Tetrahedron xxx (2015) 1–6

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of furoxan derivatives: DABCO-mediated cascade sulfonylation/cyclization reaction of α-nitro-ketoximes

Jian-Qiang Zhao [a,b], Ming-Qiang Zhou [a,b], Jian Zuo [a,b], Xiao-Ying Xu [a], Xiao-Mei Zhang [a], Wei-Cheng Yuan [a,*]

[a] National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China
[b] University of Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

Article history:
Received 21 October 2014
Received in revised form 25 December 2014
Accepted 16 January 2015
Available online xxx

Keywords:
α-Nitro-ketoximes
Sulfonyl chlorides
Furoxan derivatives
Cascade reaction
DABCO

ABSTRACT

A convenient and efficient method for the synthesis of furoxan derivatives from α-nitro-ketoximes and sulfonyl chlorides is reported. A wide variety of furoxan derivatives were smoothly obtained in good yields via a DABCO-mediated cascade sulfonylation/cyclization process under mild conditions. The usefulness of this method was also demonstrated by the conversions of the furoxan products into other promising compounds.

1. Introduction

Furoxan (1,2,5-oxadiazole 2-oxide) is an old heterocyclic system well-known to chemists due to its intriguing chemistry and the unique molecular structure.[1] Although furoxan was first synthesized over 100 years ago,[2] it was not until the middle of the 20th century that a few studies regarding to the synthesis, the chemical properties and the biological activities of various furoxan derivatives had been reported.[1,3] In the past few years, some furoxan derivatives were found to exert remarkable biological activities, such as antibacterial, antifungal, antihelmintic, antitrypanosomal, anticytotoxic, anti-HIV, anticancer effects, etc.[4] Certainly, these features and their potentially promising pharmacological actions have stimulated the development of preparative methods for diverse furoxan derivatives.

To the best of our knowledge, a range of methods for the synthesis of furoxan compounds exist. Among them, the strategies include oxidation of α-dioximes,[5] dehydration of α-nitro oximes,[6] thermolysis of α-nitro-azides,[7] dimerization of nitrile *N*-oxides,[8] and the reaction of alkenes with N_2O_3, $NaNO_2$, $NOBF_4$, etc.[9] Although each of the aforementioned methods could result in a different class of furoxan derivatives, unfortunately, many of those procedures suffered some limitations such as harsh reaction conditions, limited substrate scope, difficulties of handling, low chemical yields, not readily available starting materials, and use of hazardous reagents. In this context, the development of efficient methods for the synthesis of structurally diverse furoxan derivatives should be highly desirable. Moreover, further research on this aspect will not only greatly enrich the furoxan compounds but also will contribute to in-depth study on furoxan-based drug discovery. In this paper, we report a convenient and efficient protocol for accessing furoxan compounds from α-nitro-ketoximes and sulfonyl chlorides. We found that a wide variety of furoxan derivatives could be obtained smoothly in good yields via a DABCO-mediated sulfonylation/cyclization cascade process under mild reaction conditions.

2. Results and discussion

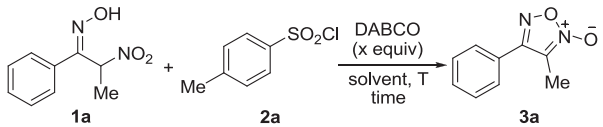
Initially, we examined the reaction of α-nitro-ketoxime[10] **1a** with *p*-toluene sulfonyl chloride (TsCl) **2a** in the presence of 2 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) in CH_2Cl_2 at 30 °C. The furoxan product **3a** was smoothly obtained in 57% yield within 5 min (Table 1, entry 1). Bases were investigated first, such as K_2CO_3, Na_2CO_3, ^tBuOK, triethylamine, and DBU. However, only DBU gave the desired furoxan product **3a** in acceptable yield (Table 1, entry 2) and other bases afforded furoxan product **3a** in very low

* Corresponding author. E-mail address: yuanwc@cioc.ac.cn (W.-C. Yuan).

http://dx.doi.org/10.1016/j.tet.2015.01.031
0040-4020/

yield.[11] When the same reaction was conducted in various solvents, **3a** was also able to be obtained in moderate yields within 5 min (Table 1, entries 3–9), but it was found that mesitylene as a reaction medium was superior to others (Table 1, entry 6). Afterward, the loading of DABCO was investigated. When 4 equiv of DABCO was used, the reaction delivered **3a** in 61% yield (Table 1, entry 10). Comparing this result with that in entry 6, it suggested that the reaction did not need excess DABCO. Conversely, conducting the reaction with 1 equiv of DABCO, 66% yield could be readily achieved (Table 1, entry 11). Having identified 1 equiv of DABCO as the optimal amount of the base for the reaction, we examined the effect of the reaction temperature (Table 1, entries 12–15). A screening of different reaction temperatures showed that the reaction gave the best result at 0 °C (Table 1, entry 14). No beneficial effect on the yield was observed when the substrate concentration was increased (Table 1, entry 16). However, **3a** could be obtained in high to 88% yield within 20 min by greatly lowering the substrate concentration (Table 1, entry 17). From an operational standpoint, we chose to use 1 equiv of DABCO at 0 °C with 0.03 M of substrate concentration in mesitylene as the optimal reaction conditions (Table 1, entry 17). It is worth mentioning that the structure of product **3a** was unequivocally confirmed by means of the single-crystal X-ray diffraction (Fig. 1)[12] and further confirmed by NMR (^{1}H, ^{13}C) spectra.

Table 1
Optimization of the reaction conditions[a]



Entry	Solvent	*x*	*T* (°C)	Time (min)	Yield[b] (%)
1	CH_2Cl_2	2	30	<5	57
2	CH_2Cl_2	2	30	10	52[c]
3	$CHCl_3$	2	30	<5	43
4	THF	2	30	<5	62
5	Toluene	2	30	<5	60
6	Mesitylene	2	30	<5	64
7	EtOH	2	30	<5	62
8	CH_3CN	2	30	<5	46
9	Hexane	2	30	<5	48
10	Mesitylene	4	30	<5	61
11	Mesitylene	1	30	<5	66
12	Mesitylene	1	50	<5	60
13	Mesitylene	1	20	<5	71
14	Mesitylene	1	0	15	74
15	Mesitylene	1	−10	30	70
16	Mesitylene	1	0	15	71[d]
17	Mesitylene	1	0	20	88[e]

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), **2a** (0.25 mmol), and DABCO in 2.0 mL solvent at the specified temperature for the stated period of time.
[b] Isolated yield.
[c] DBU (2 equiv) was used.
[d] Solvent (1.0 mL) was used.
[e] Solvent (6.0 mL) was used.

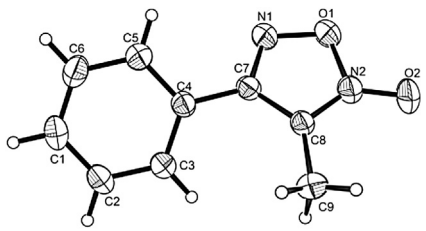
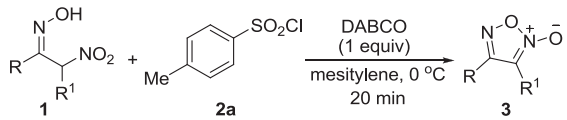


Fig. 1. Single-crystal X-ray structure of furoxan **3a**.

We next explored the scope of the DABCO-mediated the synthesis of various furoxan compounds using different α-nitro-ketoximes **1** and TsCl **2a** (Table 2). Firstly, we investigated the effects of the substituted position of fluoro group (entries 1–3), no significant difference in the reaction outcomes was observed with the changes of the substituted position. Then, different electron-withdrawing groups (Br, Cl) were incorporated into the aryl ring of α-nitro-ketoxime **1a**, still giving the corresponding furoxans **3e** and **3f** in very good yields (entries 4 and 5). In addition, the substrates bearing various electron-donating substituents on the aryl moiety successfully reacted with TsCl **2a**, affording furoxans **3g**–**l** in the chemical yields ranged from 82% to 89% (entries 6–11). Moreover, the results of these cases revealed that the size and steric hindrance of substituent had no significant influence on the reactivity. Naphthyl substituent was also compatible group and gave the expected product **3m** in 93% yield (entry 12). To our delight, an ethyl group at the α-position of α-nitro-ketoxime substrate was also tolerated (entry 13). Ultimately, it was demonstrated that the replacement of phenyl group on **1a** with benzyl group was also feasible for the sulfonylation/cyclization cascade process to give **3o** in 82% yield (entry 14). When the R^1 group of **1** was H, the corresponding substrate **1p** reacted with TsCl **2a** under the standard reaction conditions, disappointingly, the expected furoxan product **3p** was not able to be obtained (entry 15).[13] The results of this case suggested the R^1 ($R^1 \neq H$) group in α-nitro-ketoximes **1** was crucial for the generation of furoxan heterocyclic ring.

Table 2
DABCO-mediated the synthesis of furoxans: α-nitro-ketoxime scope[a]



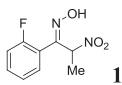
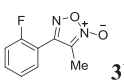
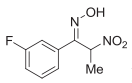
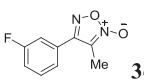
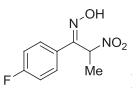
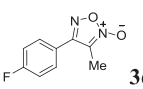
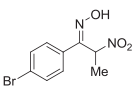
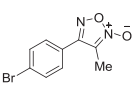
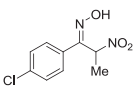
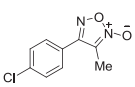
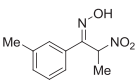
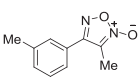
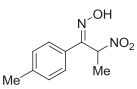
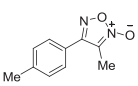
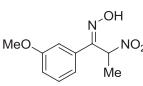
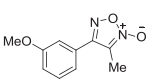
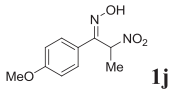
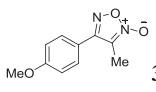
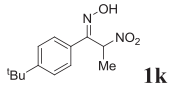
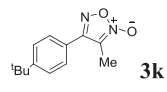
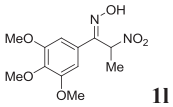
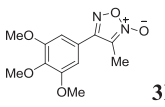
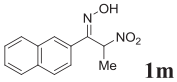
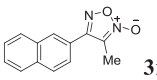
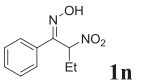
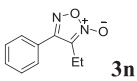
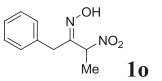
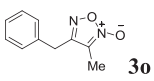
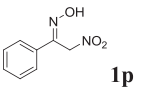
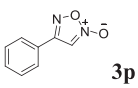
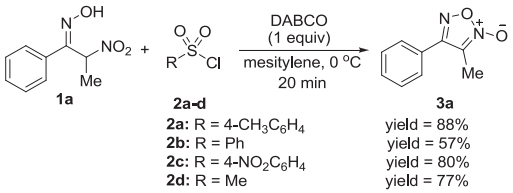
Entry	1	3	Yield[b] (%)
1	 1b	 3b	88
2	 1c	 3c	92
3	 1d	 3d	90
4	 1e	 3e	84
5	 1f	 3f	88
6	 1g	 3g	85
7	 1h	 3h	82
8	 1i	 3i	89

Table 2 (*continued*)

Entry	1	3	Yield[b] (%)
9	 **1j**	 **3j**	86
10	 **1k**	 **3k**	82[c]
11	 **1l**	 **3l**	83
12	 **1m**	 **3m**	93[c]
13	 **1n**	 **3n**	79
14	 **1o**	 **3o**	82
15	 **1p**	 **3p**	nd[d]

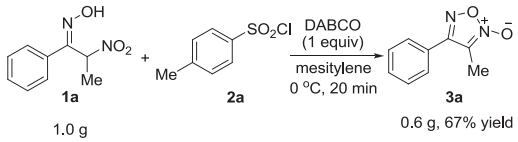
[a] Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), **2a** (0.25 mmol) and DABCO in 6.0 mL mesitylene at 0 °C for 20 min.
[b] Isolated yield.
[c] Run for 60 min.
[d] nd=not determined.

In the course of the further studies, the sulfonyl chloride scope was evaluated (Scheme 1). As the aforementioned, the model reaction could provide furoxan **3a** in 88% yield under the standard conditions. And then, instead of TsCl **2a**, **1a** reacted with benzenesulfonyl chloride **2b** under the same conditions, giving **3a** in 57% yield. Furthermore, we also found that the reaction of 4-nitrobenzene sulfonyl chloride **2c** with **1a** also proceeded well and delivered **3a** in 80% yield. These results indicated that the electronic nature of the aromatic moiety of the starting sulfonyl chlorides had no pernicious effect on the reaction since both electron-rich and -poor sulfonyl chlorides were successfully employed in the reaction. Nevertheless, an alkyl sulfonyl chloride, methanesulfonyl chloride, could also be applied in the developed protocol, affording **3a** in 77% yield.



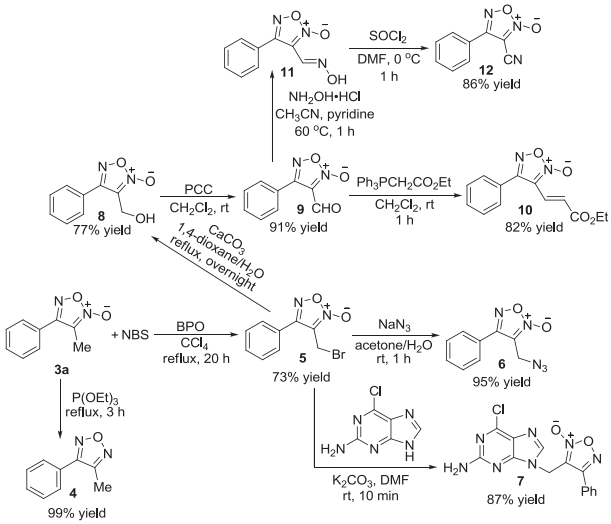
Scheme 1. DABCO-promoted the synthesis of furoxans: sulfonyl chloride scope.

In order to examine the utility of our method, the exemplar reaction of α-nitro-ketoxime **1a** and TsCl **2a** was carried out at 5 mmol scale under the standard conditions, which is 25 times larger than the scale of the original reaction shown in Table 1. As shown in Scheme 2, furoxan **3a** was able to be obtained smoothly in 67% yield within 20 min. This result suggested that the protocol was amenable to large-scale production.



Scheme 2. Scaled-up reaction on a gram scale.

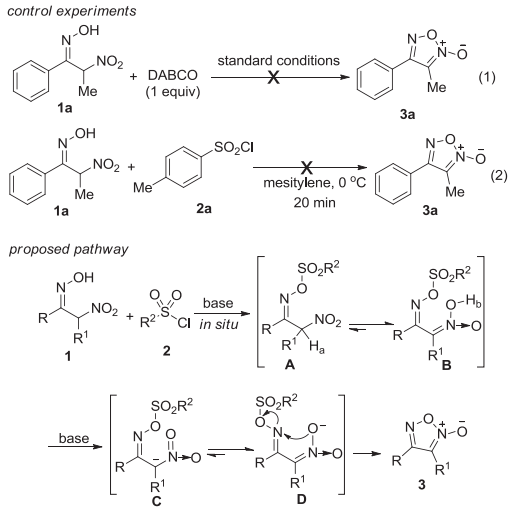
To further expand the potential of this reaction, the diverse transformation of product **3a** into various furoxan derivatives was illustrated in Scheme 3. Firstly, treatment of furoxan **3a** in triethyl phosphate under reflux conditions for 3 h gave the reduction product **4** in quantitative yield. On the other hand, the reaction of **3a** with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide (BPO) in carbon tetrachloride at reflux temperature could afford the corresponding brominated furoxan **5** in 73% yield. Then, compound **5** could be readily converted to the azide **6** in 95% yield by reacting with sodium azide in acetone/water solvent at room temperature. Additionally, the reaction of compound **5** and 6-chloro-9*H*-purin-2-amine with K_2CO_3 as a base in DMF at room temperature immediately furnished **7** in 87% yield. Moreover, hydrolyzing brominated furoxan **5** led to the formation of furoxanmethanol derivative **8** in 77% yield. Compound **8** could be smoothly converted to aldehyde derivative **9** in 91% yield by the oxidation of pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature. Then, the oxime derivative **11** was obtained by the traditional method from aldehyde **9**, and further transformed into nitrile derivative **12** in 86% yield by dehydration with thionyl chloride according to the reported procedure, which shows anti-schistosomiasis activity.[4d,l,14] Aldehyde derivative **9** also could be converted into α,β-unsaturated ester **10** in 82% yield via Wittig reaction.



Scheme 3. Transformation of furoxan **3a** to other furoxan derivatives.

To gain insight into the mechanism of the chemical process, several control experiments were conducted (Scheme 4). First, no furoxan product **3a** could be detected when **1a** was treated with DABCO in the absence of sulfonyl chloride under the standard conditions (Scheme 4, (1)). Subsequently, it was also found that the reaction of **1a** and TsCl **2a** did not occur without DABCO (Scheme 4, (2)). These observations suggested that the reaction might start

with the DABCO-mediated reaction of **1a** and **2a**. Based on these experimental results and the observation in Table 2, entry 15, a plausible mechanism for the above reaction of the synthesis of furoxan derivatives is proposed. As shown in Scheme 4, initially, the reaction was triggered by DABCO for sulfonylation of the α-nitro-ketoximes **1** with sulfonyl chlorides, leading to the in situ formation of oxime sulfonate **A**. However, perhaps due to the instability of oxime sulfonate, intermediate **A** could not be isolated. Meanwhile, intermediate **A** preferentially tautomerized to oxime sulfonate **B** in the mixture partly owe to the delocalized conjugate system. And then, the protons H_a and H_b in intermediates **A** and **B** were able to be striped by the base, resulting in the formation of anion intermediates **C** and **D**. Subsequently, furoxan products **3** will be generated in high priority via a cyclization process based on the nucleophilic attack of oxygen-anion in intermediate **D** to the nitrogen center.



Scheme 4. Control experiments and proposed pathway for the reaction of α-nitro-ketoximes and sulfonyl chlorides.

3. Conclusion

In conclusion, we have developed a convenient and efficient method for the synthesis of furoxan derivatives by the reaction of α-nitro-ketoximes and sulfonyl chlorides. Utilizing the developed protocol, a wide variety of furoxan compounds were smoothly obtained in good to high yields via a DABCO-mediated sulfonylation/cyclization cascade process under mild reaction conditions. The usefulness of the method was demonstrated by the conversions of the furoxan derivatives into various promising furoxan compounds. Meanwhile, a plausible reaction pathway for the DABCO-mediated reaction of α-nitro-ketoximes and sulfonyl chlorides was tentatively brought forward.

4. Experimental section

4.1. General

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hz), and integration. ^{13}C NMR chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm, DMSO-d_6 at 39.51 ppm). Melting points were recorded on a melting point apparatus.

4.2. General procedure for the synthesis of 3

To a solution of α-nitro-ketoximes **1** (0.20 mmol, 1 equiv) in 6 mL mesitylene at 0 °C were added sulfonyl chlorides **2** (0.25 mmol, 1.25 equiv) and DABCO (0.2 mmol, 1 equiv). The reaction mixture was stirred at 0 °C for 20 min. The resulting mixture was concentrated and the residue was purified by flash chromatography (hexanes/ethyl acetate=15:1) to give **3**.

*4.2.1. 3-Methyl-4-phenyl-1,2,5-oxadiazole 2-oxide (**3a**).* White solid (31.0 mg, 88% yield), mp 94.3–95.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.35 (s, 3H), 7.52–7.55 (m, 3H), 7.66–7.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.1, 112.1, 126.7, 127.4, 129.2, 131.0, 156.8; HRMS (ESI-TOF) calcd for $C_9H_8N_2O_2$ $[M+Na]^+$: 199.0478; found: 199.0483.

*4.2.2. 4-(2-Fluorophenyl)-3-methyl-1,2,5-oxadiazole 2-oxide (**3b**).* White solid (34.1 mg, 88% yield), mp 82.5–83.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.22 (d, J=2.7 Hz, 3H), 7.22–7.26 (m, 1H), 7.28–7.36 (m, 1H), 7.57–7.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 8.6 (d, J=6.4 Hz, 1C), 113.1, 114.7 (d, J=13.6 Hz, 1C), 116.4 (d, J=20.8 Hz, 1C), 125.1 (d, J=3.6 Hz, 1C), 130.6 (d, J=2.3 Hz, 1C), 133.3 (d, J=8.3 Hz, 1C), 153.8, 159.8 (d, J=249.9 Hz, 1C); HRMS (ESI-TOF) calcd for $C_9H_7FN_2O_2$ $[M+Na]^+$: 217.0384; found: 217.0393.

*4.2.3. 4-(3-Fluorophenyl)-3-methyl-1,2,5-oxadiazole 2-oxide (**3c**).* White solid (35.7 mg, 92% yield), mp 86.2–87.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.37 (s, 3H), 7.24–7.30 (m, 1H), 7.40–7.54 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.1, 111.8, 114.5 (d, J=23.5 Hz, 1C), 118.1 (d, J=20.9 Hz, 1C), 123.1 (d, J=3.2 Hz, 1C), 128.7 (d, J=8.2 Hz, 1C), 131.1 (d, J=8.2 Hz, 1C), 155.7, 162.9 (d, J=247.1 Hz, 1C); HRMS (ESI-TOF) calcd for $C_9H_7FN_2O_2$ $[M+Na]^+$: 217.0384; found: 217.0389.

*4.2.4. 4-(4-Fluorophenyl)-3-methyl-1,2,5-oxadiazole 2-oxide (**3d**).* White solid (35.0 mg, 90% yield), mp 62.8–63.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.34 (s, 3H), 7.20–7.25 (m, 2H), 7.66–7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.0, 111.9, 116.5 (d, J=22.0 Hz, 2C), 122.9 (d, J=3.4 Hz, 1C), 129.5 (d, J=8.7 Hz, 2C), 156.0, 164.2 (d, J=250.9 Hz, 1C); HRMS (ESI-TOF) calcd for $C_9H_7FN_2O_2$ $[M+Na]^+$: 217.0384; found: 217.0387.

*4.2.5. 4-(4-Bromophenyl)-3-methyl-1,2,5-oxadiazole 2-oxide (**3e**).* White solid (43.0 mg, 84% yield), mp 110.8–111.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.35 (s, 3H), 7.55–7.58 (m, 2H), 7.66–7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.2, 111.8, 125.6, 125.7, 128.8, 132.6, 156.0; HRMS (ESI-TOF) calcd for $C_9H_7BrN_2O_2$ $[M+Na]^+$: 276.9583; found: 276.9594.

*4.2.6. 4-(4-Chlorophenyl)-3-methyl-1,2,5-oxadiazole 2-oxide (**3f**).* White solid (37.0 mg, 88% yield), mp 93.5–94.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.34 (s, 3H), 7.51 (d, J=8.4 Hz, 2H), 7.62 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.1, 111.8, 125.1, 127.8, 128.6, 129.6, 129.7, 137.3, 155.9; HRMS (ESI-TOF) calcd for $C_9H_7ClN_2O_2$ $[M+Na]^+$: 233.0088; found: 233.0099.

*4.2.7. 3-Methyl-4-m-tolyl-1,2,5-oxadiazole 2-oxide (**3g**).* White solid (32.3 mg, 85% yield), mp 81.5–82.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.34 (s, 3H), 2.44 (s, 3H), 7.35–7.36 (m, 1H), 7.37–7.46 (m, 2H), 7.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.2, 21.3, 112.2, 124.4, 126.6, 127.9, 129.1, 131.8, 139.2, 157.0; HRMS

Please cite this article in press as: Zhao, J.-Q.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.01.031

(ESI-TOF) calcd for $C_{10}H_{10}N_2O_2$ $[M+Na]^+$: 213.0634; found: 213.0641.

*4.2.8. 3-Methyl-4-p-tolyl-1,2,5-oxadiazole 2-oxide (**3h**).* White solid (31.0 mg, 82% yield), mp 80.4–81.1 °C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.33 (d, J=4.2 Hz, 3H), 2.44 (s, 3H), 7.34 (d, J=7.8 Hz, 2H), 7.57 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.1, 21.4, 112.2, 123.8, 127.2, 129.4, 129.9, 141.4, 156.8; HRMS (ESI-TOF) calcd for $C_{10}H_{10}N_2O_2$ $[M+Na]^+$: 213.0634; found: 213.0645.

*4.2.9. 4-(3-Methoxyphenyl)-3-methyl-1,2,5-oxadiazole 2-oxide (**3i**).* White solid (36.7 mg, 89% yield), mp 109.3–110.1 °C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.34 (s, 3H), 3.86 (s, 3H), 7.06–7.10 (m, 1H), 7.19–7.22 (m, 2H), 7.41–7.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.2, 55.4, 112.1, 112.8, 116.7, 119.6, 127.8, 130.3, 156.7, 160.1; HRMS (ESI-TOF) calcd for $C_{10}H_{10}N_2O_3$ $[M+Na]^+$: 229.0584; found: 229.0588.

*4.2.10. 4-(4-Methoxyphenyl)-3-methyl-1,2,5-oxadiazole 2-oxide (**3j**).* White solid (35.6 mg, 86% yield), mp 99.8–100.3 °C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.33 (s, 3H), 3.88 (d, J=12.6 Hz, 3H), 7.02 (d, J=8.7 Hz, 2H), 7.61 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.2, 55.4, 112.1, 114.6, 118.9, 128.8, 156.5, 161.6; HRMS (ESI-TOF) calcd for $C_{10}H_{10}N_2O_3$ $[M+Na]^+$: 229.0584; found: 229.0589.

*4.2.11. 4-(4-tert-Butylphenyl)-3-methyl-1,2,5-oxadiazole 2-oxide (**3k**).* White solid (38.3 mg, 82% yield), mp 74.5–75.1 °C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.36 (s, 9H), 2.36 (s, 3H), 7.54–7.57 (m, 2H), 7.61–7.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.2, 31.1, 34.9, 112.2, 123.8, 126.2, 127.1, 154.5, 156.8; HRMS (ESI-TOF) calcd for $C_{13}H_{16}N_2O_2$ $[M+Na]^+$: 255.1104; found: 255.1112.

*4.2.12. 3-Methyl-4-(3,4,5-trimethoxyphenyl)-1,2,5-oxadiazole 2-oxide (**3l**).* White solid (44.2 mg, 83% yield), mp 104.9–105.4 °C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.35 (s, 3H), 3.90 (s, 9H), 6.86 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.2, 56.3, 60.9, 104.7, 104.8, 112.0, 112.1, 121.8, 140.5, 153.8, 156.7; HRMS (ESI) calcd for $C_{12}H_{14}N_2O_5$ $[M+Na]^+$: 289.0795; found: 289.0808.

*4.2.13. 3-Methyl-4-(naphthalen-2-yl)-1,2,5-oxadiazole 2-oxide (**3m**).* White solid (42.0 mg, 93% yield), mp 140.1–140.8 °C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.42 (s, 3H), 7.58–7.63 (m, 2H), 7.76–7.79 (m, 1H), 7.90–8.00 (m, 3H), 8.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.3, 112.2, 123.6, 124.0, 127.1, 127.6, 127.8, 128.5, 129.2, 132.8, 134.1, 156.8; HRMS (ESI-TOF) calcd for $C_{13}H_{10}N_2O_2$ $[M+Na]^+$: 249.0634; found: 249.0641.

*4.2.14. 3-Ethyl-4-phenyl-1,2,5-oxadiazole 2-oxide (**3n**).* Yellow oil (30.0 mg, 79% yield), ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.24 (t, J=7.5 Hz, 3H), 2.74 (q, J=7.5 Hz, 2H), 7.52–7.55 (m, 3H), 7.63–7.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.8, 16.7, 116.5, 126.7, 127.4, 129.2, 130.9, 156.7; HRMS (ESI-TOF) calcd for $C_{10}H_{10}N_2O_2$ $[M+Na]^+$: 213.0634; found: 213.0644.

*4.2.15. 4-Benzyl-3-methyl-1,2,5-oxadiazole 2-oxide (**3o**).* White solid (31.1 mg, 82% yield), mp 67.5–68.4 °C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.93 (s, 3H), 4.03 (s, 2H), 7.22–7.29 (m, 2H), 7.32–7.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 7.6, 32.1, 112.8, 127.6, 128.6, 129.0, 133.9, 156.9; HRMS (ESI-TOF) calcd for $C_{10}H_{10}N_2O_2$ $[M+Na]^+$: 213.0634; found: 213.0632.

4.3. Procedure for the synthesis of compound 4[4k]

A solution of **3a** (52.9 mg, 0.3 mmol) in 2 mL $P(OEt)_3$ was heated at reflux for 3 h. The mixture was allowed to reach room temperature, and the resulting mixture was directly purified using flash chromatography (hexanes/ethyl acetate=30:1) to afford the desired product **4**. Colorless oil (47.6 mg, 99% yield); ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.57 (s, 3H), 7.51–7.53 (m, 3H), 7.70–7.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 9.6, 126.1, 128.0, 129.1, 130.4, 149.5, 153.8; HRMS (ESI-TOF) calcd for $C_9H_8N_2O$ $[M+H]^+$: 161.0709; found: 161.0710.

4.4. Procedure for the synthesis of compound 5

Compound **3a** (176.2 mg, 1 mmol) was suspended in CCl_4 (10 mL), then NBS (356 mg, 2 mmol) was added, followed by benzoyl peroxide (242 mg, 1 mmol). The reaction mixture was stirred at reflux temperature under N_2 for 20 h. After cooling, water was added to quench the reaction. The solution was extracted with CCl_4 (three times), and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated using rotary evaporation in vacuo. Purification using flash chromatography (hexanes/ethyl acetate=25:1) afforded the desired product **5**.[15] Colorless oil (187 mg, 83% yield); ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 4.40 (s, 2H), 7.56–7.63 (m, 3H), 7.78–7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 17.3, 113.3, 125.8, 127.5, 129.5, 131.5, 155.6.

4.5. Procedure for the synthesis of compound 6

To a solution of 73 mg (0.28 mmol, 1 equiv) compound **5** in 4 mL acetone were added 29 mg (0.45 mmol, 1.5 equiv) NaN_3 and 1 mL H_2O. The reaction mixture was stirred at room temperature for 1 h. The solution was extracted with CH_2Cl_2 (three times), and the combined organic extracts dried over sodium sulfate, and concentrated using rotary evaporation in vacuo. Purification using flash chromatography (hexanes/ethyl acetate=10:1) afforded the desired product **6**. Yellow solid (57.8 mg, 95% yield); mp 59.7–60.4 °C; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 4.70 (s, 2H), 7.58–7.68 (m, 3H), 7.75–7.78 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 42.4, 112.7, 125.6, 127.7, 129.4, 131.5, 156.8; HRMS (ESI-TOF) calcd for $C_9H_7N_5O_2$ $[M+Na]^+$: 240.0492; found: 240.0491.

4.6. Procedure for the synthesis of compound 7

A mixture of compound **5** (91.8 mg, 0.36 mmol), K_2CO_3 (103.5 mg, 0.75 mmol), and 6-chloro-9*H*-purin-2-amine (50.9 mg, 0.3 mmol) in DMF (3 mL) was stirred at room temperature for 10 min. Then water was added to quench the reaction, and the solution was extracted with CH_2Cl_2 (three times). The combined organic extracts were washed with water, brine, dried over sodium sulfate, and concentrated using rotary evaporation in vacuo. Purification using flash chromatography (hexanes/ethyl acetate=2:1) afforded the desired product **7**. White solid (90.0 mg, 87% yield); mp 210.5–211.2 °C; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 5.44 (s, 2H), 6.87 (s, 2H), 7.53–7.55 (m, 3H), 7.75–7.78 (m, 2H), 8.11 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 36.3, 112.1, 122.8, 125.4, 128.0, 129.1, 131.1, 143.1, 149.4, 153.8, 157.0, 159.7; HRMS (ESI-TOF) calcd for $C_{14}H_{10}ClN_7O_2$ $[M+Na]^+$: 366.0477; found: 366.0489.

4.7. Procedure for the synthesis of compound 8[15b]

Compound **5** (104 mg, 0.4 mmol) dissolved in 1,4-dioxane (2 mL), then H_2O (2 mL) and $CaCO_3$ (200 mg, 2 mmol) were added. The reaction mixture was refluxed under stirring for overnight. After cooling, the reaction mixture was treated with 10% HCl until CO_2 ceased evolving. The solution was extracted with ethyl acetate (three times), and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated using rotary evaporation in vacuo. Purification using flash

Please cite this article in press as: Zhao, J.-Q.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.01.031

chromatography (hexanes/ethyl acetate=5:1) afforded the desired product **8**. Yellow solid (59.0 mg, 77% yield); mp 66.0–66.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 4.52 (d, J=5.7 Hz, 2H), 5.94 (t, J=5.7 Hz, 1H), 7.59–7.61 (m, 3H), 7.87–7.90 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 52.1, 115.1, 126.3, 127.6, 129.3, 131.3, 157.2; HRMS (ESI-TOF) calcd for $C_9H_8N_2O_3$ $[M+Na]^+$: 215.0427; found: 215.0435.

4.8. Procedure for the synthesis of compound 9[4d,l,14,15b]

To a solution of 192 mg (1 mmol) compound **8** in 12 mL CH_2Cl_2 was added 860 mg (4 mmol) PCC. The reaction mixture was stirred at room temperature for 24 h. After filtration on a Celite pad, the residue was washed with ethyl acetate, and the filtrate was evaporated in vacuo. Purification using flash chromatography (hexanes/ethyl acetate=10:1) afforded the desired product **9**. White solid (173.1 mg, 91% yield); mp 63.9–64.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 7.57–7.65 (m, 3H), 7.85–7.88 (m, 2H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 113.6, 125.2, 128.7, 128.9, 131.6, 155.6, 178.7; HRMS (ESI-TOF) calcd for $C_9H_6N_2O_3$ $[M+Na]^+$: 213.0271; found: 213.0284.

4.9. Procedure for the synthesis of compound 10

To a solution of 76 mg (0.4 mmol) compound **9** in 6 mL anhydrous CH_2Cl_2 was added 153.3 mg (0.44 mmol) ethyl(triphenylphosphoranylidene) acetate. The reaction mixture was stirred at room temperature for 1h, then the resulting mixture was directly purified using flash chromatography (hexanes/ethyl acetate=15:1) to afford the desired product **10**. White solid (85.0 mg, 82% yield); mp 63.7–64.6 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.23 (t, J=6.9 Hz, 3H), 4.19 (q, J=6.9 Hz, 2H), 6.98 (d, J=15.9 Hz, 1H), 7.20 (d, J=15.9 Hz, 1H), 7.65–7.73 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 13.9, 61.0, 112.3, 124.0, 124.1, 125.2, 128.4, 129.5, 131.5, 156.7, 165.0; HRMS (ESI-TOF) calcd for $C_{13}H_{12}N_2O_4$ $[M+Na]^+$: 283.0689; found: 283.0676.

4.10. Procedure for the synthesis of compound 12

To a solution of 106 mg (0.56 mmol, 1 equiv) compound **9** in 6 mL CH_3CN was added 50.6 mg (0.73 mmol, 1.3 equiv) $NH_2OH\cdot HCl$ and 58.6 uL (1.3 equiv) dry pyridine, then the reaction mixture was stirred at 60 °C for 1 h. After cooling, water was added to quench the reaction, and the solution was extracted with ethyl acetate (three times). The combined organic extracts were washed with water (three times), brine, dried over sodium sulfate, and concentrated using rotary evaporation in vacuo to yield **11** as a crude product. The crude product **11** dissolved in 3 mL anhydrous DMF and cooled to 0 °C, then 0.2 mL $SOCl_2$was added. After 1 h, the reaction mixture was poured into ice/water and extracted with Et_2O (four times). The combined ethereal layers were washed with water, brine, dried over sodium sulfate, and concentrated using rotary evaporation in vacuo. Purification using flash chromatography (hexanes/ethyl acetate=30:1) afforded the desired product **12**. White solid (90.0 mg, 86% yield); mp 76.0–76.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 7.66–7.75 (m, 3H), 7.87–7.90 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 98.4, 107.4, 123.9, 127.0, 129.7, 132.6, 155.2; HRMS (ESI-TOF) calcd for $C_9H_5N_3O_2$ $[M+H]^+$: 188.0455; found: 188.0449.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (No. 21372217), the National Basic Research Program of China (973 Program) (2010CB833300), and Sichuan Youth Science and Technology Foundation (2013JQ0021).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.01.031.

References and notes

1. (a) Boulton, A. J.; Ghosh, P. B. *Adv. Heterocycl. Chem.* **1969**, *10*, 1–41; (b) Stuart, K. L. *Heterocycles* **1975**, *3*, 651–690; (c) Gasco, A.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1981**, *29*, 251–340; (d) Gasco, A. M.; Di Stilo, A.; Fruttero, R.; Sorba, G.; Gasco, A.; Sabatino, P. *Liebigs Ann. Chem.* **1993**, 441–444.
2. kekulé, A. *Justus Liebigs Ann. Chem.* **1857**, 200–213.
3. (a) Sheremetev, A. B.; Makhova, N. N.; Friedrichsen, W. *Adv. Heterocycl. Chem.* **2001**, *78*, 65–188; (b) Cerecetto, H.; González, M. *Top. Heterocycl. Chem.* **2007**, *10*, 265–308.
4. For selected examples, see: (a) Ghigo, D.; Heller, R.; Calvino, R.; Alessio, P.; Fruttero, R.; Gasco, A.; Bosia, A.; Pescarmona, G. *Biochem. Pharmacol.* **1992**, *43*, 1281–1288; (b) Feelisch, M.; Schönafingeri, K.; Noack, E. *Biochem. Pharmacol.* **1992**, *44*, 1149–1157; (c) Calvino, R.; Fruttero, R.; Ghigo, D.; Bosia, A.; Pescarmona, G. P.; Gasco, A. *J. Med. Chem.* **1992**, *35*, 3296–3300; (d) Medana, C.; Ermondi, G.; Fruttero, R.; Stilo, A. D.; Ferretti, C.; Gasco, A. *J. Med. Chem.* **1994**, *37*, 4412–4416; (e) Fruttero, R.; Boschi, D.; Stilo, A. D.; Gasco, A. *J. Med. Chem.* **1995**, *38*, 4944–4949; (f) Takayama, H.; Shirakawa, S.; Kitajima, M.; Aimi, N.; Yamaguchi, K.; Hanasaki, Y.; Ide, T.; Katsuura, K.; Fujiwara, M.; Ijichi, K.; Konno, K.; Sigeta, S.; Yokota, T.; Baba, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1993–1996; (g) Gasco, A. M.; Boschi, D.; Di Stilo, A.; Medana, C.; Gasco, A.; Martorana, P. A.; Schönafinger, K. *Arzneim.-Forsch/Drug Res.* **1998**, *48*, 212–218; (h) Persichini, T.; Colasanti, M.; Fraziano, M.; Colizzi, V.; Medana, C.; Polticelli, F.; Venturini, G.; Ascenzi, P. *Biochem. Biophys. Res. Commun.* **1999**, *258*, 624–627; (i) Cerecetto, H.; Di Majo, R.; González, M.; Risso, M.; Saenz, P.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C.; Olea-Azar, C. *J. Med. Chem.* **1999**, *42*, 1941–1950; (j) Cena, C.; Lolli, M. L.; Lazzarato, L.; Guaita, E.; Morini, G.; Coruzzi, G.; McElroy, S. P.; Megson, I. L.; Fruttero, R.; Gasco, A. *J. Med. Chem.* **2003**, *46*, 747–754; (k) Grosso, E. D.; Boschi, D.; Lazzarato, L.; Cena, C.; Stilo, A. D.; Fruttero, R.; Moro, S.; Gasco, A. *Chem. Biodivers.* **2005**, *2*, 886–900; (l) Rai, G.; Sayed, A. A.; Lea, W. A.; Luecke, H. F.; Chakrapani, H.; Prast-Nielsen, S.; Jadhav, A.; Leister, W.; Shen, M.; Inglese, J.; Austin, C. P.; Keefer, L.; Arnér, E. S. J.; Simeonov, A.; Maloney, D. J.; Williams, D. L.; Thomas, C. J. *J. Med. Chem.* **2009**, *52*, 6474–6483; (m) Fruttero, R.; Crosetti, M.; Chegaev, K.; Guglielmo, S.; Gasco, A.; Berardi, F.; Niso, M.; Perrone, R.; Panaro, M. A.; Colabufo, N. A. *J. Med. Chem.* **2010**, *53*, 5467–5475.
5. (a) Ponzio, G. *Gazz. Chim. Ital.* **1932**, *62*, 127–131; (b) Alimenti, G.; Grifantini, M.; Gualtieri, F.; Stein, M. L. *Tetrahedron* **1968**, *24*, 395–402; (c) Bohn, H.; Brendel, J.; Martorana, K.; Schönafinger, K. *Br. J. Pharmacol.* **1995**, *114*, 1605–1612.
6. (a) Klamann, D.; Koser, W.; Weyerstahl, P.; Fligge, M. *Chem. Ber.* **1965**, *98*, 1831–1836; (b) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Ballini, R.; Bosica, G. *Tetrahedron Lett.* **2000**, *41*, 8817–8820.
7. Tabaković, K.; Tabaković, I.; Trkovnik, M.; Trinajstić, N. *Liebigs Ann. Chem.* **1983**, 1901–1909.
8. Wiley, R. H.; Wakefield, B. J. *J. Org. Chem.* **1960**, *25*, 546–551.
9. For a review see Ref. 1c and for some selected examples, see: (a) Fruttero, R.; Ferrarotti, B.; Serafino, A.; Stilo, A. D.; Gasco, A. *J. Heterocycl. Chem.* **1989**, *26*, 1345–1347; (b) Gasco, A. M.; Fruttero, R.; Sorba, G.; Gasco, A. *Liebigs Ann. Chem.* **1991**, 1211–1213; (c) Schönafinger, K. *Farmaco* **1999**, *54*, 316–320; (d) Dinh, N. H.; Ly, N. T.; Hoan, P. V. *J. Heterocycl. Chem.* **2006**, *43*, 1657–1663; (e) Matsubara, R.; Saeki, Y.; Li, J.; Eda, K. *Synthesis* **2013**, *45*, 1524–1528.
10. (a) Haning, H.; Niewöhner, U.; Schenke, T.; Lampe, T.; Hillisch, A.; Bischoff, E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3900–3907; (b) Deceuninck, J. A.; Buffel, D. K.; Hoornaert, G. J. *Tetrahedron Lett.* **1980**, *21*, 3613–3616; (c) Ballini, R.; Barboni, L.; Filippone, P. *Chem. Lett.* **1997**, *26*, 475–476; (d) Semple, G.; Ren, A.; Fioravanti, B.; Pereira, G.; Calderon, I.; Choi, K.; Xiong, Y.; Shin, Y.-J.; Gharbaoui, T.; Sage, C. R.; Morgan, M.; Xing, C.; Chu, Z.-L.; Leonard, J. N.; Grottick, A. J.; Al-Shamma, H.; Liang, Y.; Demarest, K. Y.; Jones, R. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3134–3141.
11. When the reaction was run with some other bases, such as K_2CO_3, Na_2CO_3, ^{t}BuOK, triethylamine, *N*,*N*-diisopropylethylamine, the furoxan product **3a** was observed in very low yield, but the major product was identified as 2*H*-azirine (the Neber reaction product).
12. See Supplementary data for the details of X-ray analysis.
13. In this case, the reaction mainly afforded the corresponding 2*H*-azirine product 2-nitro-3-phenyl-2*H*-azirine via a Neber reaction process.
14. (a) Fruttero, R.; Ferrarotti, B.; Serafino, A.; Gasco, A. *Liebigs Ann. Chem.* **1990**, 335–338; (b) Boiani, M.; Cerecetto, H.; González, M.; Risso, M.; Olea-Azar, C.; Piro, O. E.; Castellano, E. E.; de Ceráin, A. L.; Ezpeleta, O.; Monge-Vega, A. *Eur. J. Med. Chem.* **2001**, *36*, 771–782 and references cited therein.
15. (a) Gasco, A. M.; Boschi, D.; Gasco, A. *J. Heterocycl. Chem.* **1995**, *32*, 811–814; (b) Tosco, P.; Bertinaria, M.; Stilo, A. D.; Cena, C.; Sorba, G.; Frutteroa, R.; Alberto Gascoa, A. *Bioorg. Med. Chem.* **2005**, *13*, 4750–4759.