluent: EtOAc/PE 10:90; yield: 142mg, 98%; white solid, mp 107-108 °C (lit.[5c] mp 107-108 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.15 (m, 4H), 7.51-7.50 (m, 3H), 7.03 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 168.8, 163.2, 131.1, 130.1, 128.8, 127.5, 127.2, 116.9, 114.5, 55.5; HRMS (m/z) $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_2$, 253.0972, found 253.0970.

5-(4-Fluorophenyl)-3-phenyl-1,2,4-oxadiazole (1d).[22] Eluent: EtOAc/PE 10:90; yield: 118 mg, 98%; white solid, mp 101-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.21 (m, 2H), 8.17-8.15 (m, 2H), 7.53-7.49 (m, 3H), 7.26-7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 169.0, 165.5 (d, J_{C-F} = 253.0 Hz), 131.3, 130.6 (d, J_{C-F} = 0.9 Hz), 128.9, 127.5, 126.9, 120.7 (d, J_{C-F} = 3.0 Hz), 116.5 (d, J_{C-F} = 22.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.1; HRMS (m/z) $[M + H]^+$ calcd for $C_{14}H_{10}FN_2O$, 241.0772, found 241.0774.

5-(4-Chlorophenyl)-3-phenyl-1,2,4-oxadiazole (1e). Eluent: EtOAc/PE 10:90; yield: 133 mg, 99%; white solid, mp 118-120 °C (lit.[5j] mp 118-119 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.14 (m, 4H), 7.54-7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 169.1, 139.2, 131.3, 129.5 (2C), 128.9, 127.5, 126.8, 122.8; HRMS (m/z) $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2O$, 257.0476, found 257.0484.

3-Phenyl-5-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (1f). Eluent: EtOAc/PE 25:75; yield: 143 mg, 99%; white solid, mp 94-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.22-8.19 (m, 2H), 7.89 (d, *J* = 8.0 Hz, 1H),

7.73 (t, J = 8.0 Hz, 1H), 7.58-7.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 169.2, 131.9 (q, J_{C-F} = 33.0 Hz), 131.4, 131.2 (d, J_{C-F} = 0.9 Hz), 129.8, 129.2 (q, J_{C-F} = 3.0 Hz), 128.9, 127.6, 126.6, 125.1 (q, J_{C-F} = 4.0 Hz), 125.1, 123.5 (q, J_{C-F} = 271.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9; HRMS (m/z) $[M + H]^+$ calcd for $C_{15}H_{10}F_3N_2O$, 291.0740, found 291.0740.

5-(2-Fluorophenyl)-3-phenyl-1,2,4-oxadiazole (1g). Eluent: EtOAc/PE 5:95; yield: 111 mg, 94%; white solid, mp 93-94 °C (lit.[23] mp 94-95 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.16 (m, 3H), 7.63-7.57 (m, 1H), 7.55-7.49 (m, 3H), 7.36-7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (d, J_{C-F} = 5.0 Hz), 168.8, 160.8 (d, J_{C-F} = 259.0 Hz), 134.6 (d, J_{C-F} = 8.0 Hz), 131.3, 131.0, 128.9, 127.6, 126.8, 124.7 (d, J_{C-F} = 4.0 Hz), 117.2 (d, J_{C-F} = 21.0 Hz), 112.9 (d, J_{C-F} = 11.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.3; HRMS (m/z) $[M + H]^+$ calcd for $C_{14}H_{10}FN_2O$, 241.0772, found 241.0771.

5-(2-Bromophenyl)-3-phenyl-1,2,4-oxadiazole (1h).[9] Eluent: EtOAc/PE 20:80; yield: 149 mg, 99%; off-white solid, mp 57-58 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-8.18 (m, 2H), 8.08 (dd, J = 8.0, 1.8 Hz, 1H), 7.80 (dd, J = 8.0, 1.2 Hz, 1H), 7.54-7.48 (m, 4H), 7.43 (td, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 168.7, 143.8, 133.1, 132.2, 131.3, 128.9, 127.63, 127.61, 126.8, 125.8, 122.2; HRMS (m/z) $[M + H]^+$ calcd for $C_{14}H_{10}BrN_2O$, 300.9971, found 300.9969.

5-Mesityl-3-phenyl-1,2,4-oxadiazole (1i). Eluent: EtOAc/PE 10:90; yield: 121 mg, 91%; white solid, mp 58-59 °C (lit.[24] mp 56-57 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-8.17 (m, 2H) 7.53-7.49 (m, 3H), 6.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 168.4, 141.3, 138.4, 131.2, 129.0, 128.9, 127.52, 127.1, 121.8, 21.3, 20.4; HRMS (m/z) $[M + H]^+$ calcd for $C_{17}H_{17}N_2O$, 265.1335, found 265.1344.

3-Phenyl-5-(pyridin-3-yl)-1,2,4-oxadiazole (1j). Eluent: EtOAc/PE 10:90; yield: 107

mg, 96%; white solid, mp 116-118 °C (lit.[25] mp 117-118 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (d, *J* = 1.6 Hz, 1H), 8.85 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.48 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.19-8.17 (m, 2H), 7.55-7.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 169.1, 153.3, 149.2, 135.3, 131.5, 129.0, 127.6, 126.5, 123.8, 120.8; HRMS (m/z) $[M + H]^+$ calcd for $C_{13}H_{10}N_3O$, 224.0818, found 224.0821.

5-(Furan-2-yl)-3-phenyl-1,2,4-oxadiazole (1k).[5g] Eluent: EtOAc/PE 10:90; yield: 100 mg, 94%; light brown solid, mp 77-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.16 (m, 2H), 7.73 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.54-7.49 (m, 3H), 7.39 (dd, *J* = 3.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 167.6, 146.7, 140.2, 131.4, 128.9, 127.6, 126.5, 116.6, 112.5; HRMS (m/z) $[M + H]^+$ calcd for $C_{12}H_9N_2O_2$, 213.0659, found 213.0660.

(*E*)-3-Phenyl-5-styryl-1,2,4-oxadiazole (1l). Eluent: EtOAc/PE 10:90; yield: 122 mg, 98%; white solid; mp 93-94 °C (lit.[26] mp 95-97 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.11 (m, 2H), 7.88 (d, *J* = 16.4 Hz, 1H), 7.62-7.57 (m, 2H), 7.52-7.47 (m, 3H), 7.46-7.42 (m, 3H), 7.07 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 168.8, 131.1, 129.6, 128.8, 127.5, 127.0, 124.1, 19.0; HRMS (m/z) $[M + H]^+$ calcd for $C_{16}H_{13}N_2O$, 249.1022, found 249.1024.

(*E*)-3-Phenyl-5-(prop-1-en-1-yl)-1,2,4-oxadiazole (1m).[27] Eluent: EtOAc/PE 5:95; yield: 90 mg, 97%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13-8.08 (m, 2H), 7.52-7.45 (m, 3H), 7.16 (dq, *J* = 16.0, 6.8 Hz, 1H), 6.48 (dd, *J* = 16.0, 1.6 Hz, 1H), 2.03 (dd, *J* = 7.2, 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 168.4, 142.9, 131.1, 128.8, 127.4, 127.0, 115.0, 18.9; HRMS (m/z) $[M + H]^+$ calcd for $C_{11}H_{11}N_2O$, 187.0866, found 187.0869.

3-Phenyl-5-propyl-1,2,4-oxadiazole (1n).[28] Eluent: EtOAc/PE 10:90; yield: 91 mg, 97%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.07 (m, 2H), 7.50-7.45 (m,

3H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.91 (sext, *J* = 7.6 Hz, 2H), 1.06 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 168.3, 131.1, 128.8, 127.4, 127.0, 28.5, 20.2, 13.7; HRMS (m/z) $[M + H]^+$ calcd for $C_{11}H_{13}N_2O$, 189.1022, found 189.1023.

5-Isopropyl-3-phenyl-1,2,4-oxadiazole (1o). Eluent: EtOAc/PE 10:90; yield: 90 mg, 96%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.07 (m, 2H), 7.50-7.45 (m, 3H), 3.29 (hept, *J* = 6.8 Hz, 1H), 1.46 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9, 168.2, 131.0, 128.8, 127.4, 127.1, 27.6, 20.2; HRMS (m/z) $[M + H]^+$ calcd for $C_{11}H_{13}N_2O$, 189.1022, found 189.1010.

5-Cyclohexyl-3-phenyl-1,2,4-oxadiazole (1p). Eluent: EtOAc/PE 10:90; yield: 108 mg, 95%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.06 (m, 2H), 7.50-7.44 (m, 3H), 3.10 (tt, *J* = 11.6, 3.6 Hz, 1H), 2.16-2.11 (m, 2H), 1.90-1.84 (m, 2H), 1.76-1.66 (m, 3H), 1.48-1.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.0, 168.1, 131.0, 128.8, 127.4, 127.1, 36.4, 30.3, 25.4; HRMS (m/z) $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$, 229.1335, found 229.1334.

5-(*tert*-Butyl)-3-phenyl-1,2,4-oxadiazole (1q). Eluent: EtOAc/PE 25:75; yield: 102 mg, 99%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.06 (m, 2H), 7.50-7.44 (m, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 168.2, 131.0, 128.8, 127.5, 127.2, 33.6, 28.5; HRMS (m/z) $[M + H]^+$ calcd for $C_{12}H_{15}N_2O$, 203.1179, found 203.1183.

5-Phenyl-3-(p-tolyl)-1,2,4-oxadiazole (1r). Eluent: EtOAc/PE 10:90; yield: 123 mg, 99%; white solid, mp 105-106 °C (lit.[29] mp 105-106 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.20 (m, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.62-7.52 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 169.0, 141.5, 132.7, 129.6, 129.1, 128.2, 127.5, 124.4, 124.2, 21.6; HRMS (m/z) $[M + H]^+$ calcd for $C_{15}H_{13}N_2O$, 237.1022, found 237.1044.

3-(4-Bromophenyl)-5-phenyl-1,2,4-oxadiazole (1s). Eluent: EtOAc/PE 10:90; yield: 149 mg, 99%; white solid, mp 108-109 °C (lit.[5f] mp 110-112 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 7.6 Hz, 2H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.61-7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 168.3, 132.9, 132.2, 129.2, 129.0, 128.2, 125.9, 125.8, 124.2; HRMS (m/z) $[M + H]^+$ calcd for $C_{14}H_{10}BrN_2O$, 300.9971, found 300.9954.

5-Phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (1t). Eluent: EtOAc/PE 10:90; yield: 145 mg, 99%; white solid, mp 91-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.0 Hz, 2H), 8.23-8.21 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.65-7.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 168.0, 133.0, 132.9 (q, J_{C-F} = 32.0 Hz), 130.4 (d, J_{C-F} = 1.0 Hz), 129.2, 128.2, 127.9, 127.6, 125.9 (q, J_{C-F} = 4.0 Hz), 124.0, 123.8 (q, J_{C-F} = 270.0 Hz), 125.1, 123.5 (q, J_{C-F} = 271.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0; HRMS (m/z) $[M + H]^+$ calcd for $C_{15}H_{10}F_3N_2O$, 291.0740, found 291.0744.

5-Phenyl-3-(pyridin-4-yl)-1,2,4-oxadiazole (1u).[6] Eluent: EtOAc; yield: 108 mg, 97%; white solid, mp 146-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82-8.80 (m, 2H), 8.23-8.21 (m, 2H), 8.04-8.03 (m, 2H), 7.66-7.62 (m, 1H), 7.59-7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 167.5, 150.7, 134.4, 133.2, 129.2, 128.2, 123.9, 121.3, 121.0; HRMS (m/z) $[M + H]^+$ calcd for $C_{13}H_{10}N_3O$, 224.0818, found 224.0807.

3-Isopropyl-5-phenyl-1,2,4-oxadiazole (1v). Eluent: EtOAc/PE 10:90; yield: 90 mg, 96%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-8.13 (m, 2H), 7.59-7.49 (m, 3H), 3.17 (hept, *J* = 2.8 Hz, 1H), 1.41 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 175.3, 132.5, 129.0, 128.1, 124.5, 26.9, 20.6; HRMS (m/z) $[M + H]^+$ calcd for $C_{11}H_{13}N_2O$, 189.1022, found 189.1028.

3-Cyclopropyl-5-phenyl-1,2,4-oxadiazole (1w).[5i] Eluent: EtOAc/PE 10:90; yield: 91

mg, 97%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.99 (m, 2H), 7.50-7.47 (m, 1H), 7.46-7.39 (m, 2H), 2.10-2.03 (m, 1H), 1.08-0.98 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 173.1, 132.5, 129.0, 128.0, 124.4, 7.8, 7.0; HRMS (m/z) $[M + H]^+$ calcd for $C_{11}H_{11}N_2O$, 187.0866, found 187.0867.

5-(2-Fluorophenyl)-3-(m-tolyl)-1,2,4-oxadiazole (1x). According to *General Procedures A* and *B*, the reaction was carried out in a 5 mmol scale omitting the purification of the *N*-acyl amidine intermediate with the second step cyclization for 30 min; eluent: EtOAc/PE 5:95; yield: 1155 mg, 91%; white solid, mp 93-94 °C (lit.[11] mp 93 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (td, J = 7.6, 1.6 Hz, 1H), 8.00-7.97 (m, 2H), 7.62-7.57 (m, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.35-7.26 (m, 3H, overlapped with chloroform), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (d, J_{C-F} = 5.0 Hz), 168.9, 160.8 (d, J_{C-F} = 259.0 Hz), 138.7, 134.5 (d, J_{C-F} = 9.0 Hz), 132.1, 131.0 (d, J_{C-F} = 0.8 Hz), 128.8, 128.1, 126.6, 124.7, 124.7 (d, J_{C-F} = 4.0 Hz), 117.2 (d, J_{C-F} = 21.0 Hz), 112.9 (d, J_{C-F} = 12.0 Hz), 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.3; HRMS (m/z) $[M + H]^+$ calcd for $C_{15}H_{12}FN_2O$, 255.0928, found 255.0927.

3-(3-(Pyridin-2-yl)-1,2,4-oxadiazol-5-yl)benzonitrile (5). According to *General Procedures A* and *B*, the reaction was carried out in a 5 mmol scale omitting the purification of the *N*-acyl amidine intermediate with the second step cyclization for 30 min; eluent: EtOAc/PE 40:60; yield: 1178 mg, 95%; white solid, mp 149-150 °C (lit.[5a] mp 148-149 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (td, J = 7.6, 1.6Hz, 1H), 8.00-7.97 (m, 2H), 7.62-7.60 (m, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.35-7.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 169.1, 150.6, 145.9, 137.2, 135.9, 132.1, 131.8, 130.2, 125.9, 125.3, 123.4, 117.4, 113.9. HRMS (m/z) $[M + H]^+$ calcd for $C_{14}H_9N_4O$, 249.0771, found 249.0779.

▪Supporting Information

Copies of NMR spectra of products **1**.

▪ Author Information

Corresponding Authors

*E-mail: wenquan_yu@zzu.edu.cn

*E-mail: changjunbiao@zzu.edu.cn

Notes

The authors declare no competing financial interest.

▪ Acknowledgements

We thank the National Natural Science Foundation of China (No. 81773570 and 81330075), the Outstanding Young Talent Research Fund of Zhengzhou University (No. 1521316004) for financial support.

▪ References

1. (a) Pace, A.; Buscemi, S.; Piccionello, A. P.; Pibiri, I., *Adv. Heterocycl. Chem.* **2015**, *116*, 85-136; (b) Pace, A.; Pierro, P., *Org. Biomol. Chem.* **2009**, *7*, 4337-4348.

2. Xu, L. L.; Zhu, J. F.; Xu, X. L.; Zhu, J.; Li, L.; Xi, M. Y.; Jiang, Z. Y.; Zhang, M. Y.; Liu, F.; Lu, M. C.; Bao, Q. C.; Li, Q.; Zhang, C.; Wei, J. L.; Zhang, X. J.; Zhang, L. S.; You, Q. D.; Sun, H. P., *J. Med. Chem.* **2015**, *58*, 5419-5436.

3. (a) Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. P., *J. Med. Chem.* **2004**, *47*, 4645-4648; (b) Slassi, A.; van Wagenen, B.

C.; Stormann, T. M.; Moe, S. T.; Sheehan, S. M.; Mcleod, D. A.; Smith, D. L.; Isaac, M. B. PCT Int. Appl. WO2002068417A2, September 6, 2002.

4. Carbone, M. L., Y.; Irace, C.; Mollo, E.; Castelluccio, F.; Pascale, A. D.; Cimino G.; Santamaria, R.; Guo, Y.-W.; Gavagnin, M., *Org. Lett.* **2011**, *13*, 2516-2519.

5. (a) Grant, D.; Dahl, R.; Cosford, N. D. P., *J. Org. Chem.* **2008**, *73*, 7219-7223; (b) Suresh, D.; Kanagaraj, K.; Pitchumani, K., *Tetrahedron Lett.* **2014**, *55*, 3678-3682; (c) Rostamizadeh, S.; Ghaieni, H. R.; Aryan, R.; Amani, A. M., *Tetrahedron* **2010**, *66*, 494-497; (d) Ramu, T.; Prasanthi, S.; Mangarao, N.; Basha, G. M.; Srinuvasarao, R.; Siddaiah, V., *Chem. Lett.* **2013**, *42*, 722-724; (e) Kandre, S.; Bhagat, P. R.; Sharma, R.; Gupte, A., *Tetrahedron Lett.* **2013**, *54*, 3526-3529; (f) Kaboudin, B.; Malekzadeh, L., *Tetrahedron Lett.* **2011**, *52*, 6424-6426; (g) Baykov, S.; Sharonova, T.; Shetnev, A.; Rozhkov, S.; Kalinin, S.; Smirnov, A. V., *Tetrahedron* **2017**, *73*, 945-951; (h) Baykov, S.; Sharonova, T.; Osipyan, A.; Rozhkov, S.; Shetnev, A.; Smirnov, A., *Tetrahedron Lett.* **2016**, *57*, 2898-2900; (i) Augustine, J. K.; Akabote, V.; Hegde, S. G.; Alagarsamy, P., *J. Org. Chem.* **2009**, *74*, 5640-5643; (j) Adib, M.; Jahromi, A. H.; Tavoosi, N.; Mahdavi, M.; Bijanzadeh, H. R., *Tetrahedron Lett.* **2006**, *47*, 2965-2967; (k) Nakka, M.; Tadikonda, R.; Nakka, S.; Vidavalur, S., *Adv. Synth. Catal.* **2016**, *358*, 520-525; (l) Kaboudin, B.; Saadati, F., *J. Heterocyclic Chem.* **2005**, *42*, 699-701; (m) Draghici, B.; El-Gendy, B. E. M.; Katritzky, A. R., *Synthesis*, **2012**, *44*, 547-550; (n) He, H.-B.; Gao, L.-X.; Zhou, Y.-Y.; Liu, T.; Tang, J.; Gong, X.-P.; Qiu, W.-W.; Li, J.-Y.; Li, J.; Yang, F., *Heterocycles* **2012**, *85*, 2693-2712; (o) Telvekar, V. N.; Takale, B. S., *Synthetic Commun.* **2013**, *43*, 221-227; (p) Nakka, M.; Gajula, M. B.;

Tadikonda, R.; Rayavarapu, S.; Sarakula, P.; Vidavalur, S., *Tetrahedron Lett.* **2014**, *55*, 177-179; (q) Movassagh, B.; Talebsereshki, F., *Synthetic Commun.* **2014**, *44*, 188-194; (r) Kivrak, A.; Zora, M., *Tetrahedron* **2014**, *70*, 817-831; (s) Otaka, H.; Ikeda, J.; Tanaka, D.; Tobe, M., *Tetrahedron Lett.* **2014**, *55*, 979-981.

6. Kuram, M. R.; Kim, W. G.; Myung, K.; Hong, S. Y., *Eur. J. Org. Chem.* **2016**, 438-442.

7. (a) Lade, J. J.; Patil, B. N.; Vadagaonkar, K. S.; Chaskar, A. C., *Tetrahedron Lett.* **2017**, *58*, 2103-2108; (b) Zhang, F. L.; Wang, Y. F.; Chiba, S., *Org. Biomol. Chem.* **2013**, *11*, 6003-6007.

8. (a) Yoshimura, A.; Nguyen, K. C.; Klasen, S. C.; Saito, A.; Nemykina, V. N.; Zhdankin, V. V., *Chem. Commun.* **2015**, *51*, 7835-7838; (b) Yoshimura, A.; Nguyen, K. C.; Klasen, S. C.; Postnikov, P. S.; Yusubov, M. S.; Saito, A.; Nemykin, V. N.; Zhdankin, V. V., *Asian J. Org. Chem.* **2016**, *5*, 1128-1133.

9. Guo, W.; Huang, K.; Ji, F.; Wua, W.; Jiang, H., *Chem. Commun.* **2015**, *51*, 8857-8860.

10. (a) Götz, N.; Zeeh, B., *Synthesis* **1976**, 268-270; (b) Fuchigami, T. O., k., *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3607-3610.

11. Gupta, P. K.; Hussain, M. K.; Asad, M.; Kant, R.; Mahar, R.; Shukla, S. K.; Hajela, K., *New J. Chem.* **2014**, *38*, 3062-3070.

12. Asad, M.; Gupta, P. K.; Jaiswal, S. K.; Hajela, K., *ChemistrySelect* **2016**, *1*, 4753-4757.

13. Saikia, I.; Borah, A. J.; Phukan, P., *Chem. Rev.* **2016**, *116*, 6837-7042.

14. (a) Wang, J. Y.; Zhou, P.; Li, G.; Hao, W. J.; Tu, S. J.; Jiang, B., *Org. Lett.* **2017**, *19*, 6682-6685; (b) Liu, L.; Chen, D.; Yao, J.; Zong, Q.; Wang, J.; Zhou, H., *J. Org. Chem.* **2017**, *82*, 4625-4630; (c) Tang, B. X.; Zhang, Y. H.; Song, R. J.; Tang, D. J.; Deng, G. B.; Wang, Z. Q.; Xie, Y. X.; Xia, Y. Z.; Li, J. H., *J. Org. Chem.* **2012**, *77*, 2837-2849.

15. (a) Wei, Y.; Lin, S.; Xue, H.; Liang, F.; Zhao, B., *Org. Lett.* **2012**, *14*, 712-715; (b) Wang, X.; Xu, D.; Miao, C.; Zhang, Q.; Sun, W., *Org. Biomol. Chem.* **2014**, *12*, 3108-3113; (c) Bathula, S. R.; Reddy, M. P.; Viswanadham, K. K. D. R.; Sathyanarayana, P.; Reddy, M. S., *Eur. J. Org. Chem.* **2013**, *2013*, 4552-4557; (d) Borsoi, A. F.; Coldeira, M. E.; Pissinate, K.; Macchi, F. S.; Basso, L. A.; Santos, D. S.; Machado, P., *Synth. Commun.* **2017**, *47*, 1319-1325.

16. (a) Hu, X.-Q.; Chen, J.-R.; Wei, Q.; Liu, F.-L.; Deng, Q.-H.; You-Quan, Z.; Xiao, W.-J., *Eur. J. Org. Chem.* **2014**, *2014*, 3082-3086; (b) Huang, C.; Zeng, Y.; Cheng, H.; Hu, A.; Liu, L.; Xiao, Y.; Zhang, J., *Org. Lett.* **2017**, *19*, 4968-4971; (c) Li, Z.-S.; Wang, W.-X.; Yang, J.-D.; Wu, Y.-W.; Zhang, W., *Org. Lett.* **2013**, *15*, 3820-3823; (d) Ouyang, H. C.; Tang, R. Y.; Zhong, P.; Zhang, X. G.; Li, J. H., *J. Org. Chem.* **2011**, *76*, 223-228; (e) Wang, W.-X.; Zhang, Q.-Z.; Zhang, T.-Q.; Li, Z.-S.; Zhang, W.; Yu, W., *Adv. Synth. Catal.* **2015**, *357*, 221-226.

17. Chakrabarty, M.; Kundu, T.; Arima, S.; Harigaya, Y., *Tetrahedron Lett.* **2005**, *46*, 2865-2868.

18. (a) Song, L.; Tian, X.; Lv, Z.; Li, E.; Wu, J.; Liu, Y.; Yu, W.; Chang, J., *J. Org. Chem.* **2015**, *80*, 7219-7225; (b) Wang, B.; Meng, Y.; Zhou, Y.; Ren, L.; Wu, J.; Yu,

W.; Chang, J., *J. Org. Chem.* **2017**, *82*, 5898-5903.

19. Prat, D.; Hayler, J.; Wells, A., *Green Chem.* **2014**, *16*, 4546-4551.

20. In the absence of DBU, a plausible bromide intermediate can be detected by mass spectrometry (MS *(m/z)* $[M - H]^-$ calcd for $C_{14}H_{10}BrN_2O$ 301.00, 303.00, found 301.47, 303.43.), but cannot be isolated for further characterization due to its instability.

21. (a) Wei, Y.; Lin, S.; Liang, F.; Zhang, J., *Org. Lett.* **2013**, *15*, 852-855; (b) Wei, Y.; Liang, F.; Zhang, X., *Org. Lett.* **2013**, *15*, 5186-5189; (c) Wei, Y.; Lin, S.; Liang, F., *Org. Lett.* **2012**, *14*, 4202-42055.

22. Kumar, D.; Patel, G.; Johnson, E. O.; Shah, K., *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2739-2741.

23. Palumbo Piccionello, A.; Pace, A.; Pierro, P.; Pibiri, I.; Buscemi, S.; Vivona, N., *Tetrahedron* **2009**, *65*, 119-127.

24. Belen'kll, L. I.; Brokhovetskii, D. B.; Krayushkin, M. M., *Tetrahedron* **1990**, *46*, 1659-1668.

25. Harada, K.; Kaji, E.; Zen, S., *Chem. Pharm. Bull.* **1980**, *28*, 3296-3303.

26. Gibert, J.-P.; Petrus, C.; Petrus, F., *J. Heterocyclic Chem.* **1979**, *16*, 311-320.

27. Pattison, G.; Piraux, G.; Lam, H. W., *J. Am. Chem. Soc.* **2010**, *132*, 14373-14375.

28. Morrocohi, S.; Ricca, A.; Velo, L., *Tetrahedron Lett.* **1967**, 331-334.

29. Chiou, S.; Shine, H. J., *J. Heterocyclic Chem.* **1989**, *26*, 125-128.