Synthesis of sulfonyloxy furoxans via hydroxyfuroxan ammonium salts

Matsubara, Ryosuke ; Katsuragi, Yuki ; Sakaguchi, Takaya ; Eguchi, Shuhei ; Hayashi, Masahiko ; Ando, Akihiro

(Citation)
Tetrahedron,74(27):3642-3651

(Issue Date)
2018-07-05

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90005028

Synthesis of sulfonyloxy furoxans via hydroxyfuroxan ammonium salts

Ryosuke Matsubara,* Yuki Katsuragi, Takaya Sakaguchi, Shuhei Eguchi, Masahiko Hayashi, Akihiro Ando

Department of Chemistry, Graduate School of Science, Kobe University, Nada, Kobe, 657-8501, Japan. E-mail: matsubara.ryosuke@people.kobe-u.ac.jp,

Abstract: Furoxans are distinctive heteroaromatic compounds in that they are potentially capable of releasing nitric oxide under physiological conditions. In order to utilize the furoxan scaffold for the development of functional molecules, synthetically relevant functional groups are required for access to diverse furoxans. In this report, a facile route to furoxans with sulfonyloxy groups, which are halide surrogates, has been developed. The key features of this strategy include the synthesis and utilization of bench-stable hydroxyfuroxan salts, the use of sulfonyl anhydrides in the sulfonylation step instead of sulfonyl chlorides, and the photochemical isomerization of one regioisomer to another in order to gain access to both.

keywords: furoxan, addition reaction, sulfonylation, halogen surrogate; heteroaromatic compound

1. Introduction

Furoxan derivatives exhibit a wide range of biological activities, including antiparasitic and antimicrobial properties, anticancer effects, and platelet anti-aggregatory activity.[1] An important and distinctive feature of furoxan derivatives among heterocyclic compounds is their nitric oxide (NO)-releasing ability, which was discovered by Gasco et al. and other research groups in the 1990s.[2] It has been proposed that furoxan is one of the NO-reservoirs within organisms.[2b] Owing to the multimodal bioactive roles of NO such as immune response, vasodilation, and neurotransmission,[3] NO-releasing furoxan derivatives have been an attractive research target for pharmaceutical applications.[4] Our group has also recently reported the synthesis of furoxan molecules that are endowed with the photo-switchable NO-releasing capability and hence potentially applicable for spatially and temporally-resolved NO administration.[5]

Despite the increasing interest in the application of furoxans in biology, drug discovery, and advanced materials, there are very few robust synthetic methods such as the C–C bond formation on a furoxan ring reported in literature. This is probably because of the facile ring opening of furoxans upon treatment with nucleophiles.[6] Recently we have reported the rare examples of successful C–C bond formation on the furoxan ring.[7] Nucleophilic aromatic substitution reaction (S_NAr) of 4-nitrofuroxans, the most readily accessible substrate,[8] with carbon nucleophiles proceeded to give C–substituted furoxans. The nitro group, however, is a relatively weak leaving group (the pK_a value of the conjugated acid HNO_2 is 3.3) and consequently, the reverse reactions can sometimes be cumbersome, as observed in our previous investigation.[7b] Moreover, the nitro group is not an ideal leaving group in transition metal-catalyzed cross coupling reactions, compared to halides. Unfortunately, halofuroxans, except for fluorofuroxans, are not readily accessible.[5a]

Therefore, we sought to develop synthetic routes for furoxan derivatives having halides and halide equivalents. Herein, we report the first synthesis of both regioisomers of sulfonyloxy furoxans.

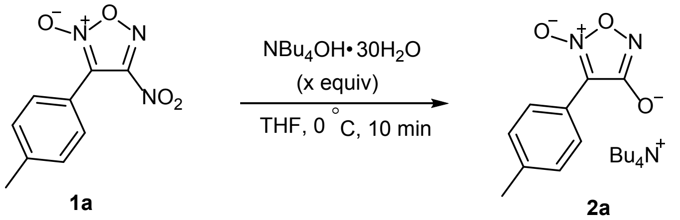
2. Results and Discussion

An ideal precursor for sulfonyloxy furoxans is the corresponding hydroxyfuroxan. A literature survey showed that nitrofuroxans were transformed into corresponding hydroxyfuroxans upon basic hydrolysis.[9] However, under the previously reported conditions, we could not obtain the desired hydroxyfuroxans in yields higher than 30%. Furthermore, the yields were not reproducible.[10] During the course of our investigation, Makhova et al. have also pointed out the difficulty in obtaining 4-hydroxyfuroxans in high yields using the previously reported procedures.[11] These authors have reported that the product yield is significantly sensitive to the base molar ratio and the nature of the co-solvent.

In our study, we found that the treatment of 4-nitrofuroxan **1a** with tetrabutylammonium (TBA) hydroxide 30-hydrate in THF afforded the 4-hydroxyfuroxan TBA salt **2a** (Table 1, entry 1). The TBA salt

(**2a**) moved to the organic phase in the usual phase separation (H_2O/CH_2Cl_2) and subsequent concentration of the organic phase gave compound **2a** in high yield and sufficient purity as a white solid (Figure 1). In the phase separation step, the excess NBu_4OH was transferred to the water phase. It is worth noting that TBA salt **2a** stayed in the salt form even on the standard SiO_2 chromatography column.[12] In contrast to the reaction conditions reported by Makhova et al. (NaOH was used as a base), the excess of base did not have any adverse effect on the product yield (entries 1–3). Furthermore, commercially available aqueous solution of NBu_4OH could also be used for the transformation (entry 4). Thus, the simplicity of the reaction and the insensitivity of the product yield to the base molar ratio ensured a reliable formation of hydroxyfuroxan salts. The structure of **2a** was unambiguously determined by X-ray diffraction analysis (Figure 1) and showed that all non-hydrogen atoms in the anion were almost coplanar. This observation suggested that the negative charge was delocalized over the entire anion. No significant hydrogen-bonding between the anion and cation fragments was observed.

Table 1. Synthesis of 4-hydroxyfuroxan TBA salt **2a**.



Entry	Equivalents of NBu_4OH (x)	Yield of **2a** (%)
1	2.0	99
2	3.0	96
3	4.0	99
4[a]	2.0	98

[a] Aqueous solution of NBu_4OH (1.0 M) was used instead of $NBu_4OH \cdot 30H_2O$.

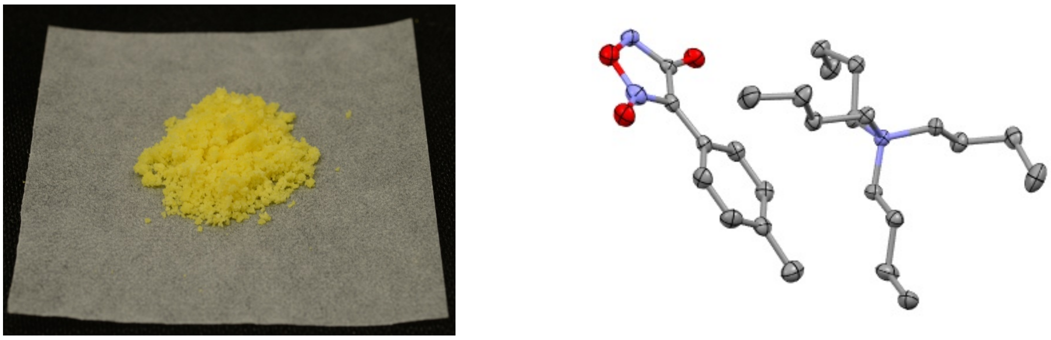
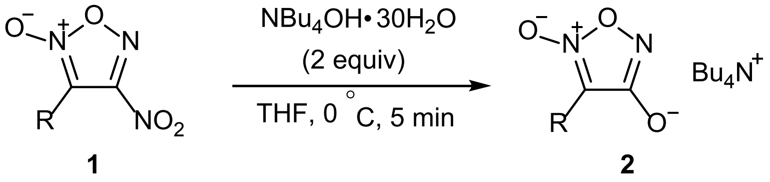
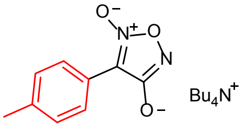
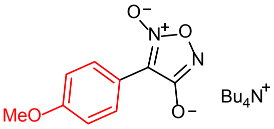
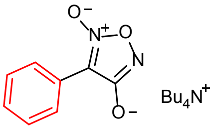
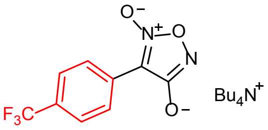


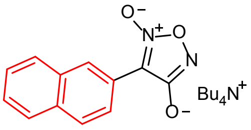
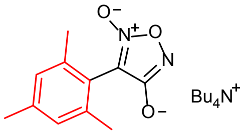
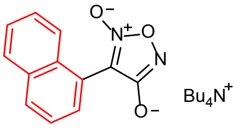
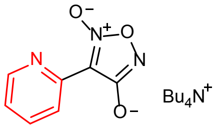
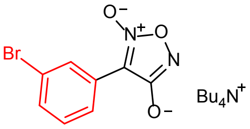
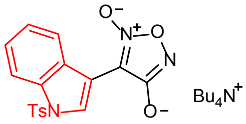
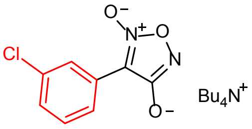
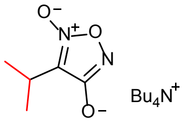
Figure 1. Photo (left) and X-ray structure (right) of **2a**.

It was found that the treatment of different 4-nitrofuroxans with NBu_4OH at 0 °C gave 4-hydroxyfuroxan TBA salts in good yields (Table 2). Substrates having various aryl groups (entries 1–9), including heteroaryl groups (entries 10 and 11), were successfully converted to 4-hydroxyfuroxan TBA salts. The bulkiness of the substituent at 3-position was tolerated (entry 9). The substrate without an aryl substituent also afforded the desired product (entry 12), suggesting that the contribution of the 3-aryl substituent to the stabilization of the product anion or the reaction transition state was insignificant.

Table 2. Synthesis of 4-hydroxyfuroxan TBA salt **2** from 4-nitrofuroxan **1**.[a]



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 **2a**	99	7	 **2g**	99
2	 **2b**	92	8	 **2h**	85

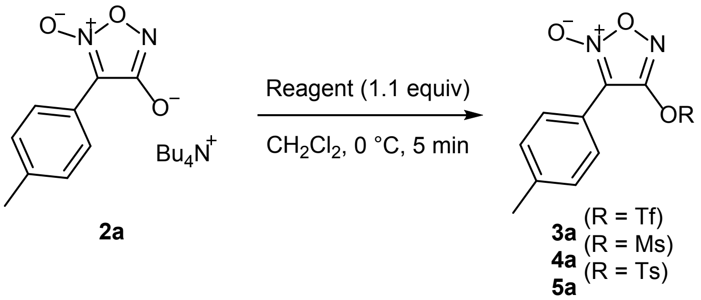
3	 **2c**	99	9	 **2i**	100
4	 **2d**	99	10	 **2j**	93
5	 **2e**	95	11	 **2k**	98
6	 **2f**	96	12	 **2l**	96

---

[a] Reaction conditions: **1** (1 equiv.) and $NBu_4OH \cdot 30H_2O$ (2 equiv.) in THF at 0 °C. Isolated yields are shown.

The facile isolation of the hydroxyfuroxan salt eliminated the need for acidification and base treatment for further sulfonylation. TBA salt **2a** was treated with triflic anhydride (Tf_2O) without the addition of a base in CH_2Cl_2 at 0 °C, and led to the formation of 4-(triflyloxy)furoxan **3a** in good yield (entry 1, Table 3). The structure of the product was determined by X-ray diffraction analysis. To the best of our knowledge, this is the first ever synthesis of a sulfonyloxy furoxan. Attempts to mesylate and tosylate **2a** using methanesulfonyl chloride (MsCl) and *p*-toluenesulfonyl chloride (TsCl), respectively, failed (entries 2 and 4). In both reactions, a significant amount of byproduct tolunitrile was observed. Fruitful results were obtained when the corresponding sulfonyl anhydrides were employed instead of sulfonyl chlorides (entries 3 and 5). It is important to mention that in contrast to the previously reported *O*-alkylation of 4-hydroxyfuroxans, in which the *N*-alkylated product was also formed,[11] the *O*-sulfonylation products were exclusively obtained in this study.

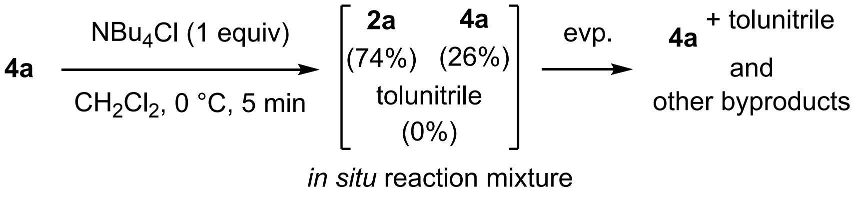
Table 3. Sulfonylation of 4-hydroxyfuroxan TBA salt **2a**.[a]



Entry	Reagent	Product	Yield (%)
1	Tf_2O	**3a**	67
2	MsCl	**4a**	<10
3	Ms_2O	**4a**	84
4	TsCl	**5a**	0
5	Ts_2O	**5a**	61

[a] Reaction conditions: **2** (1 equiv.) and sulfonylating reagent (1.1 equiv.) in CH_2Cl_2 at 0 °C. Isolated yields are shown.

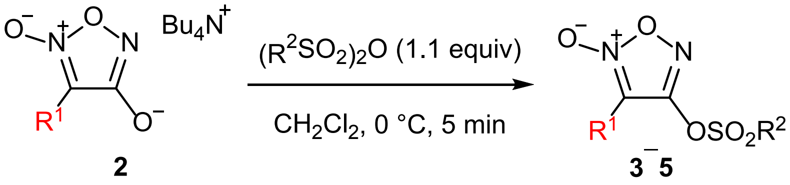
To identify the cause of the failures in sulfonylation of hydroxyfuroxan salts with sulfonyl chloride reagents (Table 3, entries 2 and 4), we checked the reactivity of the product sulfonyloxy furoxan **4a** against the co-product Bu_4NCl (Scheme 1). Direct ^1H NMR analysis of the reaction mixture at 5 min revealed that the hydroxyfuroxan salt **2a** was formed and no tolunitrile was generated at this stage. Subsequent solvent evaporation in vacuo led to the extinction of **2a** and there was a significant increase in the amount of tolunitrile. We also confirmed in an independent experiment that **2a** did not show any reactivity with Bu_4NCl (CH_2Cl_2, 0 °C, 5 min). These results suggested that the sulfonylation of the hydroxyfuroxan salt with sulfonyl chlorides failed because of the labile nature of the sulfonyloxy furoxan product against Bu_4NCl under concentrated or neat conditions, which inevitably led to their decomposition to tolunitrile.

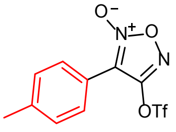
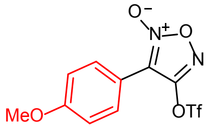


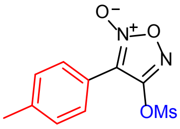
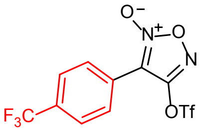
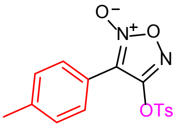
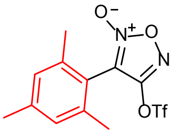
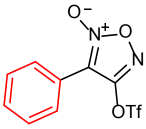
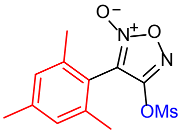
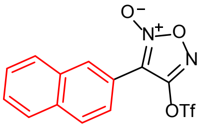
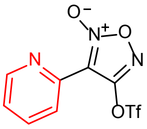
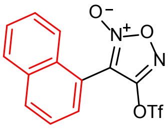
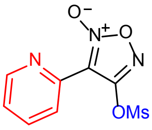
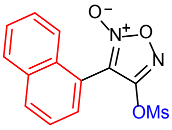
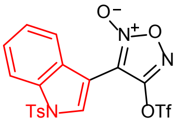
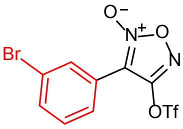
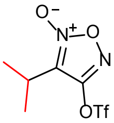
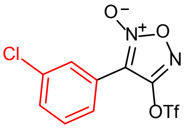
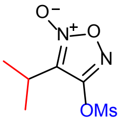
Scheme 1. Control experiment to assess the reactivity of **4a** against NBu_4Cl.

Next, we investigated the scope of the sulfonyloxy furoxan synthetic method (Table 4). A variety of 4-triflyloxyfuroxans could be obtained in good yields, albeit with some exceptions. Using substrates with bulky substituents at the 3-position (entries 6 and 12), the desired 4-(triflyloxy)furoxans **3d** and **3i**, respectively, were assumed to have formed based on the ^1H NMR analysis of the crude material. However, along with **3d** and **3i**, several byproducts were also formed. Owing to the labile properties of 4-(triflyloxy)furoxans, they could not be purified by chromatography, probably due to the strong electron-withdrawing nature of triflate group which would make the hydrolysis at the C4 carbon more facile. Consequently, these compounds could not be completely characterized. In these cases, it is likely that the bulkiness of the substituents at the 3-position decreased the degree of conjugation between the furoxan ring and aryl substituent, leading to the diminished stability of the desired products and by-product formation in situ. For the same reason, 4-(triflyloxy)furoxan having an alkyl substituent at the 3-position could not be obtained (entry 17). Fortunately, their mesyloxy variants were successfully obtained, probably because of the increased stability of the products (entries 7, 13, and 18) as compared to the triflyloxy variants.

Table 4. Scope and limitations of sulfonylation of 4-hydroxyfuroxan TBA salts.[a]



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 **3a**	67	10	 **3g**	88

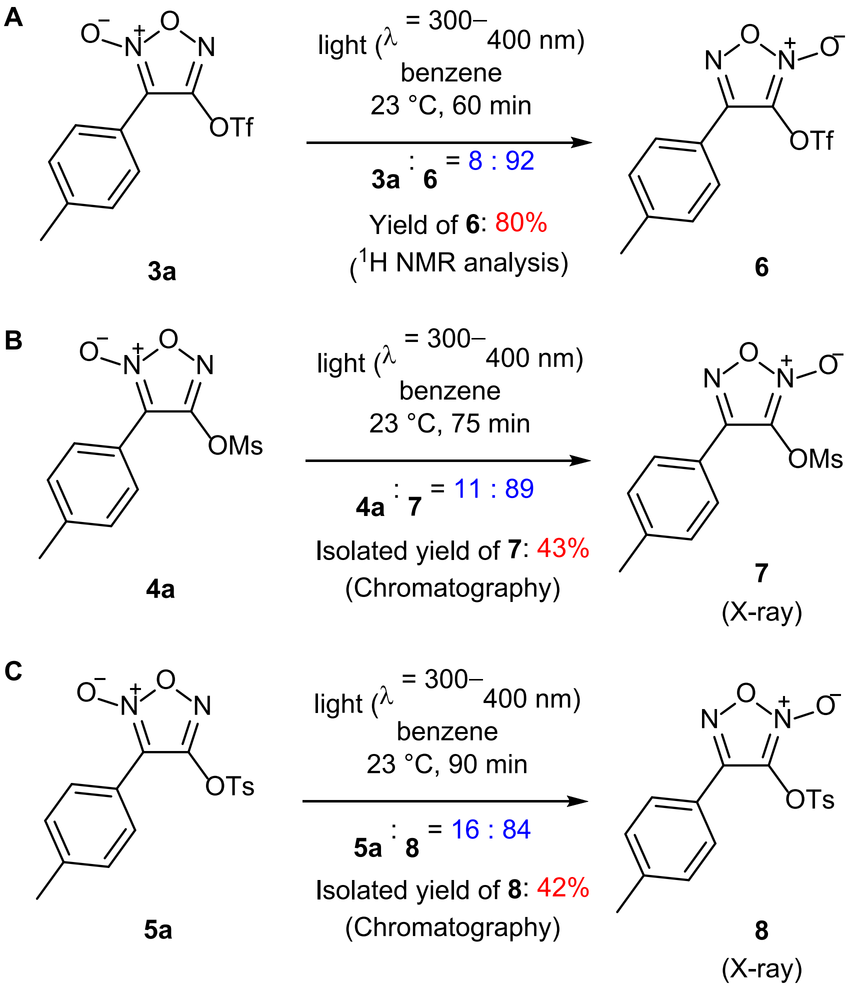
2	 **4a**	84	11	 **3h**	67
3	 **5a**	61	12	 **3i**	–[b]
4	 **3b**	58	13	 **4i**	76
5	 **3c**	85	14	 **3j**	42
6	 **3d**	–[b]	15	 **4j**	32
7	 **4d**	62	16	 **3k**	45
8	 **3e**	81	17	 **3l**	0
9	 **3f**	66	18	 **4l**	52

---

[a] Reaction conditions: **2** (1 equiv.), Tf_2O, Ms_2O, or Ts_2O (1.1 equiv.) in CH_2Cl_2 at 0 °C.

[b] ^1H NMR analysis of the crude product revealed that the desired products were obtained in an impure form. These products could not be purified by silica gel chromatography because of their labile nature.

After the successful synthesis of 4-(triflyloxy)furoxans, the synthesis of their regioisomers was investigated. It is well known that furoxans undergo isomerization upon heating through the intermediacy of dinitrosoalkene.[13] The photo-induced isomerization of some furoxans, though less developed as compared to thermal isomerization, has been previously reported by others and our group.[5a,14] Our attempt to thermally isomerize (110 °C, 2 h, in toluene) **3a** to its regioisomer, 3-(triflyloxy)furoxan (**6**) was unsuccessful, probably because **3a** is thermodynamically more stable than **6**. On the other hand, the photochemical isomerization of **3a** to **6** proceeded in a facile manner upon irradiation at 300–400 nm[15] (Scheme 2A) with the product ratio of 8:92 (**3a**:**6**) at the photostationary state (PS). Although the in situ ^{1}H NMR analysis using an internal standard (heptane) showed that the yield of **6** was 80%, the isolation of **6** in a pure form was not feasible because of the poor stability of **6**.[16] In the same manner, **4a** and **5a** were photochemically converted to **7** and **8**, respectively (Scheme 2B and 2C). High regioisomer ratios in favor of 3-sulfonyloxyfuroxan isomers **7** and **8** were observed after the PS was reached. Furoxans **7** and **8** were durable in the purification process; these compounds were obtained in a pure form after chromatographic purification, which enabled us to confirm their structures by X-ray diffraction analysis.[17] Thus, the general synthetic method for the regioisomers of sulfonyloxy furoxans was established.



Scheme 2. Photochemical isomerization of **3a** (**A**), **4a** (**B**), and **5a** (**C**).

In a batch system, the scaled up photoreaction often suffers from the problems associated with the low efficiency of light irradiation. That means that the reaction solution nearest to the lamp absorbs most of the incident light and prevents the rest of the solution from being light-irradiated.[18] Thus, flow photochemistry has proven to be a useful technique to avoid the issues associated with batch photochemistry. We conducted the photochemical isomerization of **5a** to **8** using a flow system, in which a 2.9 mM benzene solution of **5a** was passed through a quartz cell of dimensions 0.1×1.0×4.0 cm^3 (0.4 mL inner volume) at room temperature. The cell was irradiated with a high pressure Hg lamp placed in a water-cooled Pyrex glass apparatus. With the flow rate of 0.4 mL/min, i.e., the residence time of 1 min, the product ratio reached up to 12:88 (**5a**:**8**), demonstrating that it is possible to achieve a reliable and continuous supply of 3-sulfonyloxyfuroxans.

3. Conclusion

In conclusion, we developed the synthetic methods to 4-sulfonyloxy furoxans via 4-hydroxyfuroxan TBA salts.[19] The regioisomers, i.e., 3-sulfonyloxy furoxans, could also be obtained by photochemical isomerization. To date, very few methods have been reported in literature for the synthesis of furoxans with a halogen substituent, which is a useful leaving group for cross-coupling reactions. Therefore, the methods reported here to enable a facile access to furoxans with halide surrogates are useful for the future development of underdeveloped C–C bond forming reactions on the furoxan ring using transition metal-catalysts. These efforts are currently ongoing in our laboratory.

Experimental Section

Unless otherwise noted, all reactions were carried out in well cleaned glasswares with magnetic stirring. Operations were performed under an atmosphere of dry argon using Schlenk and vacuum techniques, unless otherwise noted. All starting materials were obtained from commercial sources or were synthesized using standard procedures. Melting points were measured on a Yanaco MP-500D and are not corrected. ^{1}H and ^{13}C NMR (400 and 100 MHz, respectively) were recorded on a Bruker Avance III HD 400 using TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as an internal standard, respectively. The following abbreviations are used in connection with NMR; s = singlet, d= doublet, t = triplet, q = quartet, quint = quintet, sep =septet, and m = multiple. Mass spectra were measured using a JEOL JMS=T100LP (DART method, ambient ionization). Preparative column chromatography was performed using Kanto Chemical silica gel 60N (spherical, neutral), Fuji Silysia BW-4:10MH silica gel or YMC_GEL Silica (6 nm I=40-63 μm). Thin layer chromatography (TLC) was carried out on Merck 25 TLC silica gel 60 F_{254} aluminium sheets. Preparative HPLC was performed with a silica-based normal phase HPLC packed column (YMC-SIL 06, 20 × 250 mm, 5 μm, 6 nm). Photoreactions were conducted using 300–400 nm light (a 300W Xenon lamp, Asahi Spectra MAX-303 equipped with a 300- to 600-nm ultraviolet-visible module and a 400-nm short-pass filter) in a batch system or a 450W high pressure Hg lamp in flow system. 4-Nitrofuroxans **1** were synthesized according to the previously reported methods.[7a]

Synthesis of 4-hydroxyfuroxan TBA salt 2 from 4-nitrofuroxan 1 (Table 2). *Tetrabutylammonium 3-(4-methylphenyl)furoxan-4-olate (**2a**, Table 2, entry 1).* To a solution of tetrabutylammounium hydroxide 30-hydrate (3.61 g, 4.52 mmol) in THF (20 mL) was added 3-(4-methylphenyl)-4-nitrofuroxan (**1a**) (500 mg, 2.26 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (1.06 g, 2.26 mmol, 99% yield). Single crystals of **2a** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/1,2-dichloroethane by vapor diffusion. Mp 94.0–94.3 °C; IR (neat): 2960, 2935, 2873, 1564, 1512, 1492, 1465, 1383, 1310, 1281, 1153, 1108, 1074, 1052, 1026, 935, 883, 851, 829, 801, 740, 712, 675, 639, 595, 584, 535, 525, 514, 505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 3.25 (m, 8H), 2.36 (s, 3H), 1.61 (m, 8H), 1.40 (m, 8H), 0.98 (t, J = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 138.4, 128.7, 126.3, 124.0, 110.5, 58.6, 23.9, 21.5, 19.6, 13.6; HRMS (DART); Exact mass calcd for $C_8H_7O_2$ $[M\text{-}Bu_4N\text{-}CN_2O]^-$, 135.0446. Found 135.0457. TBA salts of 4-hydroxyfuroxan did not show the corresponding molecular ion peaks regardless of whether negative or positive modes were used in DART mode of analysis. Instead, the peaks of the corresponding carboxylates were consistently observed in the negative mode. Therefore, the high resolution mass spectrometry (HRMS) assignment of most of the TBA salts of 4-hydroxyfuroxan was conducted for the corresponding carboxylates. Despite the failure to detect the molecular ion peaks of the TBA salts of 4-hydroxyfuroxans, their assigned structures were confirmed by the single-crystal X-ray diffraction analysis and the unambiguous characterization of the (sulfonyloxy)furoxan derivatives.

*Tetrabutylammonium 3-phenylfuroxan-4-olate (**2b**, Table 2, entry 2).* To a solution of tetrabutylammounium hydroxide 30-hydrate (386 mg, 0.48 mmol) in THF (3 mL) was added 3-phenyl-4-nitrofuroxan (50 mg, 0.24 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (93 mg, 0.22 mmol, 92% yield). Mp 92.7–93.6 °C; IR (neat): 2958, 2873, 1567, 1490, 1460, 1388, 1313, 1151, 1082, 934, 882, 830, 768, 742, 686, 643, 581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.70 (m, 2H), 7.41 (m, 2H), 7.33 (m, 1H), 3.26 (m, 8H), 1.62 (m, 8H), 1.39 (m, 8H), 0.98 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 128.5, 127.9, 126.9, 126.3, 110.4, 58.5, 23.8, 19.6, 13.6; HRMS (DART); Exact mass calcd for $C_7H_5O_2$ [M-Bu_4N-CN_2O]$^-$, 121.0290. Found 121.0317.

*Tetrabutylammonium 3-(naphthalen-2-yl)furoxan-4-olate (**2c**, Table 2, entry 3).* To a solution of tetrabutylammounium hydroxide 30-hydrate (622 mg, 0.78 mmol) in THF (3 mL) was added 3-(naphthalen-2-yl)-4-nitrofuroxan (100 mg, 0.39 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (181 mg, 0.39 mmol, 99% yield). Mp 135.0–135.6 °C; IR (neat): 2954, 2872, 1574, 1557, 1491, 1467, 1397, 1338, 1259, 1200, 1139, 1079, 1025, 967, 932, 905, 878, 833, 761, 742, 671, 647, 580 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.25 (s, 1H), 8.84 (d, *J* = 9.2 Hz, 1H), 7.90 (m, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.80 (m, 1H). 7.46 (m, 2H), 3.13 (m, 8H), 1.52 (m, 8H), 1.32 (m, 8H), 0.91 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 133.2, 133.0, 128.8, 127.5, 127.3, 126.4, 126.2, 125.9, 124.6, 123.7, 110.7, 58.6, 23.8, 19.6, 13.6; HRMS (DART); Exact mass calcd for $C_{11}H_7O_2$ [M-Bu_4N-CN_2O]$^-$, 171.0446. Found 171.0446.

*Tetrabutylammonium 3-(naphthalen-1-yl)furoxan-4-olate (**2d**, Table 2, entry 4).* To a solution of tetrabutylammounium hydroxide 30-hydrate (311 mg, 0.39 mmol) in THF (2 mL) was added 3-(naphthalen-1-yl)-4-nitrofuroxan (50 mg, 0.19 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (95 mg, 0.19 mmol, 99% yield). Brown oil; IR (neat): 2960, 2934, 2874, 1581, 1563, 1508, 1485, 1466, 1415, 1360, 1337, 1279, 1254, 1201, 1153, 1127, 1107, 1067, 1027, 1006, 925, 882, 861, 800, 794, 776, 726, 681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (m, 4H), 7.47 (m, 3H), 2.93 (m, 8H), 1.38 (m, 8H), 1.20 (m, 8H), 0.87 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 133.7, 130.8, 129.5, 129.0, 128.2, 126.4, 126.0, 125.9, 125.3, 113.4, 100.0, 58.2, 23.6, 19.5, 13.6; HRMS (DART); Exact mass calcd for $C_{12}H_7N_2O_3$ [M-Bu_4N]$^-$, 227.0457. Found 227.0481.

*Tetrabutylammonium 3-(3-bromophenyl)furoxan-4-olate (**2e**, Table 2, entry 5).* To a solution of tetrabutylammounium hydroxide 30-hydrate (280 mg, 0.35 mmol) in THF (2 mL) was added 3-(3-bromophenyl)-4-nitrofuroxan (50 mg, 0.18 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (83 mg, 0.17 mmol, 95% yield). Mp 89.8–90.8 °C; IR (neat): 2958, 2874, 1566, 1472, 1365, 1256, 1155, 1073, 1027, 994, 948, 899, 883, 829, 804, 770, 740, 713, 689, 664, 641, 585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 1H), 8.70 (d, J = 8.0, 1H), 7.46 (m,1H), 7.31 (m, 1H), 3.20 (m, 8H), 1.58 (m, 8H), 1.36 (m, 8H), 0.94 (t, J = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 131.4, 129.6, 129.1, 128.6, 124.8, 122.1, 109.3, 58.6, 23.8, 19.6, 13.6; HRMS (DART); Exact mass calcd for $C_7H_4{}^{79}BrO_2$ $[M\text{-}Bu_4N\text{-}CN_2O]^-$, 198.9395. Found 198.9412.

*Tetrabutylammonium 3-(3-chlorophenyl)furoxan-4-olate (**2f**, Table 2, entry 6).* To a solution of tetrabutylammounium hydroxide 30-hydrate (331 mg, 0.42 mmol) in THF (2 mL) was added 3-(3-chlorophenyl)-4-nitrofuroxan (50mg, 0.21mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (92 mg, 0.20 mmol, 96% yield). Mp 65.0–65.2 °C; IR (neat): 2958, 2874, 1569, 1491, 1465, 1367, 1265, 1157, 1109, 1078, 1027, 995, 952, 898, 884, 829, 806, 781, 741, 725, 690, 673, 643, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 1H), 8.64 (d, J = 8.0 Hz, 1H), 7.32 (m, 2H), 3.21 (m, 8H), 1.59 (m, 8H), 1.37 (m, 8H), 0.95(t, J = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 133.9, 129.3, 128.5, 125.9, 124.4, 109.5, 58.7, 23.8, 19.7, 13.6; HRMS (DART); Exact mass calcd for $C_7H_4{}^{35}ClO_2$ $[M\text{-}Bu_4N\text{-}CN_2O]^-$, 154.9900. Found 154.9880.

*Tetrabutylammonium 3-(4-methoxyphenyl)furoxan-4-olate (**2g**, Table 2, entry 7).* To a solution of tetrabutylammounium hydroxide 30-hydrate (674 mg, 0.84 mmol) in THF (3 mL) was added 3-(4-methoxyphenyl)-4-nitrofuroxan (100 mg, 0.42 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (185 mg, 0.35 mmol, 99% yield). Mp 134.0–134.9 °C; IR (neat): 2959, 2875, 1607, 1577, 1511, 1494, 1465, 1380, 1299, 1254, 1179, 1150, 1104, 1071, 1024, 933, 879, 841, 741, 673, 636, 599, 575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, J = 9.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 3.25 (m, 8H), 1.62 (m, 8H), 1.41 (m, 8H), 0.98 (t, J = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 159.6, 128.0, 119.5, 113.4, 110.4, 58.7, 55.2, 23.9, 19.7, 13.6; HRMS (DART); Exact mass calcd for C_7H_4NO $[M\text{-}Bu_4N\text{-}CNO_3\text{-}CH_3]^-$, 118.0293.

Found 118.0300.

*Tetrabutylammonium 3-[4-(trifluoromethyl)phenyl]furoxan-4-olate (**2h**, Table 2, entry 8).* To a solution of tetrabutylammounium hydroxide 30-hydrate (291 mg, 0.36 mmol) in THF (2 mL) was added 3-[4-(trifluoromethyl)phenyl]-4-nitrofuroxan (50 mg, 0.18 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (76 mg, 0.16 mmol, 85% yield). Yellow oil; IR (neat): 2961, 2875, 1732, 1615, 1572, 1516, 1493, 1466, 1392, 1322, 1252, 1163, 1121, 1104, 1063, 1017, 937, 913, 879, 852, 800, 728, 694, 658, 640, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.86$(d, $J = 8.0$ Hz, 2H), 7.65(d, $J = 8.0$ Hz, 2H), 3.23 (m, 8H), 1.61(m, 8H), 1.38(m, 8H), 0.96 (t, $J = 7.2$ Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.3$, 130.6, 129.7 (q, $J = 32$ Hz), 126.3, 124.7 (q, $J = 3.8$ Hz), 124.1 (q, $J = 270.3$ Hz), 109.7, 58.7, 23.9, 19.7, 13.6; HRMS (DART); Exact mass calcd for $C_8H_4F_3O_2$ $[M\text{-}Bu_4N\text{-}CN_2O]^-$, 189.0163. Found 189.0153.

*Tetrabutylammonium 3-(2,4,6-trimethylphenyl)furoxan-4-olate (**2i**, Table 2, entry 9).* To a solution of tetrabutylammounium hydroxide 30-hydrate (322 mg, 0.40 mmol) in THF (2 mL) was added 3-(2,4,6-trimethylphenyl)-4-nitrofuroxan (50 mg, 0.20 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (93 mg, 0.20 mmol, 100% yield). Yellow oil; IR (neat): 2961, 2874, 1565, 1478, 1371, 1173, 1147, 1072, 1033, 961, 920, 882, 851, 826, 728, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.85$ (s, 2H), 3.20 (m, 8H), 2.25 (s, 3H), 2.24 (s, 6H), 1.58 (m, 8H), 1.37 (m, 8H), 0.96 (t, $J = 7.2$ Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.6$, 138.7, 129.2, 128.2, 122.0, 114.3, 58.5, 23.9, 21.2, 19.67, 19.66, 13.7; HRMS (DART); Exact mass calcd for $C_{11}H_{11}N_2O_2$ $[M\text{-}Bu_4N\text{-}O]^-$, 203.0821. Found 203.0843.

*Tetrabutylammonium 3-(pyridin-2-yl)furoxan-4-olate (**2j**, Table 2, entry 10)* . To a solution of tetrabutylammounium hydroxide 30-hydrate (1.54 g, 1.92 mmol) in THF (10 mL) was added 3-(pyridin-2-yl)-4-nitrofuroxan (200 mg, 0.96 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (375 mg, 0.89 mmol, 93% yield). Mp 61.1–61.3 °C; IR (neat): 2960, 2872, 1585, 1567, 1484, 1467, 1429, 1386, 1290, 1151, 1118, 1075, 1052, 1025, 989, 941, 881, 822, 792, 739, 695, 656, 621, 578 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 7.74 (m, 1H), 7.24 (m, 1H), 3.23 (m, 8H), 1.60 (m, 8H), 1.37 (m, 8H), 0.94 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 149.5, 146.9, 135.9, 123.6, 122.7, 110.6, 58.5, 23.7, 19.5, 13.5; HRMS (DART); Exact mass calcd for $C_6H_4N_1O_2$ [M-Bu_4N-CN_2O]$^-$, 122.0242. Found 122.0257.

*Tetrabutylammonium 3-[1-(4-methylbenzene-1-sulfonyl)-1H-indol-3-yl]furoxan-4-olate (**2k**, Table 2, entry 11).* To a solution of tetrabutylammounium hydroxide 30-hydrate (400 mg, 0.5 mmol) in THF (3 mL) was added 3-[1-(4-methylbenzene-1-sulfonyl)-1H-indol-3-yl]-4-nitrofuroxan (100 mg, 0.25 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (150 mg, 0.24 mmol, 98% yield). Brown oil; IR (neat): 2959, 2874, 2172, 1579, 1566, 1532, 1481, 1438, 1399, 1368, 1294, 1252, 1199, 1187, 1167, 1138, 1100, 1090, 1061, 1019, 980, 934, 900, 882, 835, 812, 771, 757, 724, 709, 668, 653, 638, 616, 584, 570, 536, 528, 525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (d, *J* = 8.0 Hz, 1H), 8.71 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.30 (m, 1H), 7.21 (m, 3H), 3.15 (m, 8H), 2.31 (s, 3H), 1.54 (m, 8H), 1.31 (m, 8H), 0.90 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 145.3, 134.7, 129.9, 128.3, 126.9, 126.5, 126.0, 125.2, 124.9, 123.3, 112.8, 109.6, 109.2, 58.5, 23.8, 21.5, 19.6, 13.5. The assignable peaks in HRMS analysis (DART) were not observed, probably due to the fragmentation during the mass analysis.

*Tetrabutylammonium 3-(propan-2-yl)furoxan-4-olate (**2l**, Table 2, entry 12).* To a solution of tetrabutylammounium hydroxide 30-hydrate (924 mg, 1.16 mmol) in THF (2 mL) was added 3-(propan-2-yl)-4-nitrofuroxan (100 mg, 0.58 mmol) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, and dried over Na_2SO_4, and filtered. The filtrate thus obtained was concentrated under reduced pressure to give the analytically pure product (216 mg, 0.56 mmol, 96% yield). Brown oil; IR (neat): 2961, 2934, 2875, 1724, 1604, 1563, 1463, 1381, 1312, 1261, 1177, 1106, 1066, 1029, 974, 878, 803, 740, 675, 579, 538 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (m, 8H), 3.06 (sept, *J* = 6.8 Hz, 1H), 1.65 (m, 8H), 1.43 (m, 8H), 1.32 (d, *J* = 6.8 Hz, 6H), 1.00 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.8, 24.0, 23.4, 19.7, 17.6, 13.6. The assignable peaks in HRMS analysis (DART) were not observed, probably due to the fragmentation during the mass analysis.

Synthesis of 4-sulfonyloxy furoxans (Table 4). *3-(4-Methylphenyl)furoxan-4-yl* *trifluoromethanesulfonate (**3a**, Table 4, entry 1)*. To the solution of **2a** (50 mg, 0.12 mmol) in CH_2Cl_2 (1 mL), Tf_2O (21.6 μL, 0.13 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **3a** (25 mg, 0.077 mmol, 67% yield). Single crystals of **3a** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane at –30 °C. Mp. 35.3–36.1 °C; IR (neat): 1620, 1525, 1440, 1408, 1328, 1312, 1218, 1145, 1121, 1091, 984, 846, 815, 788, 766, 732, 700, 651, 637, 604, 591, 574, 551, 517, 505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 142.5, 130.3, 126.4, 118.4 (q, J = 320 Hz), 116.8, 108.3, 21.7; HRMS (DART); Exact mass calcd for $C_{10}H_8F_3N_2O_5S$ $[M+H]^+$, 325.0106. Found 325.0076.

*3-(4-Methylphenyl)furoxan-4-yl methanesulfonate (**4a**, Table 4, entry 2)*. To the solution of solution of **2a** (50 mg, 0.12 mmol) in CH_2Cl_2 (5 mL), Ms_2O (22 mg, 0.13 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 1/1) to give **4a** (26 mg, 0.097 mmol, 84% yield). Mp. 97.6–98.1 °C; IR (neat): 3023, 2937, 1601, 1519, 1454, 1410, 1382, 1333, 1316, 1285, 1191, 1153, 1121, 1091, 978, 848, 838, 816, 801, 787, 766, 674, 639, 585, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.4Hz, 2H), 7.35 (d, J = 8.4Hz, 2H), 3.56 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 142.0, 130.0, 126.4, 117.6, 108.6, 40.8, 21.6; HRMS (DART); Exact mass calcd for $C_{10}H_3N_2O_5S$ $[M+H]^+$, 271.0389. Found 271.0429.

*3-(4-Methylphenyl)furoxan-4-yl 4-methylbenzene-1-sulfonate (**5a**, Table 4, entry 3)*. To the solution of **2a** (50 mg, 0.12 mmol) in CH_2Cl_2 (1 mL), Ts_2O (41 mg, 0.13 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **5a** (24 mg, 0.070 mmol, 61% yield). Mp. 104.4–104.8 °C; IR (neat): 2923, 2853, 1732, 1594, 1517, 1493, 1455, 1404, 1329, 1311, 1213, 1198, 1183, 1152, 1123, 1083, 979, 839, 811, 776, 702, 677, 654, 584, 566, 539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 2.48 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 147.3, 141.6, 131.4, 130.2, 129.8, 129.2, 126.4, 117.8, 108.6, 21.9, 21.6; HRMS (DART); Exact mass calcd for $C_{16}H_{15}N_2O_5S$ $[M+H]^+$, 347.0702.

Found 347.0670.

*3-Phenylfuroxan-4-yl trifluoromethanesulfonate (**3b**, Table 4, entry 4)*. To the solution of **2b** (50 mg, 0.12 mmol) in CH_2Cl_2 (2 mL), Tf_2O (22 μL, 0.13 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **3b** (21.3 mg, 0.069 mmol, 58% yield). Colorless oil; IR (neat): 1727, 1621, 1580, 1507, 1466, 1434, 1312, 1287, 1220, 1144, 1126, 1092, 1072, 982, 922, 845, 810, 763, 729, 713, 689, 638, 602, 575, 552, 517, 509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (m, 2H), 7.60 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 130.7, 128.5, 125.5, 118.7, 117.3 (q, J = 320 Hz), 107.1; HRMS (DART); Exact mass calcd for $C_9H_6F_3N_2O_5S$ $[M+H]^+$, 310.9950. Found 310.9966.

*3-(Naphthalen-2-yl)furoxan-4-yl trifluoromethanesulfonate (**3c**, Table 4, entry 5).* To the solution of **2c** (47 mg, 0.10 mmol) in CH_2Cl_2 (1 mL), Tf_2O (19 μL, 0.11 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **3c** (30.7 mg, 0.85 mmol, 85% yield). Mp 58.1–59.0 °C; IR (neat): 2925, 1610, 1575, 1506, 1484, 1455, 1436, 1426, 1390, 1370, 1345, 1318, 1276, 1220, 1172, 1112, 1093, 1019, 1005, 968, 924, 907, 866, 844, 811, 800, 766, 755, 710, 666, 633, 624, 600, 582, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.87 (dd, J = 2.0, 8.4 Hz, 1H), 7.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 134.2, 132.8, 129.6, 128.9, 128.6, 127.9, 127.6, 127.5, 121.8, 118.4 (q, J = 320 Hz), 116.9, 108.4; HRMS (DART); Exact mass calcd for $C_{13}H_8F_3N_2O_5S$ $[M+H]^+$, 361.0106. Found 361.0127.

*3-(Naphthalen-1-yl)furoxan-4-yl methanesulfonate (**4d**, Table 4, entry 7).* To the solution of **2d** (46.3 mg, 0.099 mmol) in CH_2Cl_2 (1 mL), Ms_2O (19 mg, 0.11 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subseqeuntly, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 3/1) to give **4d** (18.6 mg, 0.061 mmol, 62% yield). Brown oil; IR (neat): 3032, 2935, 1616, 1592, 1514, 1478, 1451, 1434, 1417, 1381, 1342, 1331, 1318, 1259, 1187, 1152, 1122, 1069, 1036, 1020, 970, 952, 847, 824, 803, 773, 753, 732, 710, 672, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.0 Hz, 1H), 7.96 (m, 1H), 7.69 (dd, J = 1.2 7.2 Hz, 1H), 7.59 (m, 4H), 3.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 133.7, 132.5, 130.0, 129.6, 129.1, 127.9, 127.1, 125.2, 124.1, 116.9, 109.4, 40.5; HRMS (DART); Exact mass calcd for $C_{13}H_3N_2O_5S$ $[M+H]^+$, 307.0389. Found

307.0409.

*3-(3-Bromophenyl)furoxan-4-yl trifluoromethanesulfonate (**3e**, Table 4, entry 8).* To the solution of **2e** (33 mg, 0.066 mmol) in CH_2Cl_2 (1 mL), Tf_2O (12.5 μL, 0.073 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **3e** (20.8 mg, 0.053 mmol, 81% yield). Colorless oil; IR (neat): 1620, 1565, 1491, 1442, 1395, 1329, 1303, 1220, 1147, 1125, 1076, 994, 884, 846, 819, 786, 738, 703, 677, 657, 637, 601, 575, 517, 503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.07$ (t, $J = 1.6$ Hz, 1H), 7.81 (m, 1H), 7.71 (m, 1H), 7.47 (t, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.7$, 134.9, 131.0, 129.2, 124.9, 123.7, 121.7, 118.4 (q, $J = 320$ Hz), 107.2; HRMS (DART); Exact mass calcd for $C_9H_5{}^{81}BrF_3N_2O_5S$ $[M+H]^+$, 390.9034. Found 390.9055.

*3-(3-Chlorophenyl)furoxan-4-yl trifluoromethanesulfonate (**3f**, Table 4, entry 9).* To the solution of **2f** (50 mg, 0.11 mmol) in CH_2Cl_2 (1 mL), Tf_2O (20 μL, 0.12 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **3f** (25.2 mg, 0.073 mmol, 66% yield). Colorless oil; IR (neat): 1620, 1570, 1493, 1442, 1398, 1319, 1305, 1220, 1149, 1125, 1080, 998, 884, 847, 826, 788, 749, 707, 679, 639, 601, 575, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (m, 1H), 7.76 (m, 1H), 7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.7$, 135.9, 131.9, 130.8, 126.4, 124.5, 121.5, 118.7 (q, $J = 320$ Hz), 107.3; HRMS (DART); Exact mass calcd for $C_9H_5{}^{35}ClF_3N_2O_5S$ $[M+H]^+$, 344.9560. Found 344.9585.

*3-(4-Methoxyphenyl)furoxan-4-yl trifluoromethanesulfonate (**3g**, Table 4, entry 10).* To the solution of **2g** (50 mg, 0.11 mmol) in CH_2Cl_2 (1 mL), Tf_2O (20 μL, 0.12 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **3g** (33 mg, 0.098 mmol, 88% yield). Yellow oil; IR (neat): 1605, 1575, 1522, 1439, 1415, 1327, 1312, 1300, 1262, 1219, 1184, 1145, 1126, 1090, 1028, 1012, 983, 846, 833, 789, 766, 733, 703, 649, 633, 594, 574, 551, 524, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (m, 2H), 7.08 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.0$, 154.1, 128.2, 123.2, 120.0, 115.1, 112.2 (q, $J = 334$ Hz), 55.5; HRMS (DART); Exact mass calcd for $C_{10}H_8F_3N_2O_6S$ $[M+H]^+$, 341.0055. Found 341.0028.

*3-[4-(Trifluoromethyl)phenyl]furoxan-4-yl trifluoromethanesulfonate (**3h**, Table 4, entry 11).* To the solution of **2h** (76 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL), Tf_2O (24 μL, 0.17 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **3h** (39 mg, 0.10 mmol, 67% yield). Colorless oil; IR (neat): 1617, 1520, 1445, 1410, 1323, 1292, 1225, 1173, 1123, 1068, 1018, 985, 843, 814, 765, 746, 711, 648, 632, 602, 575, 540, 527, 516, 502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 132.4 (q, J = 33.1 Hz), 125.8, 125.6 (q, J = 37 Hz), 122.5, 122.2 (q, J = 271 Hz), 117.3(q, J = 320 Hz), 106.4; HRMS (DART); Exact mass calcd for $C_{10}H_5F_6N_2O_5S$ $[M+H]^+$, 378.9823. Found 378.9828.

*3-(2,4,6-Trimethylphenyl)furoxan-4-yl methanesulfonate (**4i**, Table 4, entry 13).* To the solution of **2i** (41.9 mg, 0.09 mmol) in CH_2Cl_2 (1 mL), Ms_2O (17 mg, 0.1 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 3/1) to give **4i** (21 mg, 0.069 mmol, 76% yield). Mp. 91.1–91.7 °C; IR (neat): 3036, 2941, 1615, 1495, 1455, 1412, 1375, 1334, 1319, 1187, 1134, 1083, 1033, 981, 971, 947, 859, 851, 838, 785, 765, 742, 689, 658, 605, 574, 567, 558, 551, 521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 2H), 3.36 (s, 3H), 2.33 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 142.0, 139.0, 129.0, 115.5, 109.7, 40.3, 21.3, 19.3; HRMS (DART); Exact mass calcd for $C_{12}H_{15}N_2O_5S$ $[M+H]^+$, 299.0702. Found 299.0697.

*3-(Pyridin-2-yl)furoxan-4-yl trifluoromethanesulfonate (**3j**, Table 4, entry 14).* To the solution of **2j** (50 mg, 0.12 mmol) in CH_2Cl_2 (1 mL), Tf_2O (20 μL, 0.12 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to give **3j** (16 mg, 0.05 mmol, 42% yield). Mp. 34.0–34.1 °C; IR (neat): 1610, 1580, 1570, 1519, 1480, 1464, 1438, 1419, 1342, 1290, 1210, 1167, 1130, 1103, 1085, 1046, 996, 985, 861, 817, 786, 737, 709, 692, 636, 598, 573, 521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.77 (dq, J = 0.8 Hz, J = 4.8 Hz, 1H), 8.24 (dt, J =1.2 Hz, J = 8.0 Hz, 1H), 7.92 (td, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.46 (qd, J = 0.8 Hz, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 150.0, 141.6, 137.4, 125.6, 121.4, 118.5 (q, J = 320 Hz), 108.9; HRMS (DART); Exact mass calcd for $C_8H_5F_3N_3O_5S$ $[M+H]^+$, 311.9902. Found 311.9930.

*3-(Pyridin-2-yl)furoxan-4-yl methanesulfonate (**4j**, Table 4, entry 15).* To the solution of **2j** (42 mg, 0.1 mmol) in CH_2Cl_2 (1 mL), Ms_2O (17 mg, 0.1 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 3/1) to give **4j** (8.3 mg, 0.03 mmol, 32% yield). Mp. 102.2–102.5 °C IR (neat):2956, 2871, 1479, 1472, 1463, 1453, 1395, 1379, 1322, 1261, 1180, 1166, 1067, 1030, 991, 922, 896, 880, 799, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (dq, *J* = 0.8 Hz, *J* =4.8 Hz, 1H), 8.21 (dt, *J* =1.2 Hz *J* =8.0 Hz, 1H), 7.91 (td, *J* =1.6, *J* =8.0, 1H), 7.43 (qd, *J* =1.2 Hz, *J* =4.8 Hz, 1H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 150.2, 142.1, 137.3, 125.3, 122.2, 109.2, 40.4; HRMS (DART); Exact mass calcd for $C_8H_8N_3O_5S$ [M+H]$^+$, 258.0185. Found 258.0178.

*3-[1-(4-Methylbenzene-1-sulfonyl)-1H-indol-3-yl]furoxan-4-yl trifluoromethanesulfon-ate (**3k**, Table 4, entry 16).* To the solution of **2k** (73 mg, 0.12 mmol) in CH_2Cl_2 (2 mL), Tf_2O (22 μL, 0.13 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 5/1) to give **3k** (27 mg, 0.053 mmol, 45% yield). Mp. 103.3–103.4 °C; IR (neat): 3128, 2924, 1639, 1596, 1551, 1490, 1458, 1439, 1425, 1376, 1349, 1294, 1245, 1221, 1197, 1187, 1175, 1147, 1124, 1113, 1087, 1021, 990, 927, 855, 811, 759, 745, 732, 703, 680, 661, 641, 613, 597, 579, 567, 536 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1H), 8.05 (d, *J* =8.4 Hz, 1H), 7.84 (m, 2H), 7.73 (m, 1H), 7.45 (m, 1H), 7.35 (m, 1H), 7.28 (d, *J* =8.0 Hz, 2H), 2.37 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 146.1, 134.6, 134.2, 130.3, 127.8, 127.2, 126.3, 126.0, 124.4, 121.4, 118.3 (q, *J* = 320 Hz), 113.8, 105.8, 101.1, 21.7; HRMS (DART); Exact mass calcd for $C_{18}H_{13}F_3N_3O_7S_2$ [M+H]$^+$, 504.0147. Found 504.0179.

*3-(Propan-2-yl)furoxan-4-yl methanesulfonate (**4l**, Table 4, entry 18).* To the solution of **2l** (108 mg, 0.28 mmol) in CH_2Cl_2 (5 mL), Ms_2O (54 mg, 0.31 mmol) was added at 0 °C and the mixture was stirred for 5 min. Subsequently, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 3/1) to give **4l** (33 mg, 0.15 mmol, 52% yield). Colorless oil; IR (neat): 2981, 2940, 1615, 1478, 1448, 1418, 1382, 1331, 1262, 1190, 1168, 1133, 1064, 1016, 970, 838, 800, 769, 739, 711, 661, 563, 521, 513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (s, 3H), 3.04 (sept, *J* =7.2 Hz, 1H), 1.34 (d, *J* =7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 112.6, 39.2, 22.8, 16.5; HRMS (DART); Exact mass calcd for $C_6H_{11}N_2O_5S$ [M+H]$^+$, 223.0389. Found 223.0395.

Isomerization of 4-sulfonyloxy furoxans to 3-sulfonyl furoxans (Scheme 2). *4-(4-Methylphenyl)furoxan-3-yl trifluoromethanesulfonate (**6**, Scheme 2A).* A solution of **3a** (5 mg, 0.015 mmol) in benzene (0.8 mL) was prepared in a Pyrex NMR tube. The solution was irradiated with 300–400-nm light at 23 °C and the reaction progress was monitored by ^{1}H NMR analysis. The isomerization ratio was determined from peak integration. **3a**: ^{1}H NMR (400 MHz, C_6D_6): δ = 7.47 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 1.92 (s, 3H); **6**: ^{1}H NMR (400 MHz, C_6D_6): δ = 7.40 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 7.6 Hz, 2H), 1.94 (s, 3H).

4-(4-Methylphenyl)furoxan-3-yl methanesulfonate (7, Scheme 2B). A solution of **4a** (32 mg, 0.11 mmol) in benzene (3.2 mL) was prepared and divided into four Pyrex NMR tubes. The solution was irradiated with 300–400-nm light at 23 °C and the reaction progress was monitored by ^{1}H NMR analysis. After stirring for 75 min, the solution in the four NMR tubes was combined and concentrated in vacuo. The residue was purified by preparative HPLC (eluent: hexane/EtOAc = 10/1) to obtain **7** (13.6 mg, 0.046 mmol, 43% yield). Single crystals of **7** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/1,2-dichloroethane by vapor diffusion. Mp. 97.4–97.9 °C; IR (neat): 3034, 3015, 2931, 1616, 1574, 1539, 1481, 1463, 1420, 1402, 1380, 1332, 1319, 1179, 1123, 1050, 1023, 974, 872, 844, 828, 801, 786, 753, 726, 697, 640, 622, 592, 580, 539 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 3.62 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 142.7, 130.1, 126.6, 121.3, 43.3, 21.7; HRMS (DART); Exact mass calcd for $C_{10}H_{11}N_2O_5S$ $[M+H]^+$, 271.0389. Found 271.0410.

*4-(4-Methylphenyl)furoxan-3-yl 4-methylbenzene-1-sulfonate (**8**, Scheme 2C).* A solution of **5a** (30 mg, 0.09 mmol) in benzene (3.2 mL) was prepared and divided into four Pyrex NMR tubes. The solution was irradiated with 300–400-nm light at 23 °C and the reaction progress was monitored by ^{1}H NMR analysis. After stirring for 90 min, the solution in the four NMR tubes was combined, and concentrated in vacuo. The residue was purified by preparative HPLC (eluent: hexane/EtOAc = 10/1) to obtain **8** (12.7 mg, 0.036 mmol, 42 % yield). Single crystals of **8** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/1,2-dichloroethane by vapor diffusion. Mp. 127.1–127.9 °C; IR (neat):1611, 1593, 1573, 15345, 1463, 1393, 1321, 1304, 1197, 1178, 1123, 1088, 1049, 978, 877, 847, 819, 801, 761, 735, 721, 705, 670, 639, 628, 594, 581, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 151.5, 147.5, 142.2, 131.9, 130.2, 129.9, 129.0, 126.7, 124.9, 121.7, 21.9, 21.6; HRMS (DART); Exact mass calcd for $C_{16}H_{15}N_2O_5S$ $[M+H]^+$, 347.0702. Found 347.0713.

Flow photochemistry for conversion of 5a to 8. The flow-system equipment was manually assembled with an HPLC double-plunger pump, fluorinated transparent plastic tubes, a quartz flow-cell (0.1 × 1.0 × 4.0 cm), and a 450 W high pressure Hg lamp with a Pyrex glass apparatus. The schematics of this system is shown in the SI. A de-aerated benzene solution of **5a** (2.9 mM) was passed through the quartz cell at 0.4 mL/min flow rate with irradiation. As the inner volume of the cell was 0.4 mL, the residence time at the chosen flow rate was 1 min. Under this condition, the product ratio was 12:88 (**5a**:**8**). The product mixture (703 mg) was recrystallized from hexane/dichloroethane solvent system to obtain pure **8** (534 mg, 76% yield).

ACKNOWLEDGMENTS

We thank Prof. Atsunori Mori and Prof. Kentaro Okano at Kobe University for their help on mass analysis and Prof. Shigeki Mori at Ehime University for help on X-ray diffraction analysis. This work was financially supported by JSPS KAKENHI Grant Numbers JP16K18844 and JP17J00025, Futaba Electronics Memorial Foundation, Suzuken Memorial Foundation, Inamori Foundation, and Daiichi Sankyo Foundation of Life Science. AA wishes to thank the JSPS for Research Fellowships for Young Scientists. This work was also supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan, and by Special Coordination Funds for Promoting Science and Technology, Creation of Innovation Centers for Advanced Interdisciplinary Research Areas (Innovative Bioproduction Kobe), MEXT, Japan.

Supplementary data

Supplementary data (flow system details and spectral data) associated to this article can be found in the online version, at http://dx.doi.org/xxxxxx.

References and notes

(1) (a) Gasco, A.; Boulton, A. J. *Adv. Heterocycl. Chem.*, **1981**, *29*, 251. (b) Sheremetev, A. B.; Makhova, N. N.; Friedrichsen, W. *Adv. Heterocycl. Chem.*, **2001**, *78*, 65. (c) Cerecetto, H.; Porcal, W. *Mini Rev. Med. Chem.*, **2005**, *5*, 57. (d) Nikonov, G. N.; Bobrov, S. In *Comprehensive Heterocyclic Chemistry III*; Katritzky,A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, J. K. Eds; Elsevier: Oxford, **2008**; Vol. 5, Ch 5.05, pp315–395.

(2) (a) Ghigo, D.; Calvino, R.; Heller, R.; Alessio, P.; Fruttero, R.; Gasco, A.; Bosia, A.; Pescarmona, G. *Biochem. Pharm.* **1992**, *43*, 1281. (b) Feelisch, M.; Schönafingeri, K.; Noack, H. *Biochem. Pharm.* **1992**, *44*, 1149. (c) Calvino, R.; Fruttero, R.; Ghigo, D.; Bosia, A.; Pescarmona, G. P.; Gasco, A. *J. Med. Chem.* **1992**, *35*, 3296. (d) Medana, C.; Ermondi, G.; Fruttero, R.; Di Stilo, A.; Ferretti, C.; Gasco, A. *J. Med. Chem.* **1994**, *37*, 4412.

(3) (a) Gruetter, C. A.; Barry, B. K.; McNamara, D. B.; Gruetter, D. Y.; Kadowitz, P. J.; Ignarro, L. *J. Cyclic Nucleotide Res.* **1979**, *5*, 211. (b) Ignarro, L. J.; Buga, G. M.; Wood, K. S.; Byrns R. E.; Chaudhuri, G. *Proc. Natl. Adad. Sci. USA* **1987**, *84*, 9265. (c) Palmer, R. M. J.; Ferrige, A. G.; Moncada, S, *Nature* **1987**, *327*, 524. For selected reviews, see: (d) Ignarro, L. J. *J. Physiol. Pharmacol.*, **2002**, *53*, 503. (e) Ignarro, L. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 1882. (f) Nathan, C.; Xie, Q.-w. *Cell* **1994**, *78*, 915.

(4) Fershtat, L. L.; Makhova, N. N.*ChemMedChem* **2017**, *12*, 622 and references therein.

(5) (a) Ando, A.; Matsubara, R.; Takazawa, S.; Shimada, T.; Hayashi, M. *Asian J. Org. Chem.* **2016**, *5*, 886. (b) Matsubara, R.; Takazawa, S.; Ando, A.; Hayashi, M.; Tohda, R.; Tsubaki, M. *Asian J. Org. Chem.* **2017**, *6*, 619.

(6) (a) Angeli, A. *Gazz. Chim. Ital.*, **1916**, *46*, 300. (b) Bigiavi, D. *Gazz. Chim. Ital.*, **1921**, *51*, 324. (c) Ponzio, G.; Longo, G. *Gazz. Chim. Ital.*, **1930**, *60*, 893.

(7) (a) Matsubara, R.; Eguchi, S.; Ando, A.; Hayashi, M. *Org. Biomol. Chem.* **2017**, *15*, 1965. (b) Matsubara, R.; Ando, A.; Hayashi, M. *Tetrahedron Lett.* **2017**, *58*, 3337.

(8) (a) Levy, N.; Scaife, C. W. *J. Chem. Soc.*, **1946**, 1100. (b) Kunai, A.; Doi, T.; Nagaoka, T.; Yagi, H.; Sasaki, K. *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 1843. (c) Fershtat, L. L.; Struchkova, M. I.; Goloveshkin, A. S.; Bushmarinov, I. S.; Makhova, N. N. *Heteroatom Chem.*, **2014**, *25*, 226.

(9) (a) Wieland, H. *Justus Liebigs Ann. Chem.* **1903**, *328*, 154. (b) 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.

(10) The starting 4-nitrofuroxan was consumed and several byproducts, one of which was tentatively assigned to be the bisfuroxanyl ether, were obtained.

(11) Fershtat, L. L.; Epishina, M. A.; Ovchinnikov, I. V.; Struchkova, M. I.; Romanova, A. A.; Ananyev, I. V.; Makhova, N. N. *Tetrahedron Lett.* **2016**, *57*, 5685.

(12) Rf value was 0.3 in CH_2Cl_2/MeOH (10/1) eluent system.

(13) Mallory, F. B.; Manatt, S. L.; Wood, C. S. *J. Am. Chem. Soc.*, **1965**, *87*, 5433.

(14) Gasco, A.; Boulton, A. J. *J. Chem. Soc. Perkin II*, **1973**, 1613.

(15) The UV-Vis absorption spectra of compounds **6–8** are shown in the Supplementary data.

(16) We assume that the direct use of crude **6** would be possible for the purpose of further transformation.

(17) Crystallographic data (excluding structure factors) with the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-1838534 (**2a**), CCDC-1838535 (**3a**), CCDC-1838536 (**7**), and CCDC-1838537 (**8**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(18) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025.

(19) During the preparation of the manuscript an ammonium salt of hydroxyfuroxan was reported: Ustyuzhanina, N. E.; Fershtat, L. L.; Gening, M. L.; Nifantiev, N. E.; Makhova, N. N. *Mendeleev Commun.* **2018**, *28*, 49.