Tetrahedron xxx (2015) 1–6

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile synthesis of pyrazolo[1,5-*a*]pyridopyrazin-one via Smiles rearrangement or direct cyclization

Youxin Xiao [a], Zhicheng Zhang [a], Yinbo Chen [a], Xusheng Shao [a], Zhong Li [a,b], Xiaoyong Xu [a,b,*]

[a] *Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China*

[b] *Shanghai Collaborative Innovation Center for Biomanufacturing Technology, 130 Meilong Road, Shanghai 200237, China*

ARTICLE INFO

Article history:
Received 21 November 2014
Received in revised form 18 January 2015
Accepted 27 January 2015
Available online xxx

Keywords:
Smiles rearrangement
Cyclization
Pyrazolo[1,5-*a*]pyridopyrazin-one

ABSTRACT

A facile access to pyrazolo[1,5-*a*]pyridopyrazin-one is presented via Smiles rearrangement or direct cyclization. The method allows the convenient construction of a novel biaryl lactam in moderate to excellent yields starting from easily available precursors (18 examples, 75–97% yield). When R is an aryl group, two regioisomeric products were obtained, Smiles rearrangement product and direct cyclization product, but when R is alkyl or benzyl, Smiles rearrangement product was afforded selectively. In order to prove the proposed mechanism, intermediate **6k** was trapped.

1. Introduction

The biaryl lactams are an important class of heterocyclic compounds that exhibit a wide range of biological properties, including anti-HIV agent 1,[1] human A_3 adenosine receptor antagonist **2**,[2–4] PARP-1 inhibitors **3** and **4**[5–7] and excitatory amino acid antagonist **5**[8–11](Fig. 1). In addition, the biaryl lactams can also be used for the assembly of 5-HT_3 receptor agonist **6**[12] (Fig. 1).

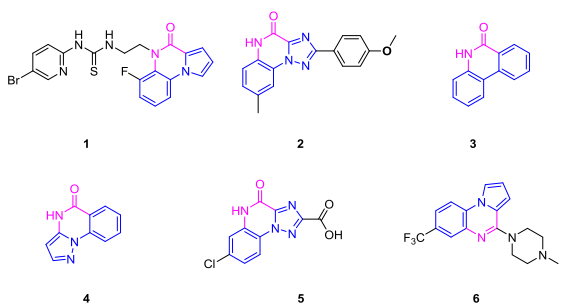


Fig. 1. Biologically active biaryl lactam compounds.

Several synthetic approaches to this scaffold have been developed, such as the triphosgene cyclization method,[13–15] palladium-catalyzed intramolecular carbon–nitrogen bond formation[16] and copper-catalyzed intermolecular coupling.[17] The method above employs hazardous or transition metal reagents, or inconvenient operations, etc., thus, it is necessary to develop a direct and facile approach for the synthesis of biaryl lactams. Recently, Smiles rearrangement has emerged as a significant strategy for constructing many heterocyclic compounds due to their numerous advantages, namely, their relatively high efficiency, transition metal free and mild reaction conditions.[18–25] Herein, we report a simple, high yield and metal free method for the synthesis of a novel-scaffold biaryl lactam: pyrazolo[1,5-*a*]pyridopyrazin-4(5*H*)-one via Smiles rearrangement or direct cyclization under mild condition (Fig. 2).

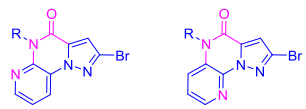


Fig. 2. Structure of pyrazolo[1,5-*a*]pyridopyrazin-4(5*H*)-one.

2. Results and discussion

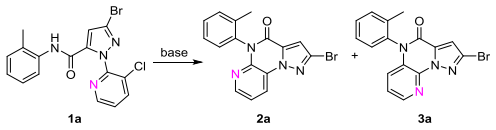
Following our group's interest in the area of lactam chemistry,[26] we wished to synthesize 2-bromo-5-(*o*-tolyl)pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrazin-4(5*H*)-one(**2a**) by intramolecular Smiles rearrangement

* Corresponding author. Tel.: +86 21 64252945; fax: +86 21 64252603; e-mail address: xyxu@ecust.edu.cn (X. Xu).

http://dx.doi.org/10.1016/j.tet.2015.01.059
0040-4020/

cyclization of 3-bromo-1-(3-chloropyridin-2-yl)-*N*-(*o*-tolyl)-1*H*-pyrazole -5-carboxamide(**1a**).

It was found that the reaction of **1a** in the presence of base afforded a mixture of two regioisomeric products: **2a** and **3a** in an approximately 1:1 ratio (Scheme 1). The structures of the tricyclic products **2a** and **3a** were established by X-ray crystallographic analysis (Fig. 3).[27] Compound **3a** was properly formed through a direct intramolecular cyclization.



Scheme 1. Synthesis of pyrazolo[1,5-*a*]pyridopyrazin-one.

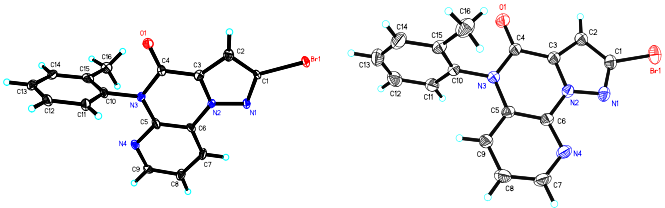
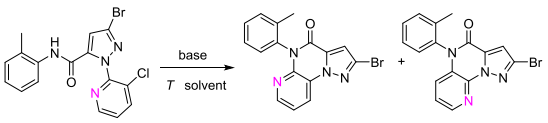


Fig. 3. X-ray structures of **2a** and **3a**.

We initiated our optimization experiments of an intramolecular cyclization reaction using **1a** (Table 1). First, the ability of various bases was examined to promote the cyclization of **1a**. It was found that the conversion was complete at 100 °C to obtain a mixture of **2a** and **3a** in 84% combined yield using K_2CO_3 (Table 1, entry 2). However, when **1a** was treated with 2 equiv Cs_2CO_3 or *t*-BuOK, the total yield decreased (Table 1, entries 3 and 4). The cyclization couldn't occur when Et_3N or DIPEA was used as base (Table 1, entries 5 and 6). To our delight, **1a** gave a highly combined yield after 4 h using 2 equiv DBU at 100 °C (Table 1, entry 7). When the base was absent in a control reaction, no cyclization product **2a** or **3a** was detected (Table 1, entry 1). Further study on solvent screening showed that other solvents, such as acetonitrile, toluene, DMF and so on, were inferior to NMP in promoting this cyclization process (Table 1, entries 8–16). In addition, altering the equivalent of DBU and the reaction temperature had no significant improvement for the reaction yield (Table 2, entries 1–9). Accordingly, the optimized reaction condition was as follows: base: DBU (2.0 equiv), solvent: NMP, temperature: 100 °C.

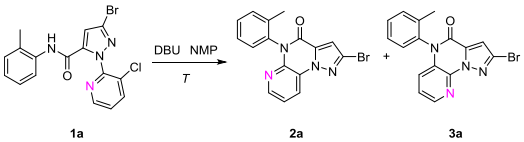
Table 1
Optimization of reaction condition (I)[a]



Entry	Base	Solvent	*T* (°C)	Time (h)	Yield[b] (%)		
					2a	**3a**	(**2a**+**3a**)
1	None	NMP	100	24	0	0	0
2	K_2CO_3	NMP	100	4	47	37	84
3	Cs_2CO_3	NMP	100	4	27	28	55
4	*t*-BuOK	NMP	100	4	26	27	53
5	Et_3N	NMP	100	24	0	0	0
6	DIPEA[c]	NMP	100	24	0	0	0
7	DBU	NMP	100	4	53	39	92
8	DBU	DMF	100	4	50	39	89
9	DBU	DMSO	100	4	48	38	86
10	DBU	Toluene	Reflux	48	45	27	72
11	DBU	CH_3CN	Reflux	48	26	27	53
12	DBU	1,2-Dichloroethane	Reflux	48	0	0	0
13	DBU	EtOH	Reflux	48	24	13	37
14	DBU	MeOH	Reflux	48	19	12	31
15	DBU	THF	Reflux	48	0	0	0
16	DBU	$CHCl_3$	Reflux	48	8	6	14

[a] The reactions were carried out in 0.5 mmol (**1a**) scale; **1a**: 1 equiv; base: 2 equiv.
[b] Yield was determined by UPLC (ultra performance liquid chromatography).
[c] DIPEA was short for *N*,*N*-diisopropylethylamine.

Table 2
Optimization of reaction condition (II)[a]



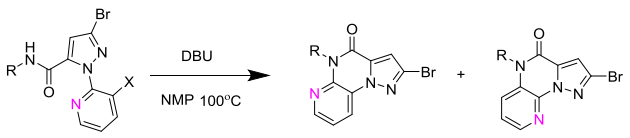
Entry	Base	No. of equiv	*T* (°C)	Time (h)	Yield[b] (%)		
					2a	**3a**	(**2a**+**3a**)
1	DBU	0.5	100	24	9	9	18
2	DBU	1	100	24	33	35	68
3	DBU	1.5	100	4	38	40	78
4	DBU	2	100	4	53	39	92
5	DBU	3	100	4	42	43	85
6	DBU	4	100	4	45	44	89
7	DBU	2	50	36	51	34	85
8	DBU	2	80	8	45	43	88
9	DBU	2	120	4	51	39	90

[a] The reaction was carried out in 0.5 mmol (**1a**) scale.
[b] Yield was determined by UPLC (ultra performance liquid chromatography).

Under the optimized reaction condition, a wide range of substrates bearing a variety of amines ranging from aromatic to aliphatic were examined. As shown in Table 3, when R was aryl, a series of substrates were attempted. The results showed that the tricyclic products **2** and **3** were obtained in good yields. As the lactam was easy to be hydrolyzed when R was electron-withdrawing group (Table 3, entries 5 and 6), so anhydrous solvent was used. As shown in Table 4, when R was alkyl or benzyl, all the substrates could be transformed into the rearrangement/cyclization products **2** with good yields (**2i**–**2r**, 87–97% yield).

From the results above, it was known that the nucleophilic ability of amine in the starting material **1** was important to the

Table 3
Synthesis of pyrazolo[1,5-*a*]pyridopyrazin-one when R was aryl[a]

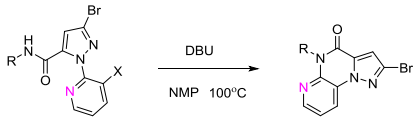


Entry	R	X	Substrate	Yield[b] (%)		Yield[b] (%) (**2**+**3**)
				2	**3**	
1	2-MeC_6H_4	Cl	**1a**	48 (**2a**)	40 (**3a**)	88
2	C_6H_4	Cl	**1b**	48 (**2b**)	33 (**3b**)	81
3	4-MeC_6H_4	Cl	**1c**	51 (**2c**)	31 (**3c**)	82
4	4-(MeO)C_6H_4	Cl	**1d**	52 (**2d**)	32 (**3d**)	84
5[c]	4-(NO_2)C_6H_4	Cl	**1e**	21 (**2e**)	54 (**3e**)	75
6[c]	4-(CN)C_6H_4	Cl	**1f**	13 (**2f**)	64 (**3f**)	77
7	3-MeC_6H_4	Cl	**1g**	45 (**2g**)	39 (**3g**)	84
8	2-MeC_6H_4	Br	**1h**	47 (**2h**)	38 (**3h**)	85

[a] The reactions were carried out in 0.5 mmol (**1**) scale; **1**: 1 equiv; base: 2 equiv; solvent: 2 ml.
[b] Isolated yield.
[c] DMF(anhydrous) was used as the solvent.

Please cite this article in press as: Xiao, Y.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.01.059

Table 4
Synthesis of pyrazolo[1,5-*a*]pyridopyrazin-one when R was alkyl or benzyl[a]



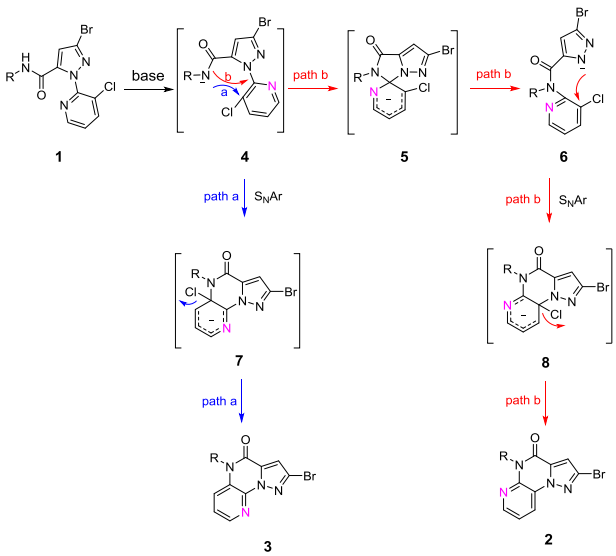
1 2

Entry	R	X	Substrate	Yield (%)[a] **2**
1	*n*-Propyl	Cl	**1i**	94 (**2i**)
2	*i*-Propyl	Cl	**1j**	97 (**2j**)
3	Butyl	Cl	**1k**	95 (**2k**)
4	Cyclopropyl	Cl	**1l**	94 (**2l**)
5	Cyclopentane	Cl	**1m**	94 (**2m**)
6	*n*-Propyl	Br	**1n**	92 (**2n**)
7	Benzyl	Cl	**1o**	96 (**2o**)
8	4-Methoxybenzyl	Cl	**1p**	93 (**2p**)
9	4-Trifluoromethylbenzyl	Cl	**1q**	87 (**2q**)
10	Benzyl	Br	**1r**	93 (**2r**)

[a] Isolated yield.

reaction. Compounds **1i**–**1r** containing aliphatic amines with good nucleophilic ability gave **2i**–**2r** selectively, while **1a**–**1h** with poor nucleophilic ability of aromatic amines afforded a mixture containing **2** and **3**. Also, it gave the similar result when the chlorine atom in pyridine displaced by bromine atom (Table 3, entry 8; Table 4, entries 6 and 10). So, the selectivity of products **2** and **3** may mainly depend on the nucleophilic ability of the amines, rather than the leaving ability of the halogen in the pyridine.

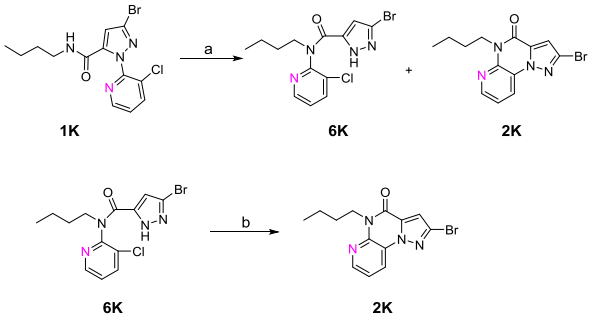
A plausible reaction mechanism was proposed in Scheme 2. In the presence of base, compound **1** formed carboxamide anion **4**. Subsequently, anion **4** followed by two paths: a and b. Path a yielded **3** by direct cyclization via **7** in S_NAr reaction, whereas path b led to spirocyclic anion intermediate **5** via Smiles rearrangement, then **6** was formed from **5**. Finally, **6** underwent an intramolecular cyclization to give **2** via **8** in S_NAr reaction.



1 4 5 6 7 8 3 2

Scheme 2. Proposed mechanism for the formation of **2** and **3**.

In order to verify the proposed mechanism, we tried to trap the intermediate **6**. Using NMP as solvent, target product was obtained with high yield, but the intermediate could not be observed and afforded. Thus, acetonitrile was chosen as solvent under mild condition to trap the intermediate **6**. It was interesting to note that TLC examination of reaction **1k** with DBU in acetonitrile after 1 h, revealed a new spot together with the spot corresponding to product **2k**. After work-up and column chromatography, two compounds were isolated, **2k** and **6k** in 5% and 92% yields, respectively (Scheme 3). Compound **6k** was confirmed by ^1H NMR, ^{13}C NMR, HRMS. Furthermore, reaction of isolated **6k** with DBU in NMP after 4 h gave **2k** as sole product in 97% yield (Scheme 3).



1K 6K 2K 6K 2K

Scheme 3. Reagents and conditions: (a) DBU, acetonitrile, 50 °C, 1 h; (b) DBU, NMP, 100 °C, 4 h.

Based on the above experiment result, we can confidently propose that compound **1** undergoes Smiles rearrangement to give **2** via intermediate **6**.

3. Conclusions

In summary, we have developed an efficient, high yielding and metal free method to prepare pyrazolo[1,5-*a*]pyridopyrazin-one via direct cyclization or Smiles rearrangement/cyclization reaction. The product selectivity was mainly dominated by the nucleophilic ability of amine in the substrate. Substrate bearing aromatic amine gives a mixture of **2** and **3**, while substrate containing aliphatic amine gives only Smiles rearrangement/cyclization product selectively with the increasing the nucleophilic ability of amines. Also, similar result was found when the chlorine atom on pyridine ring displaced by bromine atom. Further studies on the application of this cyclization reaction are in progress in our laboratory.

4. Experimental section

4.1. General procedure for the synthesis of 1a–1r

A mixture of 3-bromo-1-(3-chloro(bromo)pyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (1.0 mmol), an excess of oxalyl chloride (3 ml) was stirred at room temperature for 10 min, then 1 drop DMF was added, the reaction mixture was stirred at room temperature for another 3 h and concentrated in vacuo to give corresponding acyl chloride. The corresponding acyl chloride was dissolved in 2 ml anhydrous DCM, then added dropwise to a solution of various amines (1.0 mmol), DIPEA (1.2 mmol) in 15 ml anhydrous DCM in an ice bath. The reaction mixture was then stirred at room temperature and monitored by TLC, after completion, the solvent was evaporated under reduced pressure. The residual solid was purified by column chromatography on silica gel with ethyl acetate–petroleum ether as eluent to afford compounds **1a**–**1r**.

4.2. General procedure for the synthesis of 2a–2h and 3a–3h

The mixtures of **1** (1 equiv) and DBU (2 equiv) in NMP (2 ml) were heated to 100 °C and stirred for 4–10 h. The reaction was monitored by TLC. After completion, the mixtures were poured into water (20 ml) and extracted with ethyl acetate (20 ml×3). The organic phase was combined, evaporated under reduced pressure,

Please cite this article in press as: Xiao, Y.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.01.059

then purified by column chromatography (SiO_2; petroleum ether/ethyl acetate=3:1) to obtain **2** and **3**, respectively.

*4.2.1. 2-Bromo-5-(o-tolyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrazin-4(5H)-one (**2a** or **2h**).* Yield 48%; white solid; mp: 263.3–264.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J=8.0, 1.2 Hz, 1H), 8.37 (dd, J=4.8, 1.2 Hz, 1H), 7.51–7.41 (m, 3H), 7.32 (dd, J=8.0, 4.8 Hz, 1H), 7.28 (s, 1H), 7.23 (d, J=7.2 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 146.9, 141.5, 136.3, 134.2, 134.1, 131.3, 130.9, 129.6, 128.9, 127.3, 123.6, 120.5, 119.6, 110.8, 17.7; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O^+$, 354.0116, found: 354.0112; calcd for $C_{16}H_{11}{}^{81}BrN_4O^+$, 356.0096, found: 356.0096.

*4.2.2. 2-Bromo-5-(o-tolyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrazin-4(5H)-one (**3a** or **3h**).* Yield 40%; white solid; mp: 227.4–228.7 °C; ^{1}H NMR (400 MHz, CDCl3) δ 8.46 (d, J=4.0 Hz, 1H), 7.55–7.46 (m, 3H), 7.32 (s, 1H), 7.31–7.22 (m, 2H), 7.00 (d, J=8.0 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 143.7, 136.5, 135.2, 133.6, 132.3, 132.1, 130.3, 128.8, 128.2, 125.9, 124.8, 122.7, 111.7, 17.4; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O^+$, 354.0116, found: 354.0115; calcd for $C_{16}H_{11}{}^{81}BrN_4O^+$, 356.0096, found: 356.0096.

*4.2.3. 2-Bromo-5-phenylpyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2b**).* Yield 48%; white solid; mp: 286.3–286.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, J=8.0, 1.6 Hz, 1H), 8.34 (dd, J=4.8, 1.6 Hz, 1H), 7.63–7.52 (m, 3H), 7.35–7.31 (m, 2H), 7.29 (dd, J=8.0, 4.8 Hz, 1H), 7.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 146.6, 142.0, 134.9, 134.0, 130.9, 129.6, 129.2, 129.0, 123.6, 120.5, 119.6, 110.7; HRMS (EI) calcd for $C_{15}H_9{}^{79}BrN_4O^+$, 339.9960, found: 339.9955; calcd for $C_{15}H_9{}^{81}BrN_4O^+$, 341.9939, found: 341.9933.

*4.2.4. 2-Bromo-5-phenylpyrazolo[1,5-a]pyrido[3,2-e]pyrazin-4(5H)-one (**3b**).* Yield 33%; white solid; mp: 234.1–234.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J=4.4 Hz, 1H), 7.68–7.58 (m, 3H), 7.34 (d, J=7.2 Hz, 2H), 7.29–7.24 (m, 2H), 7.11 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 143.6, 135.1, 135.0, 134.7, 132.3, 130.6, 130.0, 128.8, 126.6, 125.2, 122.5, 111.6; HRMS (EI) calcd for $C_{15}H_9{}^{79}BrN_4O^+$, 339.9960, found: 339.9958; calcd for $C_{15}H_9{}^{81}BrN_4O^+$, 341.9939, found: 341.9945.

*4.2.5. 2-Bromo-5-(p-tolyl)pyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2c**).* Yield 51%; white solid; mp: 289.7–291.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J=8.0 Hz, 1H), 8.36 (d, J=4.0 Hz, 1H), 7.39 (d, J=7.6 Hz, 2H), 7.30–7.27 (m, 1H), 7.24–7.19 (m, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 146.6, 142.2, 139.1, 134.0, 132.3, 130.9, 130.4, 128.7, 123.5, 120.5, 119.5, 110.7, 21.4; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O^+$, 354.0116, found: 354.0117; calcd for $C_{16}H_{11}{}^{81}BrN_4O^+$, 356.0096, found: 356.0082.

*4.2.6. 2-Bromo-5-(p-tolyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrazin-4(5H)-one (**3c**).* Yield 31%; white solid; mp: 280.3–281.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J=4.0 Hz, 1H), 7.44 (d, J=8.0 Hz, 2H), 7.28 (s, 1H), 7.27–7.23 (m, 1H), 7.21 (d, J=8.0 Hz, 2H), 7.14 (d, J=8.0 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 143.6, 140.2, 135.2, 135.1, 132.3, 132.0, 131.3, 128.5, 126.8, 125.3, 122.5, 111.6, 21.3; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O^+$, 354.0116, found: 354.0115; calcd for $C_{16}H_{11}{}^{81}BrN_4O^+$, 356.0096, found: 356.0086.

*4.2.7. 2-Bromo-5-(4-methoxyphenyl)pyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2d**).* Yield 52%; white solid; mp: 279.6–280.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J=8.0, 1.2 Hz, 1H), 8.36 (dd, J=4.8, 1.2 Hz, 1H), 7.28 (dd, J=8.0, 4.8 Hz, 1H), 7.25–7.21 (m, 3H), 7.09 (d, J=8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 153.9, 146.6, 142.3, 134.1, 130.9, 129.9, 127.3, 123.5, 120.5, 119.5, 114.9, 110.7, 55.5; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O^{2+}$, 370.0065, found: 370.0064; calcd for $C_{16}H_{11}{}^{81}BrN_4O^{2+}$, 372.0045, found: 372.0044.

*4.2.8. 2-Bromo-5-(4-methoxyphenyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrazin-4(5H)-one (**3d**).* Yield 32%; white solid; mp: 263.3–264.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, J=4.8, 1.2 Hz, 1H), 7.29–7.22 (m, 4H), 7.18–7.10 (m, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 152.9, 143.5, 135.2, 135.1, 132.2, 129.8, 127.0, 126.9, 125.3, 122.5, 115.8, 111.5, 55.6; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O_2^+$, 370.0065, found: 370.0067; calcd for $C_{16}H_{11}{}^{81}BrN_4O_2^+$, 372.0045, found: 372.0053.

*4.2.9. 2-Bromo-5-(4-nitrophenyl)pyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2e**).* Yield 21%; white solid; mp: 309.0–309.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, J=8.0, 1.6 Hz, 1H), 8.46 (d, J=8.8 Hz, 2H), 8.31 (dd, J=4.8, 1.6 Hz, 1H), 7.55 (d, J=8.8 Hz, 2H), 7.35 (dd, J=8.0, 4.8 Hz, 1H), 7.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 147.9, 146.4, 141.3, 140.6, 133.5, 131.3, 130.6, 124.8, 123.9, 120.6, 120.3, 111.3; HRMS (EI) calcd for $C_{15}H_8{}^{79}BrN_5O^{3+}$, 384.9811, found: 384.9808; calcd for $C_{15}H_8{}^{81}BrN_5O^{3+}$, 386.9790, found: 386.9781.

*4.2.10. 2-Bromo-5-(4-nitrophenyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrazin-4(5H)-one (**3e**).* Yield 54%; white solid; mp: 306.4–307.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J=8.8 Hz, 2H), 8.49 (d, J=4.0 Hz, 1H), 7.60 (d, J=8.8 Hz, 2H), 7.33–7.28 (m, 2H), 7.08 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 148.6, 144.3, 140.3, 135.1, 134.6, 132.6, 130.5, 125.9, 125.7, 124.5, 122.7, 112.2; HRMS (EI) calcd for $C_{15}H_8{}^{79}BrN_5O^{3+}$, 384.9811, found: 384.9809; calcd for $C_{15}H_8{}^{81}BrN_5O^{3+}$, 386.9790, found: 386.9791.

*4.2.11. 4-(2-Bromo-4-oxopyrazolo[1,5-a]pyrido[2,3-e]pyrazin-5(4H)-yl)benzonitrile (**2f**).* Yield 13%; white solid; mp: 329.7–331.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, J=8.0, 1.6 Hz, 1H), 8.31 (dd, J=4.8, 1.6 Hz, 1H), 7.91–7.87 (m, 2H), 7.51–7.45 (m, 2H), 7.34 (dd, J=8.0, 4.8 Hz, 1H), 7.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 146.4, 141.3, 139.1, 133.6, 133.4, 131.3, 130.5, 123.9, 120.6, 120.2, 118.1, 113.2, 111.2; HRMS (EI) calcd for $C_{16}H_8{}^{79}BrN_5O^+$, 364.9912, found: 364.9910; calcd for $C_{16}H_8{}^{81}BrN_5O^+$, 366.9892, found: 366.9890.

*4.2.12. 4-(2-Bromo-4-oxopyrazolo[1,5-a]pyrido[2,3-e]pyrazin-5(4H)-yl)benzonitrile (**3f**).* Yield 64%; white solid; mp: 370.5–371.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, J=4.8, 1.2 Hz, 1H), 7.97 (d, J=8.4 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H), 7.32–7.28 (m, 2H), 7.06 (dd, J=8.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 144.3, 138.7, 135.1, 134.6, 134.5, 132.6, 130.29, 125.8, 124.6, 122.7, 117.5, 114.4, 112.1; HRMS (EI) calcd for $C_{16}H_8{}^{79}BrN_5O^+$, 364.9912, found: 364.9913; calcd for $C_{16}H_8{}^{81}BrN_5O^+$, 366.9892, found: 366.9893.

*4.2.13. 2-Bromo-5-(m-tolyl)pyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2g**).* Yield 45%; white solid; mp: 226.8–227.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, J=8.0, 1.6 Hz, 1H), 8.36 (dd, J=4.8, 1.6 Hz, 1H), 7.48 (t, J=7.6 Hz, 1H), 7.34 (d, J=7.6 Hz, 1H), 7.28 (dd, J=8.0, 4.8 Hz, 1H), 7.24 (s, 1H), 7.14–7.11 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 146.7, 142.1, 139.7, 134.8, 134.0, 130.9, 130.1, 129.5, 129.4, 125.9, 123.5, 120.5, 119.5, 110.7, 21.5; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O^+$, 354.0116, found: 354.0115; calcd for $C_{16}H_{11}{}^{81}BrN_4O^+$, 356.0096, found: 356.0092.

*4.2.14. 2-Bromo-5-(m-tolyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrazin-4(5H)-one (**3g**).* Yield 39%; white solid; mp: 232.6–232.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J=4.8, 1.2 Hz, 1H), 7.53 (t, J=7.6 Hz, 1H), 7.40 (d, J=7.6 Hz, 1H), 7.29 (s, 1H), 7.26 (dd, J=8.0, 4.8 Hz, 1H), 7.14–7.10 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 143.6, 140.9, 135.2, 135.0, 134.6, 132.3, 130.8,

Please cite this article in press as: Xiao, Y.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.01.059

130.4, 129.2, 126.7, 125.7, 125.3, 122.5, 111.6, 21.4; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O^+$, 354.0116, found: 354.0117; calcd for $C_{16}H_{11}{}^{81}BrN_4O^+$, 356.0096, found: 356.0095.

4.3. General procedure for the synthesis of 2i–2r

The mixtures of **1** (1 equiv) and DBU (2 equiv) in NMP (2 ml) were heated to 100 °C and stirred for 4–10 h. The reaction was monitored by TLC. After completion, the mixtures were poured into ice water and filtered, and the precipitated products were washed with water and dried, then purified by column chromatography (SiO_2; petroleum ether/ethyl acetate=4:1) to obtain **2**.

*4.3.1. 2-Bromo-5-propylpyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2i** or **2n**).* Yield 94%; white solid; mp: 143.1–143.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50–8.46 (m, 2H), 7.29 (dd, J=7.2, 4.8 Hz, 1H), 7.16 (s, 1H), 4.48–4.43 (m, 2H), 1.86–1.76 (m, 2H), 1.03 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 146.4, 140.7, 133.9, 130.7, 123.3, 120.5, 119.1, 109.9, 42.6, 21.3, 11.4; HRMS (EI) calcd for $C_{12}H_{11}{}^{79}BrN_4O^+$, 306.0116, found: 306.0115; calcd for $C_{12}H_{11}{}^{81}BrN_4O^+$, 308.0096, found: 308.0097.

*4.3.2. 2-Bromo-5-isopropylpyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2j**).* Yield 97%; white solid; mp: 128.7–129.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51–8.45 (m, 2H), 7.28 (dd, J=8.0, 4.8 Hz, 1H), 7.13 (s, 1H), 5.98–5.90 (m, 1H), 1.67 (d, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 145.7, 140.9, 134.4, 130.6, 123.5, 120.6, 119.0, 109.8, 46.5, 19.6; HRMS (EI) calcd for $C_{12}H_{11}{}^{79}BrN_4O^+$, 306.0116, found: 306.0113; calcd for $C_{12}H_{11}{}^{81}BrN_4O^+$, 308.0096, found: 308.0097.

*4.3.3. 2-Bromo-5-butylpyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2k**).* Yield 95%; white solid; mp: 129.0–129.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J=6.4 Hz, 2H), 7.31–7.27 (m, 1H), 7.16 (s, 1H), 4.53–4.47 (m, 2H), 1.87–1.68 (m, 2H), 1.54–1.39 (m, 2H), 0.98 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 146.4, 140.7, 133.9, 130.7, 123.3, 120.5, 119.1, 109.9, 40.9, 30.1, 20.3, 13.8; HRMS (EI) calcd for $C_{13}H_{13}{}^{79}BrN_4O^+$, 320.0273, found: 320.0272; calcd for $C_{13}H_{13}{}^{81}BrN_4O^+$, 322.0252, found: 322.0250.

*4.3.4. 2-Bromo-5-cyclopropylpyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2l**).* Yield 94%; white solid; mp: 177.8–178.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J=4.8 Hz, 1H), 8.46 (d, J=8.0 Hz, 1H), 7.31 (dd, J=8.0, 4.8 Hz, 1H), 7.14 (s, 1H), 3.10–3.04 (m, 1H), 1.40–1.34 (m, 2H), 0.97–0.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 146.2, 142.3, 134.3, 130.7, 123.3, 120.8, 119.4, 110.1, 25.4, 9.7; HRMS (EI) calcd for $C_{12}H_9{}^{79}BrN_4O^+$, 303.9960, found: 303.9959; calcd for $C_{12}H_{11}{}^{81}BrN_4O^+$, 305.9939, found: 305.9941.

*4.3.5. 2-Bromo-5-cyclopentylpyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2m**).* Yield 94%; white solid; mp: 156.3–158.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, J=8.0, 1.6 Hz, 1H), 8.47 (dd, J=4.8, 1.6 Hz, 1H), 7.28 (dd, J=8.0, 4.8 Hz, 1H), 7.12 (s, 1H), 6.10–6.01 (m, 1H), 2.39–2.29 (m, 2H), 2.16–2.07 (m, 2H), 2.00–1.90 (m, 2H), 1.76–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 145.7, 141.0, 134.3, 130.6, 123.5, 120.7, 119.1, 109.7, 53.8, 28.6, 26.0; HRMS (EI) calcd for $C_{14}H_{13}{}^{79}BrN_4O^+$, 332.0273, found: 332.0272; calcd for $C_{14}H_{13}{}^{81}BrN_4O^+$, 334.0252, found: 334.0256.

*4.3.6. 5-Benzyl-2-bromopyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2o** or **2r**).* Yield 96%; white solid; mp: 181.3–182.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49–8.45 (m, 2H), 7.53 (d, J=7.2 Hz, 1H), 7.29–7.21 (m, 4H), 7.16 (s, 1H), 5.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 146.3, 140.6, 136.8, 133.9, 130.8, 128.9, 128.4, 127.6, 123.5, 120.6, 119.4, 110.2, 43.9; HRMS (EI) calcd for $C_{16}H_{11}{}^{79}BrN_4O^+$, 354.0116, found: 354.0117; calcd for $C_{16}H_{11}{}^{81}BrN_4O^+$, 356.0096, found: 356.0094.

*4.3.7. 2-Bromo-5-(4-methoxybenzyl)pyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2p**).* Yield 93%; white solid; mp: 188.1–189.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, J=4.8, 1.6 Hz, 1H), 8.48 (dd, J=8.0, 1.6 Hz, 1H), 7.54 (d, J=8.8 Hz, 2H), 7.29 (dd, J=8.0, 4.8 Hz, 1H), 7.17 (s, 1H), 6.81 (d, J=8.8 Hz, 2H), 5.66 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 153.8, 146.3, 140.6, 133.9, 130.7, 130.7, 129.0, 123.5, 120.6, 119.4, 113.7, 110.1, 55.2, 43.3; HRMS (EI) calcd for $C_{17}H_{13}{}^{79}BrN_4O_2{}^+$, 384.0222, found: 384.0221; calcd for $C_{17}H_{13}{}^{81}BrN_4O_2{}^+$, 386.0201, found: 386.0203.

*4.3.8. 2-Bromo-5-(4-(trifluoromethyl)benzyl)pyrazolo[1,5-a]pyrido[2,3-e]pyrazin-4(5H)-one (**2q**).* Yield 87%; white solid; mp: 205.7–207.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58–8.48 (m, 2H), 7.64 (d, J=8.0 Hz, 2H), 7.54 (d, J=8.0 Hz, 2H), 7.32 (dd, J=8.0, 4.8 Hz, 1H), 7.20 (s, 1H), 5.76 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.61 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 146.3, 140.6, 140.3, 133.7, 130.9, 129.8 (d, J=32.2 Hz), 129.2, 125.4 (q, J=3.3 Hz), 123.7, 120.8 (d, J=375.4 Hz), 120.7, 119.7, 110.5, 43.5; HRMS (EI) calcd for $C_{17}H_{10}{}^{79}BrF_3N_4O^+$, 421.9990, found: 421.9989; calcd for $C_{17}H_{10}{}^{81}BrF_3N_4O^+$, 423.9970, found: 423.9974.

4.4. Synthesis of 6k

The mixtures of **1k** (1 equiv) and DBU (2 equiv) in acetonitrile (5 ml) were heated to 50 °C and stirred for 1 h. The reaction was monitored by TLC. After completion, the solvent was evaporated, then, the mixtures were poured into water (20 ml) and extracted with ethyl acetate (20 ml×3). The organic phase was combined, evaporated under reduced pressure, then purified by column chromatography (SiO_2; petroleum ether/ethyl acetate=3:1) to obtain **6k**. Yield 92%; white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.15 (s, 1H), 8.61 (dd, J=4.8, 1.2 Hz, 1H), 8.15 (dd, J=8.0, 1.2 Hz, 1H), 7.60 (dd, J=8.0, 4.8 Hz, 1H), 4.86 (s, 1H), 3.98–3.90 (m, 1H), 3.76–3.68 (m, 1H), 1.59–1.48 (m, 2H), 1.38–1.25 (m, 2H), 0.86 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.8, 151.1, 148.8, 140.5, 138.0, 129.9, 126.5, 125.2, 107.5, 48.0, 29.9, 20.1, 14.1; HRMS (EI) calcd for $C_{13}H_{14}{}^{35}Cl^{79}BrN_4O^+$, 356.0040, found: 356.0038; calcd for $C_{13}H_{14}{}^{35}Cl^{81}BrN_4O^+$, 358.0019, found: 358.0017; calcd for $C_{13}H_{14}{}^{37}Cl^{79}BrN_4O^+$, 358.0010, found: 358.0017; calcd for $C_{13}H_{14}{}^{37}Cl^{81}BrN_4O^+$, 359.9990, found: 359.9997.

Acknowledgements

This work was financial supported by National Natural Science Foundation of China (21272071), National High Technology Research and Development Program of China (863 Program, 2011AA10A207, 2013AA065202). This work was also partly supported by the Fundamental Research Funds for the Central Universities.

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all products. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.01.059. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Campiani, G.; Aiello, F.; Fabbrini, M.; Morelli, E.; Ramunno, A.; Armaroli, S.; Nacci, V.; Garofalo, A.; Greco, G.; Novellino, E.; Maga, G.; Spadari, S.; Bergamini, A.; Ventura, L.; Bongiovanni, B.; Capozzi, M.; Bolacchi, F.; Marini, S.; Coletta, M.; Guiso, G.; Caccia, S. *J. Med. Chem.* **2001**, *44*, 305.

2. Catarzi, D.; Colotta, V.; Varano, F.; Lenzi, O.; Filacchioni, G.; Trincavelli, L.; Martini, C.; Montopoli, C.; Moro, S. *J. Med. Chem.* **2005**, *48*, 7932.
3. Colotta, V.; Cecchi, L.; Catarzi, D.; Filacchioni, G.; Martini, C.; Tacchi, P.; Lucacchini, A. *Eur. J. Med. Chem.* **1995**, *30*, 133.
4. Catarzi, D.; Colotta, V.; Varano, F.; Calabri, F. R.; Lenzi, O.; Filacchioni, G.; Trincavelli, L.; Martini, C.; Tralli, A.; Montopoli, C.; Moro, S. *Bioorg. Med. Chem.* **2005**, *13*, 705.
5. Chen, J.; Peng, H.; He, J.; Huan, X.; Miao, Z.; Yang, C. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2669.
6. Li, J.-H.; Serdyuk, L.; Ferraris, D. V.; Xiao, G.; Tays, K. L.; Kletzly, P. W.; Li, W.; Lautar, S.; Zhang, J.; Kalish, V. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1687.
7. Orvieto, F.; Branca, D.; Giomini, C.; Jones, P.; Koch, U.; Ontoria, J. M.; Palumbi, M. C.; Rowley, M.; Toniatti, C.; Muraglia, E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4196.
8. Varano, F.; Catarzi, D.; Colotta, V.; Filacchioni, G.; Galli, A.; Costagli, C.; Carlà, V. *J. Med. Chem.* **2002**, *45*, 1035.
9. Catarzi, D.; Colotta, V.; Varano, F.; Cecchi, L.; Filacchioni, G.; Galli, A.; Costagli, C. *J. Med. Chem.* **1999**, *42*, 2478.
10. Catarzi, D.; Colotta, V.; Varano, F.; Cecchi, L.; Filacchioni, G.; Galli, A.; Costagli, C.; Carlà, V. *J. Med. Chem.* **2000**, *43*, 3824.
11. Catarzi, D.; Colotta, V.; Varano, F.; Filacchioni, G.; Galli, A.; Costagli, C.; Carlà, V. *J. Med. Chem.* **2001**, *44*, 3157.
12. Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Dalla Valle, F.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362.
13. Grande, F.; Aiello, F.; Grazia, O. D.; Brizzi, A.; Garofalo, A.; Neamati, N. *Bioorg. Med. Chem.* **2007**, *15*, 288.
14. Guillon, J.; Forfar, I.; Mamani-Matsuda, M.; Desplat, V.; Saliège, M.; Thiolat, D.; Massip, S.; Tabourier, A.; Léger, J.-M.; Dufaure, B.; Haumont, G.; Jarry, C.; Mossalayi, D. *Bioorg. Med. Chem.* **2007**, *15*, 194.
15. Guillon, J.; Grellier, P.; Labaied, M.; Sonnet, P.; Léger, J.-M.; Déprez-Poulain, R.; Forfar-Bares, I.; Dallemagne, P.; Lemaître, N.; Péhourcq, F.; Rochette, J.; Sergheraert, C.; Jarry, C. *J. Med. Chem.* **2004**, *47*, 1997.
16. Beccalli, E. M.; Abbiati, G.; Broggini, G.; Paladino, G.; Rossi, E. *Synthesis* **2005**, *2005*, 2881.
17. Yuan, Q.; Ma, D. *J. Org. Chem.* **2008**, *73*, 5159.
18. Kitching, M. O.; Hurst, T. E.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 2925.
19. Dey, C.; Katayev, D.; Ylijoki, K. E.; Kundig, E. P. *Chem. Commun.* **2012**, 10957.
20. El Kaim, L.; Grimaud, L.; Le Goff, X. F.; Schiltz, A. *Org. Lett.* **2011**, *13*, 534.
21. Kumar, D. K.; Rajendran, S. P. *Tetrahedron Lett.* **2012**, *53*, 3230.
22. Castagnolo, D.; Pagano, M.; Bernardini, M.; Botta, M. *Tetrahedron Lett.* **2012**, *53*, 5008.
23. El Kaïm, L.; Grimaud, L.; Reddy Purumandla, S. *J. Org. Chem.* **2011**, *76*, 4728.
24. Zhao, Y.; Wu, Y.; Jia, J.; Zhang, D.; Ma, C. *J. Org. Chem.* **2012**, *77*, 8501.
25. Zhao, Y.; Bai, Y.; Zhang, Q.; Chen, Z.; Dai, Q.; Ma, C. *Tetrahedron Lett.* **2013**, *54*, 3253.
26. Chen, Y.; Le, V.; Xu, X.; Shao, X.; Liu, J.; Li, Z. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3948.
27. Crystallographic data have been deposited with the accession number CCDC 1032376 (**2a**), 1032377 (**3a**) in the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk; web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

Please cite this article in press as: Xiao, Y.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.01.059