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(Citation)
Journal of Organic Chemistry,85(9):5959-5972

(Issue Date)
2020-05-01

(Resource Type)
journal article

(Version)
Accepted Manuscript

# Synthesis and synthetic application of chloro- and bromofuroxans

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*KEYWORDS (Word Style "BG_Keywords"). Furoxan; Synthetic method; Radical addition; Modular synthesis; Heterocycles*

**ABSTRACT:** Furoxans are potentially useful heteroaromatic units in pharmaceuticals and agrichemicals. However, the applications for furoxan-based compounds have been hampered due to the underdevelopment of their synthetic methods. Herein we report a new synthetic approach for the synthesis of chloro- and bromofuroxans. The starting materials were dichloro- and dibromofuroxans, and the substituents were directly introduced to the furoxan ring in a modular fashion. The synthesized monohalofuroxans served as substrates for the installation of a second substituent to prepare further functionalized furoxans.

## INTRODUCTION

The majority of pharmaceuticals and agrichemicals contain heteroaromatic units. Heteroaromatic units are indispensable in drug discovery[1] because they not only serve as rigid backbones to maintain the shape of a molecule, but also affect the interaction and reactivity of the molecule towards the target proteins via their unique electronic states and coordination ability, which can contribute to improved biological activity.

The heteroaromatic unit furoxan was first synthesized 150 years ago.[2] In the past few decades, it has attracted attention for its ability to enable spontaneous or stimulus-sensitive nitrogen oxide release,[3] which is a unique characteristic that distinguishes it from other heteroaromatics. Furoxan is generally air and moisture stable, which enables easy isolation, manipulation and storage; therefore, it is expected to have high potential as a structural unit for fine chemicals.[4] However, a literature survey reveals that furoxan has seen little application in fine-chemical-based fields.[5]

Our group has recently been interested in the overlooked potential of furoxan as a surrogate for other five- or six-membered heterocyclic rings. Simple replacement of a more common heterocyclic architecture or hazardous functionality (e.g. nitrate esters) by a furoxan ring could improve the biological activity and safety of a molecule with minimal change to its overall shape (Figure 1A).[6] Additionally, from an industrial viewpoint, patent violations would not be an issue for such compounds, given the scarcity of furoxan-containing functional molecules.

The underdevelopment of applications for furoxan-based compounds can be largely ascribed to the limited general synthetic methods of furoxans. Conventionally, the required substituents, especially carbon substituents, have had to be pre-installed before the formation of the furoxan ring ("pre-ring" modification strategy). In such cases, multi-step synthesis is required to obtain each targeted molecule; thus, this methodology is unsuitable in drug discovery studies. To tackle this issue, our laboratory has recently focused on the development of "post-ring" furoxan modification; i.e., methods in which the designated substituents are introduced directly onto the furoxan ring.[7] Using post-ring methods, libraries of furoxans can be synthesized in a modular fashion from common intermediates.

Chloro- and bromofuroxanyl groups, which are small heteroaromatic units comprising seven atoms, are potentially useful for several reasons. (1) Such compact monovalent atomic groups, e.g., $CF_3$ and $CF_2H$,[8] are often installed in drug candidate molecules to adjust their pharmacological activity (Figure 1B). (2) They contain reactive C–X bonds that can serve as versatile handles for further functionalization, making them useful intermediates for the divergent synthesis of functionalized furoxans. (3) Monohalofuroxans can be utilized as photolabile nitric oxide donors.[3c, 3e] Only sporadic reports of the synthesis of monochloro- and monobromofuroxans have been published.[9] Most previous methods have relied on pre-ring modifications starting from 1-haloalkenes, halo α-dioximes, and 1-haloalkynes, in which the designated substituents had to be pre-installed. To the best of our knowledge, monohalofuroxan syntheses based on post-ring modification strategies have so far been limited to the synthesis of 3-chlorofuroxans from 3-chloro-4-nitrofuroxan developed by Rakitin[9a, 9b, 10] and our previous synthesis of chloro- and fluorofuroxans via halide installation into 4-nitrofuroxans.[3e]

Here, we report a variety of substitution reactions of dichloro- and dibromofuroxans, including reactions in which carbon–carbon bonds are formed on the furoxan ring, that enable easy access to various monochloro- and monobromofuroxans. The halogen atom on the obtained monohalofuroxans serves as a synthetic handle for the introduction of the second substituent to generate the desired functionalized furoxans.

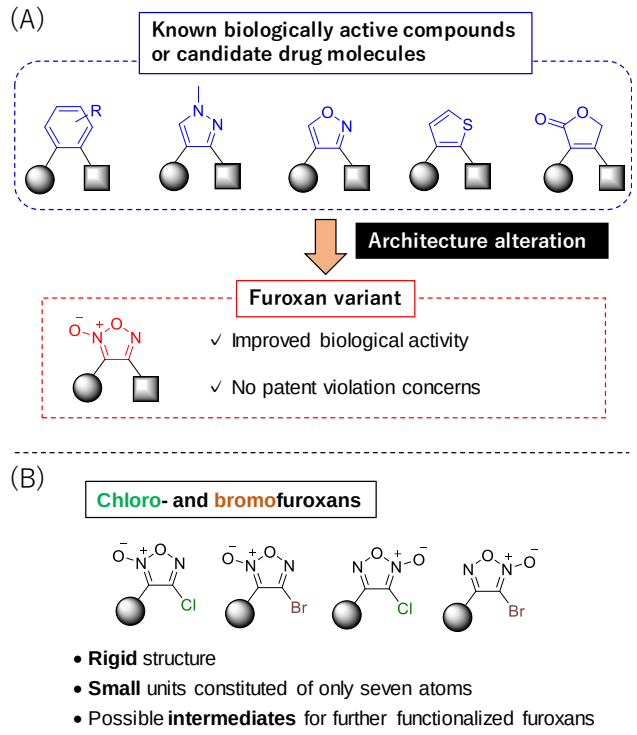



**Figure 1.** (A) Furoxan as a surrogate for known five- or six-membered ring architectures. (B) Advantages of chloro- and bromofuroxans.

## RESULTS AND DISCUSSION

### 1. Synthesis of dihalofuroxans

The synthesis of dichlorofuroxan (**1**) and dibromofuroxan (**2**) is known in the literature. However, the reported methods require toxic and non-user-friendly reagents such as chlorine gas,[9f] mercury oxide,[11] and explosive mercury(II) fulminate.[2, 12] Therefore, we have investigated new synthetic routes for these compounds; our modified methods are shown in Figure 2.[13] Glyoxal (**3**) was used as a starting material for **1**, while glyoxylic acid oxime (**6**) was used for **2**. Both routes were scalable and gave the dihalofuroxans in acceptable yields. Additionally, only reagents that are readily accessible in an ordinary laboratory are employed in these syntheses. The structure of **2** was unambiguously determined by single crystal X-ray diffraction analysis (sc-XRD).[14]

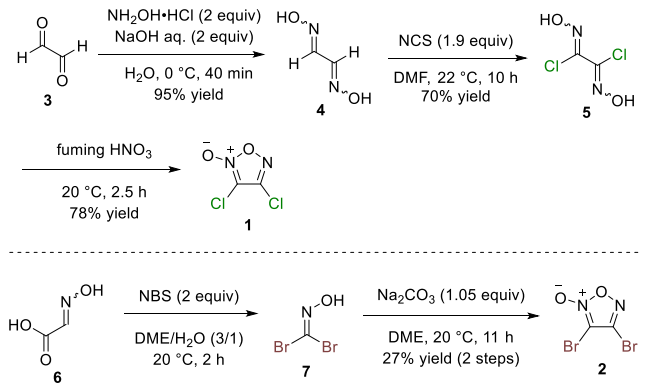
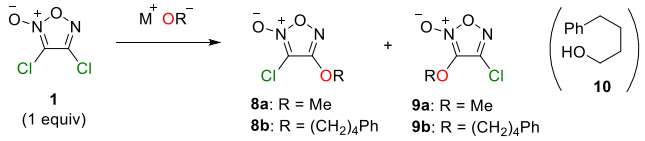



**Figure 2.** Synthesis of dichloro- and dibromofuroxans

### 2. Synthesis of 4-alkoxy-3-halofuroxans

4-Nitro- and 4-(arylsulfonyl)furoxans readily react with alkoxides in an aromatic nucleophilic substitution ($S_NAr$) manner to afford 4-alkoxyfuroxans in generally high yields.[4e] Anticipating that dihalofuroxans would also undergo $S_NAr$ reactions with alkoxides to afford 4-alkoxy-3-halofuroxans, we began our investigation using **1**, alkali metal methoxides, and THF as a solvent (Table 1). The reaction of **1** with NaOMe proceeded to give product **8a** regioselectively, although in moderate yield (entry 1). HMBC NMR analysis of **8a** revealed that the protons of the methyl group showed a cross-peak with the most deshielded $^{13}C$ peak (161 ppm), which was assigned to C4 of the furoxan, confirming the regiochemistry of **8a**. The choice of alkali metal proved to be important; potassium and lithium methoxides afforded **8a** in lower yields (entries 2 and 3). A slight increase in the loading of NaOMe dramatically decreased the yield (entry 4), indicating that product decomposition could occur under these conditions, and could be one of the reasons for the moderate yield. Thus, the loading of NaOMe was further decreased (1.2 equiv) and the reaction was conducted at lower temperature (–20 °C), which resulted in a slight improvement in the yield (entry 5). However, regioisomer **9a** was obtained as a minor product along with **8a** under these conditions for unclear reasons.

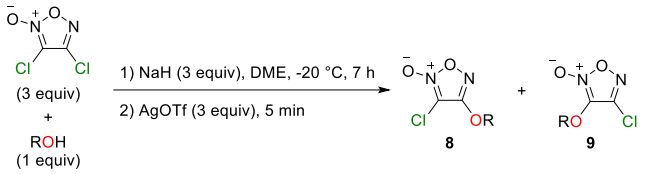
**Table 1.** Optimization of the alkoxylation of dichlorofuroxan (**1**)




| entry | $M^+OR^-$ (equiv) | solvent | temp /°C | time /h | yield /%[a] | **8**:**9** |
|---|---|---|---|---|---|---|
| 1 | NaOMe (1.5) | THF | 0 | 12 | 31 | 100:0 |
| 2 | KOMe (1.5) | THF | 0 | 24 | 15 | 100:0 |
| 3 | LiOMe (1.5) | THF | 0 | 35 | 3 | 100:0 |
| 4 | NaOMe (2.0) | THF | 0 | 12 | 3 | 100:0 |
| 5 | NaOMe (1.2) | THF | –20 | 24 | 39 (25)[b] | 87:13 |
| 6[c] | **10** (1.0) NaH (3.0) | DME | –20 | 7 | 40 (41)[e] | N.D. |
| 7[c,d] | **10** (1.0) NaH (3.0) | DME | –20 | 7 | 85[b] (7)[e] | 84:16 |

[a] Determined by $^1H$ NMR analysis using durene as an internal standard. The combined yield of **8** and **9** is shown. [b] Isolated yield. [c] 3 equiv of **1** was used. [d] AgOTf (3 equiv) was added after the reaction. [e] Recovery of **1**. N.D. = not determined.

**Table 2.** Alkoxylation of dichlorofuroxan (**1**)



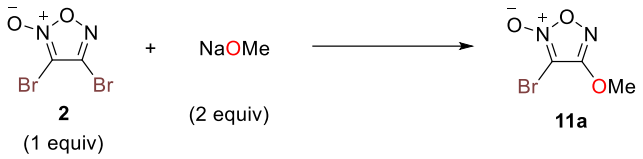

| entry | ROH | yield /%[a] | **8**:**9** | product |
|---|---|---|---|---|
| 1 | cyclohexanol | 44 | 70:30 | **8c** and **9c** |
| 2 | $^t$BuOH | 65 | 67:33 | **8d** and **9d** |
| 3 | $CF_3CH_2OH$ | 59 | 100:0 | **8e** |
| 4 | PhOH | 27 | 100:0 | **8f** |

[a] Isolated yield.

The use of the alcohol as the limiting reagent is desirable for larger and more valuable alcohols than methanol. Thus, we investigated the reaction conditions for the alkoxylation of **1** using alcohol **10** as the limiting reagent. We found that the use of 3 equivalents of **1** and NaH as a base in the solvent DME provided promising results, giving adduct **8b** in 40% yield (Table 1, entry 6). The structure of **8b** was unambiguously determined by sc-XRD.[14] Careful analysis of the reaction course revealed an anomalous phenomenon in this reaction; although TLC analysis of an in situ sample indicated the complete consumption of alcohol **10**, a significant amount of **10** (41%) was recovered after aqueous work-up. We observed a similar phenomenon in our previous cyanation reaction of 4-nitrofuroxans.[7b] We surmised that a Meisenheimer complex may be formed in situ and remain stable until the addition of water, upon which it may either be converted to product **8b** or revert to the starting **1** and **10**. Based on this assumption, we added AgOTf (3 equiv) after the reaction was completed but before the aqueous work-up to selectively remove the chloride anion from the Meisenheimer complex. To our delight, the yield of **8b** improved to 85% (entry 7). Under these optimized conditions, a secondary and tertiary alcohol (entries 1 and 2, Table 2), a fluorinated alcohol (entry 3, Table 2), and phenol (entry 4, Table 2) reacted with **1** to give the corresponding adducts,[14] demonstrating the wide scope of the established method.

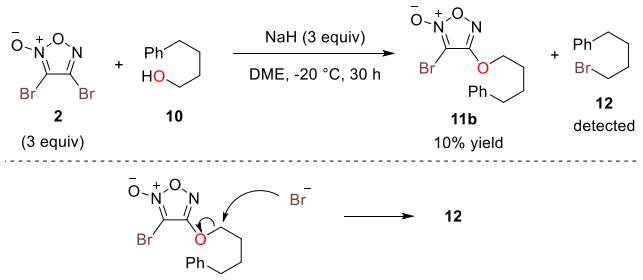
Next, we investigated the alkoxylation of dibromofuroxan (**2**) (Table 3). The methoxylation of **2** proceeded in DME to afford adduct **11a** (entry 1), the structure of which was determined by sc-XRD.[14] To our regret, the conditions that improved the yields in the alkoxylation of **1** resulted in a low yield in the methoxylation of **2** (entries 1–3). Prolonging the reaction decreased the yield (entry 1 vs entry 4), indicating that the decomposition of product **11a** might occur in this reaction system. Solvent screening revealed that DMF, DMSO, and THF all gave unpromising results (entries 5–7). Finally, the use of NaOMe (2 equiv) in the solvent MeOH improved the yield to 62% (entry 8).

**Table 3.** Optimization of the reaction of dibromofuroxan (**2**)




| entry | solvent | temp /°C | time /h | yield /%[a] |
|---|---|---|---|---|
| 1 | DME | –20 | 1 | 21 |
| 2[b] | DME | –20 | 1 | 11 |
| 3[c] | DME | –20 | 1 | 11 |
| 4 | DME | –20 | 24 | 12 |
| 5 | DMF | 20 | 18 | trace |
| 6 | DMSO | 20 | 30 | trace |
| 7 | THF | 20 | 24 | 19 |
| 8 | MeOH | 0 | 8 | 62[d] |

[a] Determined by $^1$H NMR analysis using durene as an internal standard. [b] AgOTf (3 equiv) was added after the reaction. [c] 3 equiv of **2** and 1 equiv of NaOMe were used. [d] Isolated yield.




**Scheme 1.** Byproduct formation in the alkoxylation of **2**

Although the use of the alcohol nucleophile as the solvent is acceptable if the alcohol is volatile and liquid, it is not practical when the alcohol nucleophile is non-volatile, solid, or valuable. Thereby, we reinvestigated the reaction conditions for the alkoxylation of **2** using **10** as a limiting reagent (Scheme 1). However, the yield of the desired product **11b** did not exceed 10% even after extensive screening. 1-Bromo-4-phenylbutane (**12**) was detected as a byproduct in this reaction; we attributed its formation to the $S_N2$ reaction of the bromide anion with the initial product **11b** (bottom, Scheme 1). In this case, the 3-bromofuroxan-4-yloxy group acts as a leaving group, which is unsurprising considering the electron-deficient nature of the furoxan ring. The low yields observed in the reaction of **1** and NaOMe (Table 3) could be partially ascribed to the same type of side-reaction.

### 3. C–C bond forming reactions of dihalofuroxans

C–C bond formation on the furoxan ring has been underdeveloped. Before we began our investigation of C–C bond formation on the furoxan ring, only one report by Gasco et al.[15] was available in the literature, in which two selected substrates reacted with an aryl Grignard reagent. Recently, our group developed the alkynylation of 4-nitro- and 4-sulfonylfuroxans, which represented the first general reaction for C–C bond formation on furoxan rings.[7c] Thereafter, we

reported cyanation reactions and radical addition-elimination reactions of 4-nitro- and 4-sulfonylfuroxans.[7a,7b] We expected that dihalofuroxans **1** and **2** could also undergo C–C bond formation on the furoxan ring to enable facile synthesis of carbon-substituted monohalofuroxans.

### 3-1. Attempted alkylation of the dihalofuroxans

We began our initial investigation using alkyl metal reagents (M = Li, Mg, Zn, and Cu), which are known to be hard nucleophiles. Despite extensive screening of the reaction conditions, the reactions of dihalofuroxan **1** or **2** with the alkyl metal reagents failed to give the desired alkyl-substituted monohalofuroxans in more than 10% yield. A representative example of the attempted reactions is shown in Figure 3 (top). The targeted alkyl-halofuroxans **13** and **14** were not obtained, and the sole identified byproduct in the reaction of **1** and BuLi was ring-opened compound **15**, the structure of which was determined by single sc-XRD.[14] The formation mechanism of byproduct **15** is proposed to be halogen-metal exchange of **1** to give the transient nitrile oxide intermediate **16**, followed by the second attack of a butyl anion at the nitrile oxide moiety (Figure 3, bottom).

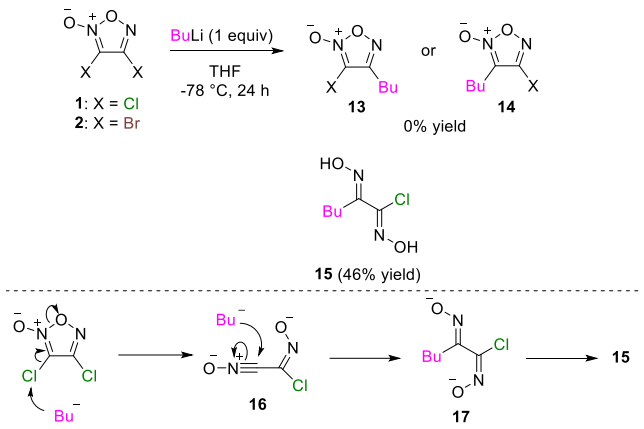
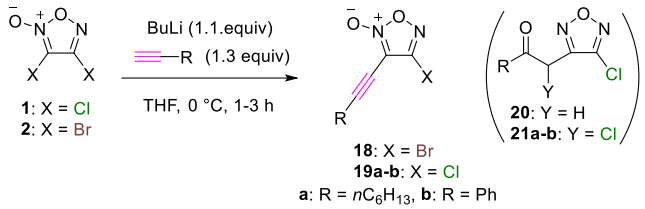



**Figure 3.** Attempted alkylation of dihalofuroxans

### 3-2. Alkynylation of dihalofuroxans

The alkynylation of dihalofuroxans **1** and **2** was then investigated (Table 4). Whereas the attempted alkynylation of **2** resulted in a complex mixture (entry 1), that of **1** afforded the desired adduct **19** in good yield (entries 2 and 3). Fortunately, both alkyl and aryl ethynyl lithium compounds served as good nucleophiles for **1**. The structure of **19b** was determined by sc-XRD.[14] The observed regioselectivity favoring nucleophilic attack at the 3-position was surprising; generally, the C4 carbon of the furoxan, which is more electrophilic compared to C3 carbon, undergoes nucleophilic attack with high regioselectivity.[4d, 4e, 16] This anomalous selectivity probably arises from the directing effect of the exo-ring oxygen atom via its coordination to the lithium metal. In the reactions of **1** and alkynyl lithium compounds, the furazan byproducts **20** and **21** were observed. The structure of **21b** was determined by sc-XRD,[14] and those of **20** and **21a** were determined by analogy to **21b**. The proposed mechanism for the formation of **20** and **21**, which is reminiscent of that of dioxime **15** (vide supra), is shown in Figure 4. The alkynyl anion undergoes halogen-metal exchange at the 3-position of furoxan to generate nitrile oxide **16** and chloroalkyne **22**. Nitrile oxide **16** reacts with either the starting acetylene or **22** in a [3+2]-cycloaddition manner to give 1,2-oxazole **23**, followed by ring rearrangement to give **20** or **21**.

**Table 4.** Alkynylation of dihalofuroxans




| | | | yield /%[a] | | |
|---|---|---|---|---|---|
| entry | X | R | **18** or **19** | **20**[b] | **21**[b] |
| 1 | Br | $nC_6H_{13}$ | messy | – | – |
| 2 | Cl | $nC_6H_{13}$ | 67 | trace | 12 |
| 3 | Cl | Ph | 55 | 10 | 12 |

[a] Isolated yield.

[b] Determined by $^1$H NMR analysis using durene as an internal standard.

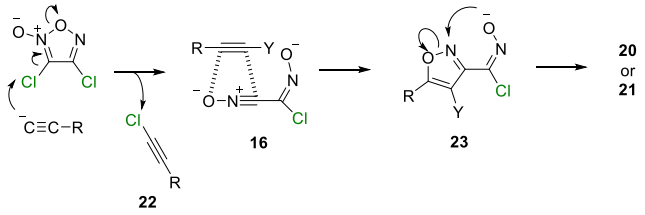



**Figure 4.** Proposed mechanism for the formation of **20** and **21**

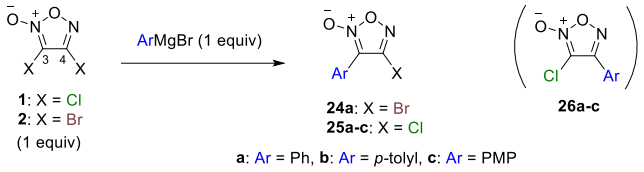
### 3-3. Arylation of dihalofuroxans

The arylation of dihalofuroxans was then investigated (Table 5). The reaction of **2** with PhMgBr afforded a complex mixture of products, and the desired product **24a** was not obtained (entries 1 and 2). To our delight, the reaction of **1** and PhMgBr provided 4-chloro-3-phenylfuroxan (**25a**) (entries 3–6), the structure of which was determined by sc-XRD.[14] The regioisomer **26a** was not detected. Similarly to in the alkynylation of **1**, anomalous regioselectivity favoring the 3-position attack was observed, again probably due to the directing effect of the exo-ring oxygen atom of furoxan. The use of phenyl lithium gave product **25a** in low yield (entry 7). Other aryl groups could also be installed smoothly (entries 8 and 9).

### 3-4. Alkylation of dihalofuroxans

Alkylation of the dihalofuroxans using alkyl metal reagents to synthesize alkyl-substituted monohalofuroxans failed due to a side reaction (vide supra). Our group recently developed the radical-mediated alkylation of 3-(arylsulfonyl)furoxans,[7a] in which aliphatic carboxylic acids serve as an alkyl radical source in the presence of a silver catalyst and the arylsulfonyl radical acts as a good radical leaving group. In analogy, we proposed that dihalofuroxans might also react with alkyl radicals and that the halogen atom could serve as a radical leaving group to

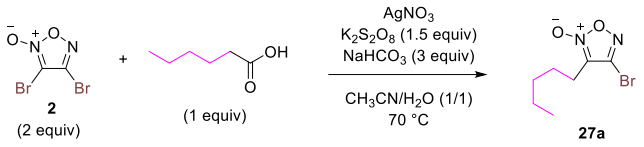
**Table 5.** Arylation of dihalofuroxans




| entry | Ar | X | temp /°C | time /h | yield /%[a] (**24** or **25**) |
|---|---|---|---|---|---|
| 1 | Ph | Br | –78 | 36 | **24a**: 0 |
| 2 | Ph | Br | –40 | 36 | **24a**: 0 |
| 3 | Ph | Cl | –78 | 36 | **25a**: 2 |
| 4 | Ph | Cl | –55 | 24 | **25a**: 22 |
| 5 | Ph | Cl | –40 | 5 | **25a**: 33 |
| 6[b] | Ph | Cl | –40 | 24 | **25a**: 42(41)[d] |
| 7[c] | Ph | Cl | –55 | 24 | **25a**: 8 |
| 8[b] | *p*-tolyl | Cl | –40 | 5 | **25b**: 37 [d] |
| 9[b] | PMP | Cl | 28 | 6 | **25c**: 38(39)[d] |

[a] Determined by $^1$H NMR analysis using durene as an internal standard. [b] 1.5 equiv of ArMgBr was used. [c] PhLi (1 equiv) was used instead of PhMgBr. [d] Isolated yield. PMP = *p*-methoxyphenyl.

**Table 6.** Optimization study for the alkylation of dibromofuroxan (**2**)

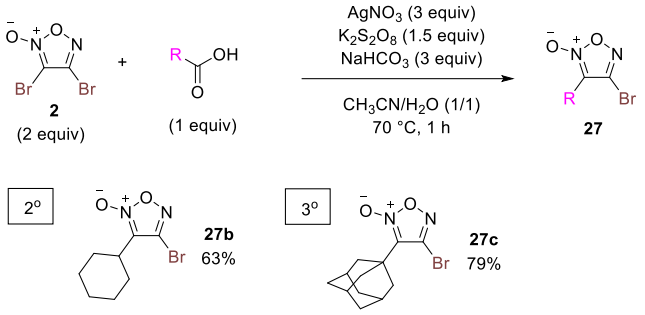



| entry | amount of $AgNO_3$ /equiv | time /h | yield /%[a] |
|---|---|---|---|
| 1 | 0.2 | 30 | trace |
| 2 | 2.0 | 24 | 44 |
| 3[b] | 2.0 | 24 | 40 |
| 4 | 2.0 | 1 | 46 |
| 5[c] | 2.0 | 1 | 51 |
| 6 | 3.0 | 1 | 57 (50)[d] |
| 7[e] | 3.0 | 1 | 3 |

[a] Determined by $^1$H NMR analysis using durene as an internal standard. [b] 5 equiv of **2** was used. [c] 3.0 equiv of $K_2S_2O_8$ was used. [d] Isolated yield. [e] 1,2-Dichloroethane/$H_2O$ (1/1) was used as the solvent.

afford alkyl-substituted monohalofuroxans. **1** did not react with the alkyl radical during our attempted trials (data not shown), but to our delight, **2** reacted with the carboxylic acid-derived alkyl radical to afford 3-alkyl-4-bromofuroxan **27a** (Table 6), although in low yield (entry 1). The use of a superstoichiometric amount of $AgNO_3$ improved the yield to 44%, with the majority of the remaining carboxylic acid being recovered (entry 2). Optimization of the reaction conditions (entries 3–7) revealed that 3 equiv of $AgNO_3$ were required to obtain a higher yield. Under the optimized conditions (entry 6 in Table 6), secondary and tertiary alkyl groups were also successfully introduced to the furoxan in good yields (Scheme 2).[14]

**Scheme 2.** Alkylation of dibromofuroxan (**2**)




Based on precedents in the literature,[17] a proposed mechanism for the radical-mediated alkylation of **2** is delineated in Figure 5. An Ag(II) salt is generated in the presence of the persulfate anion. The carboxylic acid reacts with Ag(II), and then generates an alkyl radical through decarboxylation. The alkyl radical reacts with **2** at the 3-position to afford 3-alkyl-4-bromofuroxan **27** and generate a bromo radical. In contrast to our previous report, in which 3-sulfonylfuroxans were used as the substrate,[7a] a stoichiometric amount of the silver salt was required in this reaction. This was probably due to the reaction of in-situ generated bromide radicals or bromide anions with the silver salt to form inactive silver bromide (AgBr).

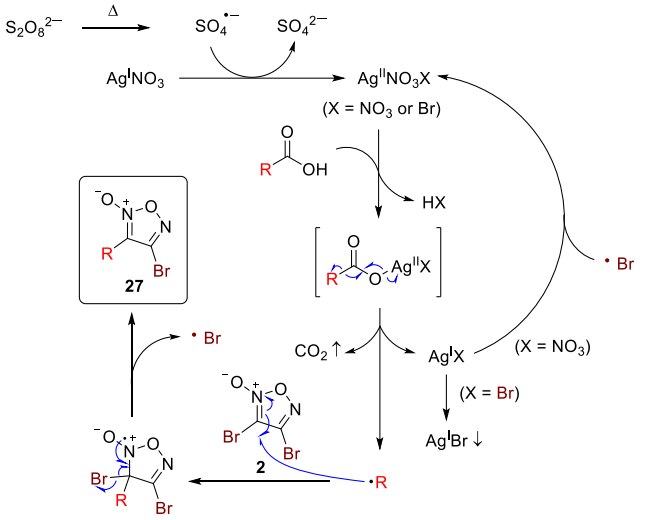



**Figure 5**. Proposed mechanism for the radical-mediated alkylation of dibromofuroxan (**2**)

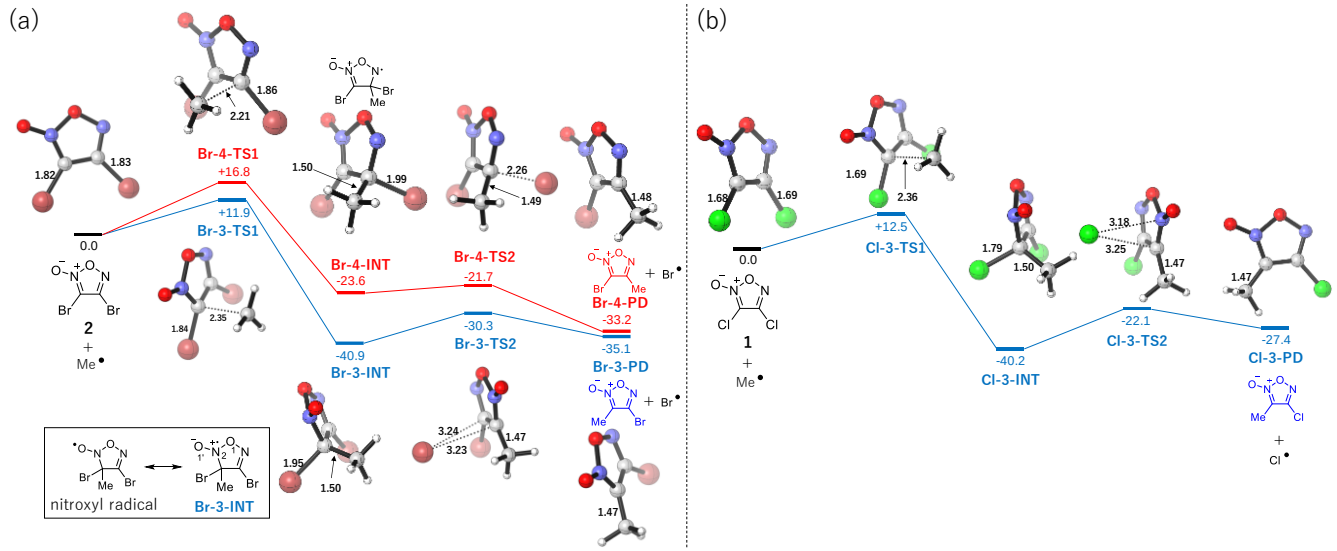



**Figure 6.** Computed potential energy surfaces and relative Gibbs free energies for the radical addition reactions to dibromofuroxan (a) and dichlorofuroxan (b) at the (u)LC-BLYP/6-31G(d) level using the SMD polarizable continuum solvation model (DMSO). All energies are indicated in kcal mol$^{-1}$, and interatomic distances are shown in angstroms. Inset: The delocalized structure of **Br-3-INT** is a nitroxyl radical; these radicals are known to be stable.

Long-range corrected (LC) density functional theory (DFT) calculations,[18] which were developed to determine orbital energies with chemical accuracy[19] and correct for the charge transfer nature of reactions,[20] were performed for the radical addition and elimination reactions of **1** and **2** using a simplified alkyl radical (methyl radical) (Figure 6). To clarify the origin of the regioselective addition at the 3-position over the 4-position, both routes were calculated. In the case of **2**, the radical addition step is exoergonic for both the 3- and 4-position attacks (Figure 6a), but **Br-3-INT**, the radical intermediate generated by the 3-position radical attack, is lower in energy than **Br-4-INT** by 17.3 kcal mol$^{-1}$. The transition state **Br-3-TS1** is also lower in energy than **Br-4-TS1** by 4.9 kcal mol$^{-1}$. The same tendency was observed for the radical addition reaction to 3,4-bis(arylsulfonyl)furoxan in our previous work.[7a] The preference for the 3-position attack of alkyl radical can be intuitively understood from the fact that the delocalized structure of **Br-3-INT** is a nitroxyl radical; nitroxyl radicals are well-known as stable oxy-radical species (inset of Figure 6a). In contrast to in our previous work,[7a] the subsequent elimination step (from **Br-3-INT** to **Br-3-PD**) proved to be slightly endoergonic ($\Delta\Delta G$ = +5.8 kcal mol$^{-1}$). This result indicates that the reverse reaction, i.e., the reaction of product **27** with a bromide radical to afford **Br-3-INT**, is possible. In this context, the use of a stoichiometric amount of silver salt would be required to scavenge the free bromide radical in order to overcome the unfavorable equilibrium. On the other hand, in the radical addition to **1**, **Cl-3-TS2**, the transition state for the elimination step from **Cl-3-INT** to **Cl-3-PD**, involves a significant increase in energy ($\Delta\Delta G$ = +18.1 kcal mol$^{-1}$), which can be attributed to the relative strength of the C–Cl bond compared to the C–Br bond. Thus, the calculations do not contradict the experimental finding that **1** did not give the radical addition product.

## 4. Modular synthesis of functionalized furoxans via monohalofuroxans

Since furoxans have two open sites (at the 3- and 4-positions) at which a substituent can be installed, the ideal synthesis of disubstituted furoxans would proceed via the sequential "post-ring" installation of the two substituents of interest to the furoxan ring. However, to the best of our knowledge, no general strategy enabling the sequential installation of two different substituents on a furoxan ring was reported prior to our first example of such a methodology using bis(arylsulfonyl)furoxan substrates.[7a]

With the synthetic routes to various types of monohalofuroxans in hand, the installation of a second substituent to the monohalofuroxans was investigated. 3-Aryl-4-chlorofuroxan **25b** was photochemically isomerized to its regioisomer **26b** in high yield using our previously developed method (Figure 7A, left).[3e] 3-Chlorofuroxan **26b** could be arylated with an aryl Grignard reagent to form diarylfuroxan **28** (Figure 7A, right), demonstrating that chloride substituents at both the 3- and 4-positions are not necessarily required for the replacement of Cl by an aryl nucleophile. Diarylfuroxans are known to have anticancer activity.[21] Monochlorofuroxan **25b** successfully underwent methoxylation to afford 4-alkoxy-3-arylfuroxan **29** (Figure 7B left).[22] The same compound could also be synthesized from **8a** via arylation in good yield (Figure 7B, right). Although both routes in Figure 7B provide the same product, each route has potential applications for the creation of furoxan-based chemical libraries. When diversity in the aryl group is required, the arylation should follow the alkoxylation of **1**. However, when diversity in the alkoxy group is required, the alkoxylation should follow the arylation of **1**. Furoxan **11a** could be alkylated under the developed radical-mediated conditions to form 3-alkyl-4-methoxyfuroxan **30** (Figure 7C, left). Compound **30** was also synthesized by the methoxylation of **27a** (Figure 7C, right). Dialkylfuroxans **32a–d** were synthesized from **27a** by photochemical isomerization (Figure 7D, left) followed by radical-mediated reaction (Figure 7D, right). Dialkylfuroxan regioisomers have very similar polarity and are difficult to separate chromatographically, especially when the two alkyl groups are similar, e.g., an n-hexyl and an n-heptyl group. It is thus noteworthy that, using our route, dialkylfuroxans can be obtained as a regiochemically pure isomer.[23]

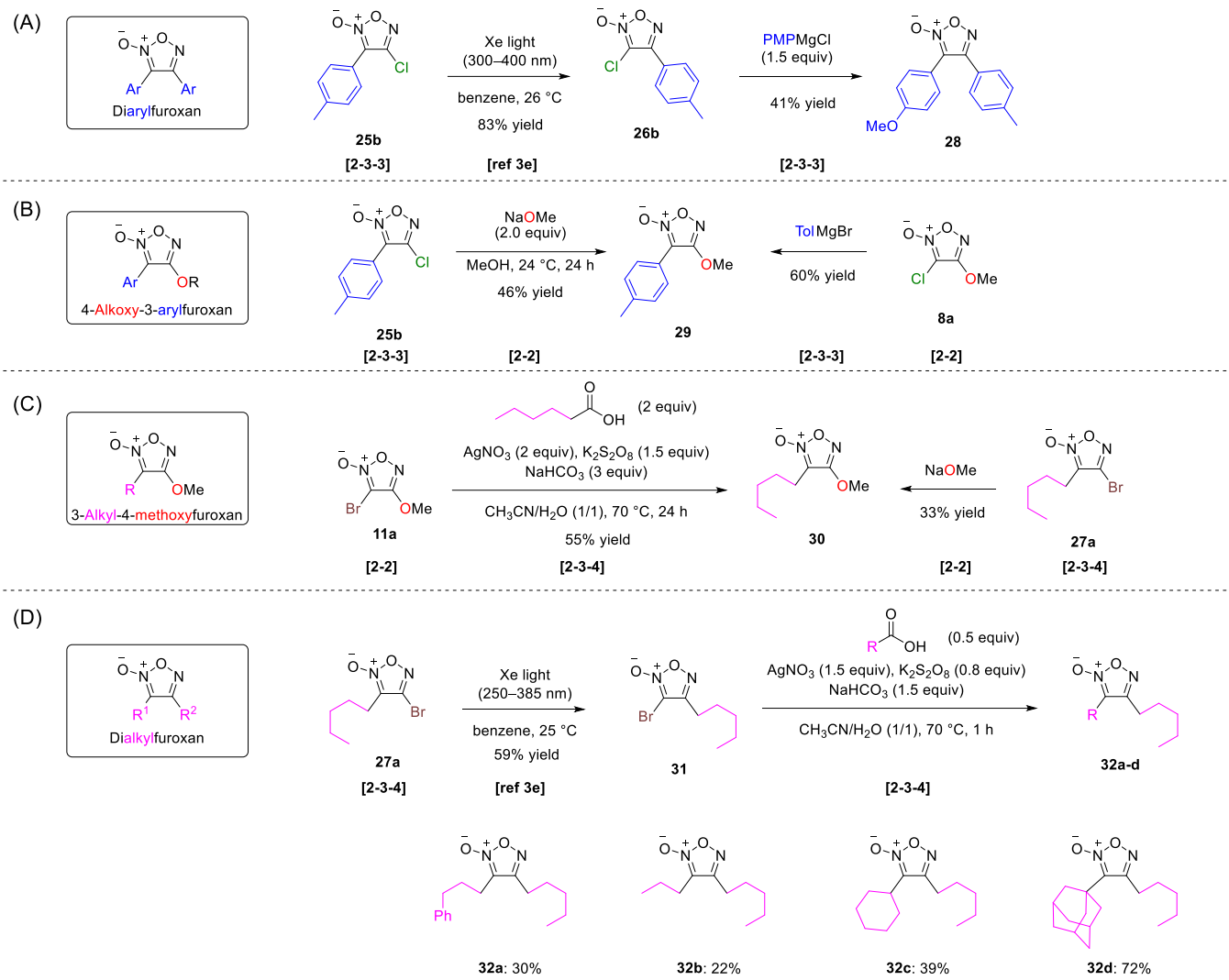



**Figure 7.** Modular synthesis of functionalized furoxans via monohalofuroxans. Numbers in brackets refer to the section numbers of this manuscript and relevant literature citations. See the experimental section for details.

## Conclusion

In this work, we have established synthetic methods to obtain dihalofuroxans and monohalofuroxans (X = Cl, Br). Dichlorofuroxan was synthesized from glyoxal, and dibromofuroxan was synthesized from glyoxylic acid oxime. Both routes are scalable and avoid the use of toxic or explosive reagents. Alkoxylation of dichlorofuroxan proceeded predominantly at the 4-position. Because of the equilibrium that exists in this reaction, the use of Ag salt to scavenge the chloride anion was effective to obtain a higher yield. The alkoxylation of dibromofuroxan has a severely limited substrate scope due to the over-reaction caused by the liberated bromide anion; only methoxylation was feasible. The alkynylation and arylation of dichlorofuroxan proceeded to afford monochlorofuroxans. These additions showed exclusive unusual regioselectivity towards 3-position attack, which was ascribed to the directing effect of the exo-ring oxygen atom of furoxan. Neither the alkynylation nor arylation of dibromofuroxan was feasible. Alkyl radical addition to dibromofuroxan occurred selectively at the 3-position to give 3-alkyl-4-bromofuroxans; the use of a stoichiometric amount of silver salt was important in this reaction. The synthesized monohalofuroxans served as substrates for the installation of a second substituent to prepare further functionalized furoxans. Diarylfuroxan, 4-alkoxy-3-arylfuroxan, 3-alkyl-4-methoxyfuroxan, and dialkylfuroxans were synthesized in a modular fashion. An overview of this work is provided in Figure 8. The developed methodology should provide easy access to a variety of furoxan molecules, and will hopefully trigger the development of pharmaceuticals and agrichemicals based on furoxan architectures, which remains a relatively underdeveloped area.

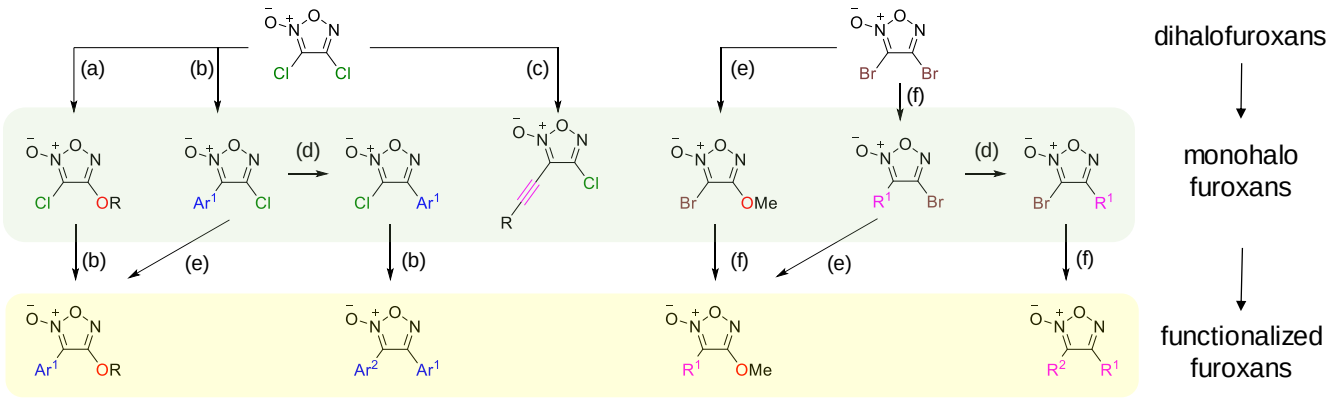



**Figure 8.** Summary of the results

## EXPERIMENTAL SECTION

***General*** 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. Heated reactions were conducted in an oil bath, 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 $^{13}C\{^{1}H\}$ 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 = multiplet, br = broad. Mass spectra were measured using a JEOL JMS-T100LP (DART method, ambient ionization) or a LTQ Orbitrap Elite (Thermo Fisher Scientific, Brehmen, Germany) with an electrospray ionization (ESI) ion source. Preparative column chromatography was performed using Kanto Chemical silica gel 60 N (spherical, neutral), Fuji Silysia BW-4:10MH silica gel or YMC_GEL Silica (6 nm I-40-63 um). 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). GC analyses were performed using a Shimazu GC-2025 gas chromatograph equipped with GL Science Inertcap5. Photoreactions were conducted using a 300W Xenon lamp, Asahi Spectra MAX-303 equipped with a combination of module and optical filters suitable for the designated wavelength.

***3,4-Dichlorofuroxan (1)*** 3,4-Dichlorofuroxan (**1**) was synthesized by modified method reported in the literature.[9f, 24] To a solution of hydroxylamine hydrochloride (123.7 g, 1.78 mol, 2.0 eq.) and glyoxal (**3**) (129.1 g, 40% aqueous solution, 0.89 mol, 1.0 eq.) in distilled water (310 mL) was added NaOH (71.2g, 1.78 mol, 2.0 eq.) in distilled water (310 mL) slowly at 0 °C. The reaction mixture was stirred for 40 min at 0 °C. The resultant white solid was collected by vacuum filtration and washed with distilled water to give glyoxime (**4**) (74.2 g, 843 mmol, 95% yield) as a white solid. To a solution of glyoxime (**4**) (20.7 g, 235 mmol, 1.0 eq.) in DMF (132 mL) was added NCS (40.1 g, 300 mmol, 1.3 eq.) portionwise at 0 °C. The reaction mixture was stirred for 4.5 h at 22 °C. *N*-Chlorosuccinimide (20.0 g, 150 mmol, 0.6 eq.) was added portionwise and the mixture was stirred for 5.5 h at 22 °C. The reaction was quenched by the addition of distilled water (100 mL). The aqueous phase was extracted three times with $Et_2O$. The combined organic extracts were washed three times with water, dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo. The white solid was washed with toluene at 70 °C. The resultant white solid was collected by vacuum filtration washing with toluene to give dichloroglyoxime (**5**) (25.7 g, 163.7 mmol, 70% yield) as a white solid. To fuming nitric acid (47 mL) was added dichloroglyoxime (**5**) (4.7 g, 30 mmol) slowly at 0 °C. The reaction mixture was stirred for 2.5 h at 20 °C, poured into ice and extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane/benzene = 3/1) to give **1** as a colourless oil (3.6 g, 23.2 mmol, 78% yield). The total yield over 3 steps was 52%. IR (neat): 2857, 1614, 1462, 1387, 1321, 1296, 1244, 1077, 1040, 986, 820, 706 $cm^{-1}$; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 146.3 (furoxan 4C), 109.7 (furoxan 3C) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_2H^{35}Cl_2N_2O_2$ 154.9415; Found 154.9397.

***3,4-Dibromofuroxan (2)*** 2-(Hydroxyimino)acetic acid (**6**) was known in the literature[25] and were synthesized without modification. To a solution of 2-(hydroxyimino)acetic acid (**6**) (35.6 g, 400 mmol, 1.0 eq.) in 1,2-dimethoxyetane (360 mL) and distilled water (107 mL) was added *N*-bromosuccinimide (142 g, 800 mmol, 2.0 eq.) portionwise at 0 °C. The reaction mixture was stirred for 2 h at 20 °C, and then extracted three times with $Et_2O$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude mixture (49 g) as an orange oil. To this crude mixture in 1,2-dimethoxyethane (243 mL) was added an aqueous solution of $Na_2CO_3$ (0.25 M, 268 mmol, 1072 mL) dropwise over 30 min. The reaction mixture was stirred for 20 h at 20 °C, and then extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude mixture. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/0 to 10/1) to give **2** as a yellow solid (13 g, 107 mmol, 27% yield over 2 steps). The total yield over 3 steps from glyoxylic acid (**6**) was 21%. Single crystals of **2** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/1,2-dichloroethane by vapor

diffusion. Mp: 46.6-47.6 °C; IR (neat): 2809, 1763, 1643, 1601, 1582, 1501, 1451, 1374, 1352, 1292, 1248, 1228, 1009, 993, 960, 844, 807, 697 $cm^{-1}$; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 136.8 (furoxan 4C), 98.1 (furoxan 3C) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_2H^{79}Br^{81}BrN_2O_2$ 244.8384; Found 244.8350.

***3-Chloro-4-methoxyfuroxan (8a)*** To a solution of 3,4-dichlorofuroxan (**1**) (774.7 mg, 5.0 mmol, 1.0 eq.) in THF (16.8 mL) was added NaOMe (324.1 mg, 6.0 mmol, 1.2 eq.) at –20 °C. The reaction mixture was stirred for 24 h at –20 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by silica gel column chromatography (eluent: hexane/benzene = 3/1 to 1/1) to give an inseparable mixture of **8a** and **9a** (188.4 mg, 1.25 mmol, 25%) as a white solid. The ratio of **8a** and **9a** was determined by $^1H$ NMR analysis. Mp (**8a**): 49.1-50.1 °C; IR (neat): 3054, 2982, 2948, 2880, 2765, 2275, 1622, 1558, 1453, 1411, 1262, 1200, 1143, 993, 948, 836, 723, 710, 684 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): **8a**: δ = 4.16 (s, 3H, OC$H_3$) ppm, **9a**: δ = 4.16 (s, 3H, OC$H_3$) ppm.; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): **8a**: δ = 161.1 (furoxan 4C), 103.4 (furoxan 3C), 57.6 (O$C$H$_3$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_2H_4{}^{35}ClN_2O_3$ 150.9910; Found 150.9923.

***3-Chloro-4-(4-phenylbutoxy)furoxan (8b)*** To a deaerated solution of NaH (60.0 mg, 60% dispersion, 1.5 mmol, 3.0 eq., washed by hexane before use) in 1,2-dimethoxyethane (1.5 mL) was added 4-phenylbutan-1-ol (**10**) (76.3 µL, 0.5 mmol, 1.0 eq.) at 28 °C. The reaction mixture was stirred for 15 min at 28 °C. To this solution **1** (232.4 mg, 1.5 mmol, 3.0 eq.) was added at –20 °C. The mixture was stirred for 7 h at –20 °C. After the addition of AgOTf (385.4 mg, 1.5 mmol, 3.0 eq.), the reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was filtered and extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The recovery of **10**, determined by $^1H$ NMR analysis using durene as an internal standard, was 7%. The residue was purified by preparative TLC (eluent: hexane/ethyl acetate = 10/1, hexane/benzene = 2/1) twice to give a mixture of **8b** and **9b** (133.7 mg, 0.50 mmol, 85%) as a colorless oil. The ratio of **8b** and **9b** was determined by $^1H$ NMR analysis. Single crystals of **8b** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/dichloromethane by vapor diffusion. Mp (**8b**): 28.3-28.5 °C; IR (neat): 2358, 2224, 1613, 1590, 1503, 1476, 1437, 1299, 1260, 1042, 1009, 995, 777, 757, 687 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): **8b**: δ = 7.32-7.28 (m, 2H, Ph 3C-*H*), 7.22-7.18 (m, 3H, Ph 2C-*H*, Ph 4C-*H*), 4.43 (t, *J* = 6.4 Hz, 2H, OC$H_2$), 2.70 (t, *J* = 7.6 Hz, 2H, PhC$H_2$), 1.94-1.87 (m, 2H, OCH$_2$C$H_2$), 1.84-1.76 (m, 2H, PhCH$_2$C$H_2$) ppm; **9b**: (distinguishable peak) δ = 3.60 (t, *J* = 6.4 Hz, 2H, OC$H_2$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): **8b**: δ = 160.7 (furoxan 4C), 141.5 (Ph 1C), 128.43 (Ph 2C or Ph 3C), 128.37 (Ph 2C or Ph 3C), 126.0 (Ph 4C), 103.4 (furoxan 3C), 71.1 (O$C$H$_2$), 35.3 (OCH$_2$$C$H$_2$), 28.0, 27.2 ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}{}^{35}ClN_2O_3$ 269.0693; Found 269.0698.

***3-Chloro-4-(cyclohexyloxy)furoxan (8c)*** To a deaerated solution of NaH (36.0 mg, 1.5 mmol, 3.0 eq.) in 1,2-dimethoxyethane (1.5 mL) was added cyclohexanol (52.8 µL, 0.5 mmol, 1.0 eq.) at 26 °C. The reaction mixture was stirred for 15 min at 26 °C. To this solution **1** (232.4 mg, 1.5 mmol, 3.0 eq.) was added at –20 °C. The mixture was stirred for 7 h at –20 °C. After the addition of AgOTf (385.4 mg, 1.5 mmol, 3.0 eq.), the reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was filtered and extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 2/1) to give a mixture of **8c** and **9c** (48.3 mg, 0.22 mmol, 44%) as a colorless oil. The ratio of **8c** and **9c** was determined by $^1H$ NMR analysis using durene as an internal standard. IR (neat): 2938, 2861, 1624, 1551, 1447, 1368, 1261, 1161, 1147, 1119, 1008, 993, 928, 906, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): **8c**: δ = 4.87 (tt, J = 9.2, 3.6 Hz, 1H, OC$H$), 2.11-2.07 (m, 2H), 1.84-1.80 (m, 2H), 1.68-1.57 (m, 3H), 1.45-1.35 (m, 3H) ppm, **9c**: (distinguishable peak) δ = 4.75 (tt, *J* = 8.8, 4.0 Hz, 1H, OC$H$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): **8c**: δ = 160.0 (furoxan 4C), 103.8 (furoxan 3C), 80.6 (O$C$H), 31.1, 25.1, 23.4 ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_8H_{13}{}^{35}ClN_2O_3$ 220.0615; Found 220.0588.

***4-(tert-Butoxy)-3-chlorofuroxan (8d)*** To a deaerated solution of NaH (36.0 mg, 1.5 mmol, 3.0 eq.) in 1,2-dimethoxyethane (1.5 mL) was added *tert*-butyl alcohol (47.9 µL, 0.5 mmol, 1.0 eq.) at 26 °C. The reaction mixture was stirred for 15 min at 26 °C. To this solution **1** (232.4 mg, 1.5 mmol, 3.0 eq.) was added at –20 °C. The mixture was stirred for 7 h at –20 °C. After the addition of AgOTf (385.4 mg, 1.5 mmol, 3.0 eq.), the reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was filtered and extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 2/1) to give a mixture of **8d** and **9d** (62.6 mg, 0.33 mmol, 65%) as a yellow oil. The ratio of **8d** and **9d** was determined by $^1H$ NMR analysis using durene as an internal standard. IR (neat): 3031, 2924, 2614, 2358, 1948, 1601, 1495, 1454, 1412, 1173, 1076, 1021, 1007, 836 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): **8d**: δ = 1.63 (s, 9H, OC(C$H_3$)$_3$) ppm, **9d**: δ = 1.59 (s, 9H, OC(C$H_3$)$_3$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 158.9 (furoxan 4C), 104.6 (furoxan 3C), 87.1 (O$C$), 27.7 (OC($C$H$_3$)$_3$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_6H_{10}{}^{35}ClN_2O_3$ 193.0380; Found 193.0394.

***3-Chloro-4-(2,2,2-trifluoroethoxy)furoxan (8e)*** To a deaerated solution of NaH (36.0 mg, 1.5 mmol, 3.0 eq.) in 1,2-dimethoxyethane (1.5 mL) was added 2,2,2-trifluoroethanol (36.0 µL, 0.5 mmol, 1.0 eq.) at 22 °C. The reaction mixture was stirred for 15 min at 22 °C. To this solution **1** (232.4 mg, 1.5 mmol, 3.0 eq.) was added at –20 °C. The mixture was stirred for 7 h at –20 °C. After the addition of AgOTf (385.4 mg, 1.5 mmol, 3.0 eq.), the reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was filtered and extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 2/1) to give **8e** (65.6 mg, 0.30 mmol, 59%) as a yellow oil. IR (neat): 2973, 2877, 1728, 1630, 1558, 1471, 1274, 1167, 1148, 1027, 998, 962, 866, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 4.79 (q, *J* = 7.6 Hz, 2H, OC$H_2$$CF_3$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 159.5 (furoxan 4C), 121.9 (q, *J* = 275.7 Hz, $CF_3$), 103.0 (furoxan 3C), 65.9 (q, *J* = 38 Hz, O$C$H$_2$) ppm; $^{19}F$ NMR

(376 MHz, $CDCl_3$): δ = –72.2 ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_4H_3{}^{35}ClN_2O_3$ 218.9784; Found 218.9770.

***3-Chloro-4-phenoxyfuroxan (8f)*** To a deaerated solution of NaH (36.0 mg, 1.5 mmol, 3.0 eq.) in 1,2-dimethoxyethane (1.5 mL) was added phenol (47.1 mg, 0.5 mmol, 1.0 eq.) at 24 °C. The reaction mixture was stirred for 15 min at 22 °C. To this solution **1** (232.4 mg, 1.5 mmol, 3.0 eq.) was added at –20 °C. The mixture was stirred for 7 h at 22 °C. After the addition of AgOTf (385.4 mg, 1.5 mmol, 3.0 eq.), the reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was filtered and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 30/1), preparative TLC (eluent: hexane/benzene = 3/1), and HPLC (eluent: hexane/ethyl acetate = 30/1) to give **8f** (28.9 mg, 0.14 mmol, 27%) as a white solid. Single crystals of **8f** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/acetone by vapor diffusion. Mp: 134.3–135.3 °C; IR (neat): 3357, 3309, 3187, 2920, 2852, 1626, 1540, 1447, 1258, 1184, 1096, 997, 920, 843 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.49-7.44 (m, 2H, Ph 3C-*H*) ppm, 7.36-7.30 (m, 3H, Ph 2C-*H*, 4C-*H*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 160.2 (furoxan 4C), 152.2 (Ph 1C), 130.1 (Ph 3C), 126.7 (Ph 4C), 119.6 (Ph 2C) ppm.

***3-Bromo-4-methoxyfuroxan (11a)*** To a solution of NaOMe (1.08 g, 20 mmol, 2.0 eq.) in MeOH (33.6 mL) was added **2** (2.44 g, 10 mmol, 1.0 eq.) at 0 °C. The reaction mixture was stirred for 8 h at 0 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 10/1) to give **11a** (1.22 g, 6.2 mmol, 62%) as a white solid. Single crystals of **11a** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/1,2-dichloroethane by vapor diffusion. Mp: 64.5-65.1 °C; IR (neat): 3051, 3002, 2944, 2852, 1620, 1557, 1466, 1450, 1408, 1366, 1240, 1200, 1130, 986, 948, 827, 712, 684 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 4.15 (s, 3H, OC*H*$_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.5 (furoxan 4C), 89.2 (furoxan 3C), 57.5 (O*C*H$_3$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_3H_4{}^{79}BrN_2O_3$ 194.9405; Found 194.9414.

***3-Bromo-4-(4-phenylbutoxy)furoxan (11b)*** To a solution of NaH (36.0 mg, 1.5 mmol, 3.0 eq.) in 1.2-dimethoxyethane (1.5 mL) was added **10** (76.3 µL, 0.5 mmol, 1.0 eq.) at 32 °C. The reaction mixture was stirred for 10 min at –20 °C. To this solution **2** (365.8 mg, 1.5 mmol, 3.0 eq.) was added at –20 °C. The mixture was stirred for 12 h at 32 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 3/1) to give **11b** (14.8 mg, 0.047 mmol, 10%) as a colorless oil. 4-(Bromobutyl)benzene (**12**) was detected by GC-MS analysis. Mp: 31.9–32.5 °C; IR (neat): 3082, 3024, 2962, 2934, 2917, 2859, 1612, 1554, 1495, 1442, 1383, 1368, 1235, 1146, 988, 963, 946, 842, 799, 751 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.32-7.28 (m, 2H, Ph 3C-*H*), 7.22-7.18 (m, 3H, Ph 2C-*H*, Ph 4C-*H*), 4.42 (t, *J* = 6.0 Hz, 2H, OC*H*$_2$), 2.70 (t, *J* = 7.6 Hz, 2H, PhC*H*$_2$), 1.93-1.86 (m, 2H, OCH$_2$C*H*$_2$), 1.84-1.76 (m, 2H, PhCH$_2$C*H*$_2$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.1 (furoxan 4C), 141.5 (Ph 1C), 128.42 (Ph 2C or Ph 3C), 128.37 (Ph 2C or Ph 3C), 126.0 (Ph 4C), 89.3 (furoxan 3C), 70.9 (O*C*H$_2$), 35.3 (OCH$_2$*C*H$_2$), 28.0, 27.2 ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}{}^{79}BrN_2O_3$ 313.0188; Found 313.0188.

***(1E,2E)-1-Butyl-2-chloroglyoxime (15)*** To a solution of **1** (154.9 mg, 1.0 mmol, 1.0 eq.) in THF (0.9 mL) was added $^n$BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol, 1.0 eq.) dropwise at –78 °C. The reaction mixture was stirred for 24 h at –78 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/ethyl acetate = 10/1) to give **15** (82.9 mg, 0.46 mmol, 46%) as a yellow solid. Single crystals of **15** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/1,2-dichloroethane by vapor diffusion. Mp: 138.0-139.0 °C; IR (neat): 3211(br), 2950, 2872, 1704, 1622, 1427, 1406, 994, 936, 912 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 12.56 (s, 1H, NO*H*), 11.99 (s, 1H, NO*H*), 2.59 (t, *J* = 7.6 Hz, 2H, C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.46-1.39 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.33-1.23 (m, 2H, C*H*$_2$CH$_3$), 0.87 (t, *J* = 7.2 Hz, 3H, C*H*$_3$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$): δ = 153.2 (Cl*C*NOH), 135.5 (CH$_2$*C*NOH), 28.3, 25.3, 22.7, 14.2 (*C*H$_3$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_6H_{12}{}^{35}ClN_2O_2$ 179.0587; Found 179.0593.

***4-Chloro-3-(oct-1-yn-1-yl)furoxan (19a)*** To a solution of 1-hexyne (95.5 µL, 0.65 mmol, 1.3 eq.) in THF (2.0 mL) was added $^n$BuLi (1.6 M in hexane, 0.34 mL, 0.55 mmol, 1.1 eq.) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. To this solution **1** (77.5 mg, 0.5 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 3/1) to give **19a** (76.2 mg, 0.33 mmol, 67%) as a yellow oil. IR (neat): 2957, 2930, 2589, 2240, 1609, 1437, 1284, 1085, 802 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 2.53 (t, *J* = 7.2 Hz, 2H, CCC*H*$_2$), 1.65 (quint, *J* = 7.6 Hz, 2H, CCCH$_2$C*H*$_2$), 1.48-1.41 (m, 2H, CC(CH$_2$)$_2$C*H*$_2$), 1.36-1.32 (m, 4H, (C*H*$_2$)$_2$CH$_3$), 0.9 (t, *J* = 6.8 Hz, 3H, C*H*$_3$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 147.3 (furoxan 4C), 109.8 (*C*≡CCH$_2$), 103.8 (furoxan 3C), 60.9 (C≡*C*CH$_2$), 31.2, 28.4, 27.6, 22.5, 20.0, 14.0 (*C*H$_3$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{10}H_{14}{}^{35}ClN_2O_2$ 229.0744; Found 229.0753.

***1-Chloro-1-(4-chloro-1,2,5-oxadiazol-3-yl)octan-2-one (21a)*** This compound was obtained in the synthesis of **19a** shown above. The yield was determined at the crude stage by $^1H$ NMR analysis using durene as an internal standard (12%). Analytically pure sample of **21a** was obtained by purification using preparative TLC (eluent: hexane/benzene = 3/1) as a yellow oil. IR (neat): 2956, 2930, 2859, 1725, 1442, 1153, 1006, 727 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 5.59 (s, 1H, C(O)CCl*H*), 2.98-2.70 (m, 2H, C*H*$_2$C(O)), 1.72-1.64 (m, 2H, C*H*$_2$ CH$_2$C(O)), 1.38-1.26 (m, 6H, (C*H*$_2$)$_3$CH$_3$), 0.89 (t, *J* = 7.2 Hz, 3H, C*H*$_3$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 198.9 (*C*(O)), 150.2 (furazan C), 145.9 (furazan C), 51.8 (*C*HCl), 39.1 (*C*H$_2$CO), 31.4, 28.6, 23.5, 22.4, 14.0 (*C*H$_3$) ppm;

HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{10}H_{15}{}^{35}Cl^{37}ClN_2O_2$ 267.0481; Found 267.0448.

***3-(Phenylethynyl)-4-chlorofuroxan (19b)*** To a solution of ethynylbenzene (71.4 µL, 0.65 mmol, 1.3 eq.) in THF (2.0 mL) was added $^n$BuLi (1.6 M in hexane, 0.34 mL, 0.55 mmol, 1.1 eq.) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. To this solution **1** (77.5 mg, 0.5 mmol, 1.0 eq.) was added at 0 °C. The mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 3/1) to give **19b** (61.0 mg, 0.28 mmol, 55%) as a white solid. Single crystals of **19b** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/1,2-dichloroethane by vapor diffusion. See Supporting Information for the details of sc-XRD data. Mp: 66.3-67.2 °C; IR (neat): 3087, 3029, 2942, 2920, 2859, 2360, 1624, 1560, 1447, 1385, 1256, 1156, 998, 752, 717 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.61-7.58 (m, 2H, Ph 2C-*H*), 7.50-7.46 (m, 1H, Ph 4C-*H*), 7.43-7.39 (m, 2H,Ph 3C-*H*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 147.0 (furoxan 4C), 132.1 (Ph 2C), 130.7 (Ph 4C), 128.7 (Ph 3C), 119.9 (Ph 1C), 106.3 (*C*≡CPh), 103.9 (furoxan 3C), 68.7 (C≡*C*Ph) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{10}H_6{}^{35}ClN_2O_2$ 221.0118; Found 221.0128.

***2-(4-Chloro-1,2,5-oxadiazol-3-yl)-1-phenylethan-1-one (20b)*** This compound was obtained in the synthesis of **19b** shown above. The yield was determined at the crude stage by $^1H$ NMR analysis using durene as an internal standard (10%). Analytically pure sample of **20b** was obtained by purification using preparative TLC (eluent: hexane/benzene = 3/1) as a white solid. Mp: 29.3-30.0 °C; IR (neat): 3057, 2958, 2921, 2854, 2360, 1672, 1447, 1331, 1218, 1140, 1007, 749 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.05-8.02 (m, 2H, Ar-*H*), 7.70-7.65 (m, 1H, Ar-*H*), 7.57-7.53 (m, 2H, Ar-*H*), 4.54 (s, 2H, PhC(O)C$H_2$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 191.6 (*C*(O)), 149.2 (furazan C), 147.2 (furzan C), 135.2 (Ph 1C), 134.4 (Ph 4C), 129.1 (Ph 2C or Ph 3C), 128.4 (Ph 2C or Ph 3C), 32.8 (*C*$H_2$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{10}H_8{}^{35}ClN_2O_2$ 223.0274; Found 223.0274.

***2-Chloro-2-(4-chloro-1,2,5-oxadiazol-3-yl)-1-phenylethan-1-one (21b)*** This compound was obtained in the synthesis of **19b** shown above. The yield was determined at the crude stage by $^1H$ NMR analysis using durene as an internal standard (12%). Analytically pure sample of **21b** was obtained by purification using preparative TLC (eluent: hexane/benzene = 3/1). Single crystals of **21b** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/ethyl acetate by vapor diffusion. White solid. Mp: 46.5-47.3 °C; IR (neat): 3070, 2967, 2358, 1690, 1443, 1311, 1229, 1154, 998, 818, 750 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.05-8.03 (m, 2H, Ar-*H*), 7.71-7.66 (m, 1H, Ar-*H*), 7.57-7.53 (m, 2H, Ar-*H*), 6.51 (s, 1H, PhC(O)CCl*H*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 187.3 (*C*O)), 150.2 (furazan C), 146.5 (furazan C), 134.9 (Ph 1C), 132.5 (Ph 4C), 129.4 (Ph 2C or 3C), 129.1 (Ph 2C or 3C), 48.4 (*C*HCl) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{10}H_7{}^{35}Cl_2N_2O_2$ 256.9885; Found 256.9914.

***4-Chloro-3-phenylfuroxan (25a)*** To a solution of **1** (77.5 mg, 0.5 mmol, 1.0 eq.) in THF (2.0 mL) was added PhMgBr (1.03 M in THF, 0.73 mL, 0.75 mmol, 1.5 eq.) at –78 °C. The reaction mixture was stirred for 24 h at –40 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 3/1) to give **25a** (40.3 mg, 0.21 mmol, 41%) as a yellow solid. Single crystals of **25a** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/ethyl acetate by vapor diffusion. This compound is known in the literature.[9c]

***4-Chloro-3-(p-tolyl)furoxan (25b)*** To a solution of **1** (77.5 mg, 0.5 mmol, 1.0 eq.) in THF (2.0 mL) was added *p*-tolylmagnesium bromide (1.44 M in THF, 0.52 mL, 0.75 mmol, 1.5 eq.) at –78 °C. The reaction mixture was stirred for 5 h at –40 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 3/1) to give **25b** (39.3 mg, 0.19 mmol, 37%) as a yellow solid. This compound is known in the literature.[3e]

***4-Chloro-3-(p-methoxyphenyl)furoxan (25c)*** To a solution of **1** (77.5 mg, 0.5 mmol, 1.0 eq.) in THF (2.0 mL) was added *p*-methoxyphenylmagnesium bromide (0.54 M in THF, 1.38 mL, 0.75 mmol, 1.5 eq.) at 0 °C. The reaction mixture was stirred for 6 h at 28 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/ethyl acetate = 5/1, hexane/ethyl acetate = 10/1) twice to give **25c** (44.4 mg, 0.20 mmol, 39%) as a greenish oil. IR (neat): 3010, 2970, 2938, 2913, 2895, 2840, 1587, 1516, 1463, 1433, 1394, 1403, 1306, 1254, 1186, 1110, 1036, 1022, 961, 830 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.91-7.87 (m, 2H, C*H*CHCOCH$_3$), 7.08 -7.04 (m, 2H, C*H*COCH$_3$), 3.88 (s, 3H, OC$H_3$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ =161.6 (*C*(OCH$_3$)), 146.0 (furoxan 4C), 129.1 (*C*HCHCOCH$_3$), 114.6 (*C*HCOCH$_3$), 113.9 (furoxan 3C), 112.8 (*C*CHCHCOCH$_3$), 55.5 (OC$H_3$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_9H_8{}^{35}ClN_2O_3$ 227.0218; Found 227.0245.

***4-Bromo-3-pentylfuroxan (27a)*** To a solution of **2** (146.3 mg, 0.6 mmol, 2.0 eq.), $AgNO_3$ (152.9 mg, 0.9 mmol, 3.0 eq.), $K_2S_2O_8$ (121.6 mg, 0.45 mmol, 1.5 eq.), $NaHCO_3$ (75.6 mg, 0.9 mmol, 3.0 eq.) in $CH_3CN$ (1.5 mL) and distilled water (1.5 mL) was added hexanoic acid (37.5 µL, 0.30 mmol, 1.0 eq.) at 20 °C. The reaction mixture was stirred for 1 h at 70 °C. The reaction was quenched by the addition of distilled water. The mixture was filtered with ethyl acetate, and then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/ethyl acetate = 10/1) to give **27a** (35.3 mg, 0.15 mmol, 50%) as a yellow oil. IR (neat): 2958, 2930, 2861, 1602, 1563, 1463, 1412, 1113, 1012 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 2.57 (t, *J* = 7.6 Hz, 2H, C$H_2$(CH$_2$)$_3$CH$_3$), 1.65 (quint, *J* = 7.6 Hz, 2H, C$H_2$(CH$_2$)$_2$CH$_3$), 1.41-1.24 (m, 4H, (C$H_2$)$_2$CH$_3$), 0.91 (t, *J* = 6.8 Hz, 3H, C$H_3$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 135.4 (furoxan 4C), 115.9 (furoxan 3C), 31.0 (*C*H$_2$(CH$_2$)$_3$CH$_3$), 24.9, 22.5, 22.1, 13.8 (*C*H$_3$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_7H_{12}{}^{79}BrN_2O_2$ 235.0082; Found 235.0096.

***4-Bromo-3-cyclohexylfuroxan (27b)*** To a solution of **2** (146.3 mg, 0.6 mmol, 2.0 eq.), $AgNO_3$ (152.9 mg, 0.9 mmol, 3.0 eq.), $K_2S_2O_8$ (121.6 mg, 0.45 mmol, 1.5 eq.), $NaHCO_3$ (75.6 mg, 0.9 mmol, 3.0 eq.) in $CH_3CN$ (1.5 mL) and distilled water (1.5 mL) was added cyclohexanoic acid (38.5 mg, 0.30 mmol, 1.0 eq.) at 20 °C. The reaction mixture was stirred for 1 h at 70 °C. The reaction was quenched by the addition of distilled water. The mixture was filtered with ethyl acetate, and then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/ethyl acetate = 5/1) to give **27b** (46.7 mg, 0.19 mmol, 63%) as a white solid. Mp: 84.3-85.1 °C; IR (neat): 2960, 2941, 2860, 1576, 1448, 1414, 1275, 1227, 1004, 983, 796, 661 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 2.72 (tt, *J* = 12.0, 4.0 Hz, 1H, C*H*), 1.89-1.80 (m, 4H), 1.76-1.70 (m, 3H), 1.40-1.21 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 134.5 (furoxan 4C), 117.9 (furoxan 3C), 33.7 ($CH_2(CH_2)_3CH_3$), 27.0, 25.8, 25.1 ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_8H_{12}{}^{79}BrN_2O_2$ 247.0082; Found 247.0098.

***3-(Adamantan-1-yl)-4-bromofuroxan (27c)*** To a solution of **2** (146.3 mg, 0.6 mmol, 2.0 eq.), $AgNO_3$ (152.9 mg, 0.9 mmol, 3.0 eq.), $K_2S_2O_8$ (121.6 mg, 0.45 mmol, 1.5 eq.), $NaHCO_3$ (75.6 mg, 0.9 mmol, 3.0 eq.) in $CH_3CN$ (1.5 mL) and distilled water (1.5 mL) was added adamantane-1-carboxylic acid (54.1 mg, 0.30 mmol, 1.0 eq.) at 18 °C. The reaction mixture was stirred for 1 h at 70 °C. The reaction was quenched by the addition of distilled water. The mixture was filtered with ethyl acetate, and then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/ethyl acetate = 5/1) to give **27c** (71.3 mg, 0.24 mmol, 79%) as a white solid. Single crystals of **27c** suitable for X-ray diffraction analysis were obtained by recrystallization from hexane/1,2-dichloroethane by vapor diffusion. Mp: 143.0-144.0 °C; IR (neat): 2933, 2912, 2851, 2163, 1574, 1435, 1343, 1229, 1077, 989, 795, 762 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 2.20-2.16 (m, 6H), 2.11 (br, 3H), 1.78-1.76 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 132.7 (furoxan 4C), 118.4 (furoxan 3C), 37.3, 36.1, 34.5, 27.8 ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{12}H_{16}{}^{79}BrN_2O_2$ 299.0395; Found 299.0395.

***3-Chloro-4-(p-tolyl)furoxan (26b)*** A solution of **25b** (10 mg, 0.048 mmol) in benzene (0.8 mL) was prepared in a Pyrex NMR tube. The same reaction sets were prepared in another two NMR tubes. These three NMR tubes were irradiated with 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) for 2 h at 26 °C and the reaction progress was monitored by $^1H$ NMR analysis. After 2 h of the reaction the isomerization ratio reached 90:10 (**26b**:**25b**) on average. The reaction solutions in the three NMR tubes were combined and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 3/1) to give **26b** (25.0 mg, 0.12 mmol, 83%) as a yellow solid. This compound is known in the literature.[3e]

***3-(p-Methoxyphenyl)-4-(p-methylphenyl)furoxan (28)*** To a solution of **26b** (23.7 mg, 0.11 mmol, 1.0 eq.) in THF (0.5 mL) was added *p*-methoxyphenylmagnesium bromide (0.72 M in THF, 0.24 mL, 0.17 mmol, 1.5 eq.) at 0 °C. The reaction mixture was stirred for 6 h at 25 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/ethyl acetate = 5/1) to give **28** (12.6 mg, 0.045 mmol, 41%) as a white solid. Mp: 95.3-96.3 °C; IR (neat): 2918, 2848, 1609, 1590, 1568, 1519, 1447, 1438, 1414, 1328, 1298, 1253, 1177, 1112, 1025, 989, 960, 836, 820 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.50-7.46 (m, 2H, Ar-*H*), 7.41 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 7.25 (d, 2H, J = 8.0 Hz, Ar-*H*), 6.97-6.93 (m, 2H, Ar-*H*), 3.84 (s, 3H), 2.42 (s, 3H, OC*H*$_3$) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.0 (*C*$OCH_3$), 156.3 (furoxan 4C), 141.3 (*C*$CH_3$), 130.2, 129.7, 128.2, 123.9 (*C*$CHCHCCH_3$), 114.8 (*C*$CHCHCOCH_3$), 114.4 (*C*$HCOCH_3$), 114.3 (furoxan 3C), 55.4 (O*C*$H_3$) , 21.5 (C*C*$H_3$) ppm; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O_3$ 283.1077; Found 283.1073.

***3-(p-Tolyl)-4-methoxyfuroxan (29)*** This compound known in the literature.[3d]

**Path a**: To a solution of **25b** (63.2 mg, 0.3 mmol, 1.0 eq.) in MeOH (1.0 mL) was added NaOMe (32.4 mg, 0.60 mmol, 2.0 eq.) at 20 °C. The reaction mixture was stirred for 24 h at 20 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude material. The yield (46%) was determined by $^1H$ NMR analysis using durene as an internal standard.

**Path b**: To a solution of **8a** (45.2 mg, 0.3 mmol, 1.0 eq.) in THF (1.2 mL) was added *p*-tolylmagnesium bromide (1.44 M in THF, 0.31 mL, 0.45 mmol, 1.5 eq.) at –78 °C. The reaction mixture was stirred for 24 h at –40 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude material. The yield (60%) was determined by $^1H$ NMR analysis using durene as an internal standard.

***4-Methoxy-3-pentylfuroxan (30)*** This compound is known in the literature.[3d]

**Path a**: To a solution of **11a** (58.5 mg, 0.3 mmol, 1.0 eq.), $AgNO_3$ (101.9 mg, 0.6 mmol, 2.0 eq.), $K_2S_2O_8$ (121.6 mg, 0.45 mmol, 1.5 eq.), $NaHCO_3$ (75.6 mg, 0.9 mmol, 3.0 eq.) in $CH_3CN$ (1.5 mL) and distilled water (1.5 mL) was added hexanoic acid (75.0 µL, 0.6 mmol, 2.0 eq.) at 20 °C. The reaction mixture was stirred for 24 h at 70 °C. The reaction was quenched by the addition of distilled water. The mixture was filtered with ethyl acetate, and then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude material. The yield (55%) was determined by $^1H$ NMR analysis using durene as an internal standard.

**Path b**: To a solution of **27a** (70.5 mg, 0.3 mmol, 1.0 eq.) in THF (1.0 mL) was added NaOMe (32.4 mg, 0.6 mmol, 2.0 eq.) at 20 °C. The reaction mixture was stirred for 24 h at 20 °C. The reaction was quenched by the addition of saturated aqueous solution of $NH_4Cl$. The mixture was extracted three times with $CH_2Cl_2$. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude material. The yield (33%) was determined by $^1H$ NMR analysis using durene as an internal standard.

***3-Bromo-4-pentylfuroxan (31)*** A solution of **27a** (36.8 mg, 0.16 mmol) in benzene (3.1 mL) was prepared in a Pyrex test tube. The solution was irradiated with 250–385 nm light (a 300W Xenon lamp, Asahi Spectra MAX-303 equipped with a

250- to 385-nm ultraviolet module) for 30 min at 20 °C and the reaction progress was monitored by $^1$H NMR analysis. The ratio reached 67:33 (**31**:**27a**) at the photostationary state. The reaction mixture was concentrated in vacuo to give the residue. The residue was purified by preparative TLC (eluent: hexane/benzene = 1/1) to give **31** (21.6 mg, 0.092 mmol, 59%) as a yellow oil. IR (neat): 2957, 2930, 2861, 1600, 1509, 1454, 1435, 1416, 1226, 1083, 962, 828 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.68 (t, *J* = 7.6 Hz, 2H, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.80-1.72 (quint, *J* = 7.6 Hz, 2H, CH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.39 (m, 4H, (CH$_2$CH$_2$(C*H*$_2$)$_2$CH$_3$), 0.93 (t, *J* = 6.8 Hz, 3H, C*H*$_3$) ppm; $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 158.1 (furoxan 4C), 96.9 (furoxan 3C), 31.0, 26.0, 25.8, 22.2, 13.8 (*C*H$_3$) ppm; HRMS (DART) m/z: [M + H]$^+$ Calcd for $C_7H_{12}{}^{79}BrN_2O_2$ 235.0077; Found 235.0083.

***4-Pentyl-3-(3-phenyl)propylfuroxan (32a)*** To a solution of **31** (48.8 mg, 0.21 mmol, 2.0 eq.), $AgNO_3$ (52.7 mg, 0.31 mmol, 3.0 eq.), $K_2S_2O_8$ (43.3 mg, 0.16 mmol, 1.5 eq.), $NaHCO_3$ (26.0 mg, 0.31 mmol, 3.0 eq.) in $CH_3CN$ (0.5 mL) and distilled water (0.5 mL) was added 4-phenylbutanoic acid (16.4 mg, 0.10 mmol, 1.0 eq.) at 20 °C. The reaction mixture was stirred for 1 h at 70 °C. The reaction was quenched by the addition of distilled water. The mixture was filtered with ethyl acetate. And then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude material. The yield (30%) was determined by $^1$H NMR analysis using dimethyl sulfone as an internal standard. This compound is known in the literature.[7a]

***4-Pentyl-3-propylfuroxan (32b)*** To a solution of **31** (47.0 mg, 0.2 mmol, 2.0 eq.), $AgNO_3$ (51.0 mg, 0.3 mmol, 3.0 eq.), $K_2S_2O_8$ (40.5 mg, 0.15 mmol, 1.5 eq.), $NaHCO_3$ (25.2 mg, 0.3 mmol, 3.0 eq.) in $CH_3CN$ (0.5 mL) and distilled water (0.5 mL) was added *n*-butyric acid (9.2 μL, 0.10 mmol, 1.0 eq.) at room temperature. The reaction mixture was stirred at 70 °C for 1 h. The reaction was quenched by the addition of distilled water. The mixture was filtered with ethyl acetate. And then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude material. The yield (22%) was determined by $^1$H NMR analysis using 1,4-dioxane as an internal standard. The crude was purified by preparative TLC (eluent: hexane/ethyl acetate = 10/1) to give **32b** (2.8 mg, 0.014 mmol, 14%) as a colourless oil. IR (neat): 2957, 2926, 2870, 2862, 1599, 1505, 1462, 1424, 1376, 1144, 1042, 1009, 967 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.63 (t, *J* = 7.6 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H) 1.77-1.61 (m, 4H), 1.41-1.37 (m, 4H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.92 (t, *J* = 6.8 Hz, 3H) ppm; $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 158.0 (furoxan 4C), 115.9 (furoxan 3C), 31.2, 26.4, 25.6, 24.3, 22.2, 19.0, 13.9, 13.7 ppm; HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{10}H_{18}N_2NaO_2$ 221.1260; Found 221.1252.

***3-Cyclohexyl-4-pentylfuroxan (32c)*** To a solution of **31** (47.0 mg, 0.2 mmol, 2.0 eq.), $AgNO_3$ (51.0 mg, 0.3 mmol, 3.0 eq.), $K_2S_2O_8$ (40.5 mg, 0.15 mmol, 1.5 eq.), $NaHCO_3$ (25.2 mg, 0.3 mmol, 3.0 eq.) in $CH_3CN$ (0.5 mL) and distilled water (0.5 mL) was added cyclohexanecarboxylic acid (12.8 mg, 0.10 mmol, 1.0 eq.) at room temperature. The reaction mixture was stirred at 70 °C for 1 h. The reaction was quenched by the addition of distilled water. The mixture was filtered with ethyl acetate. And then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude material. The yield (39%) was determined by $^1$H NMR analysis using 1,4-dioxane as an internal standard. The crude was purified by preparative TLC (eluent: hexane/benzene = 1/1) to give **32c** (5.9 mg, 0.014 mmol, 25%) as a colourless oil. IR (neat): 2931, 2856, 1589, 1503, 1467, 1451, 1379, 1367, 1302, 1267, 1245, 1149, 1148, 1100, 1077, 1043, 1022, 987 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 7.6, 2H, C*H*$_2$(CH$_2$)$_4$CH$_3$), 2.59 (tt, *J* = 7.6, 3.6 Hz, 1H), 1.89-1.68 (m, 9H), 1.44-1.24 (m, 7H), 0.93 (t, *J* = 6.8 Hz, 3H, CH$_2$(CH$_2$)$_4$C*H*$_3$) ppm; $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 157.6 (furoxan 4C), 118.6 (furoxan 3C), 33.7, 31.2, 27.3, 26.7, 26.0, 25.3, 22.3, 13.9 (*C*H$_3$) ppm; HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{22}N_2NaO_2$ 261.1573; Found 261.1566.

***3-Adamantyl-4-pentylfuroxan (32d)*** To a solution of **31** (47.0 mg, 0.2 mmol, 2.0 eq.), $AgNO_3$ (51.0 mg, 0.3 mmol, 3.0 eq.), $K_2S_2O_8$ (40.5 mg, 0.15 mmol, 1.5 eq.), $NaHCO_3$ (25.2 mg, 0.3 mmol, 3.0 eq.) in $CH_3CN$ (1.5 mL) and distilled water (1.5 mL) was added 1-adamantanecarboxylic acid (18.0 mg, 0.10 mmol, 1.0 eq.) at room temperature. The reaction mixture was stirred at 70 °C for 1 h. The reaction was quenched by the addition of distilled water. The mixture was filtered with ethyl acetate. And then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give the crude material. The yield (72%) was determined by $^1$H NMR analysis using 1,4-dioxane as an internal standard. The crude was purified by preparative TLC (eluent: hexane/ethyl acetate = 5/1) to give **32d** (11.2 mg, 0.039 mmol, 39%) as a white solid. Mp: 84.5-84.9 °C; IR (neat): 2967, 2953, 2913, 2849, 1567, 1490, 1463, 1451, 1429, 1416, 1374, 1358, 1342, 1313, 1252, 1215, 1117, 1096, 987 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.77 (t, *J* = 7.6 Hz, 2H, C*H*$_2$(CH$_2$)$_4$CH$_3$), 2.11-2.09 (m, 9H), 1.78-1.73 (m, 8H), 1.44-1.35 (m, 4H, CH$_2$CH$_2$(C*H*$_2$)$_2$CH$_3$), 0.93 (t, *J* = 7.2 Hz, 3H, CH$_2$(CH$_2$)$_4$C*H*$_3$) ppm; $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ = 157.2 (furoxan 4C), 120.3 (furoxan 3C), 36.9, 36.3, 34.4, 31.4 (*C*H$_2$(CH$_2$)$_4$CH$_3$), 28.1, 27.8, 27.2, 22.3, 14.0 (*C*H$_3$) ppm; HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{17}H_{26}N_2NaO_2$ 313.1886; Found 313.1874.

**DFT calculations** All calculations were performed with the Gaussian 09 package.[26] The promising pathway was investigated by the (U)LC-BLYP[18-20] DFT method with 6-31G* basis set and the conductor-like polarizable continuum solvation model (CPCM, DMSO).[27] The transition states were optimized with Berny algorithm[28] and verified by the intrinsic reaction coordinate (IRC) calculation.[29] Frequency analyses were also carried out to identify the stationary points (RT, INT, PD: no imaginary frequency, TS: one imaginary frequency) and to estimate thermodynamic properties at 298.15 K and 1 atm and Gibbs free energies. The molecular structures were depicted by using the CYLview v1.0.561 β.[30]

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

DFT calculations, crystallographic data, and NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENT

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.

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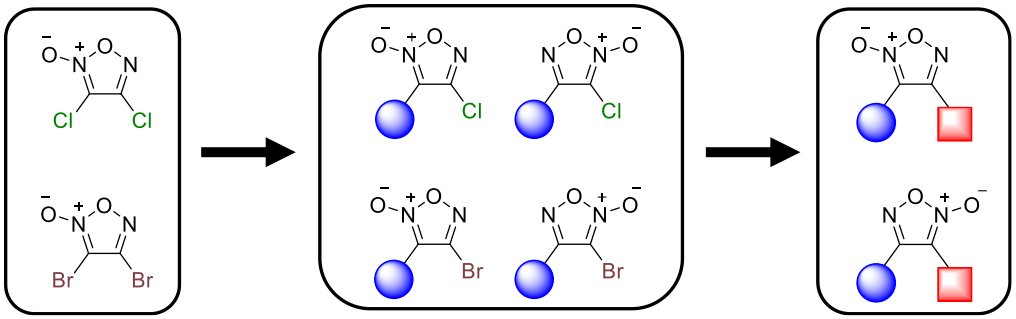
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