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

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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

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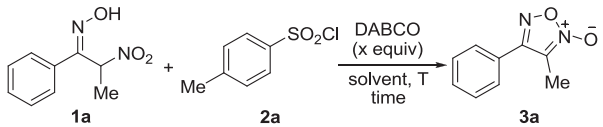
yield.[11] When the same reaction was conducted in various solvents, **3a** was also able to be obtained in moderate yields within 5 min (Table 1, entries 3–9), but it was found that mesitylene as a reaction medium was superior to others (Table 1, entry 6). Afterward, the loading of DABCO was investigated. 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.

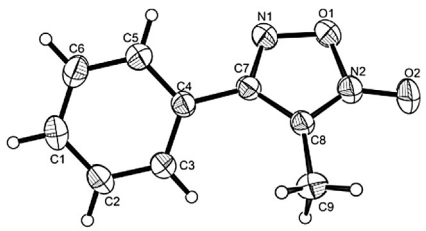
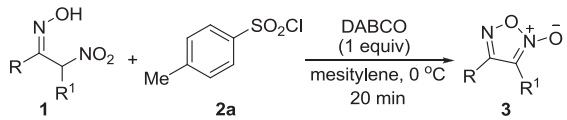
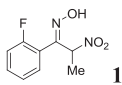
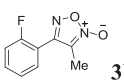
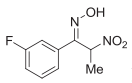
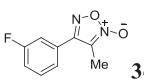
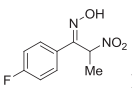
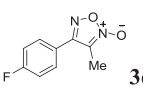
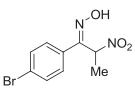
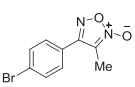
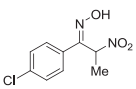
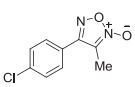
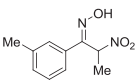
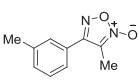
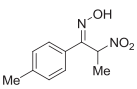
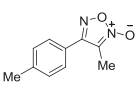
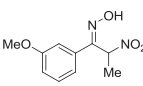
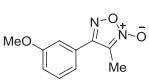


Fig. 1. Single-crystal X-ray structure of furoxan **3a**.

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