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# Borylfuroxans: Synthesis and applications

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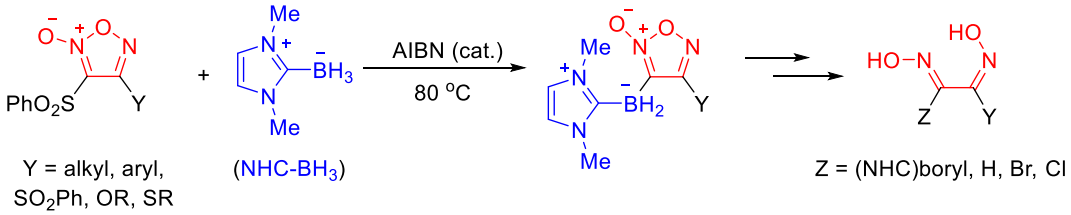



**ABSTRACT:** Herein we report the first synthesis of borylfuroxans via the reaction of sulfonylfuroxans with Lewis base-ligated boranes under radical conditions. As a synthetic application, the transformation of borylfuroxans to a range of 1,2-dioximes and their derivatives is demonstrated.

Furoxans have long been studied because of their wide spectrum of biological activities such as nematocidal, antimicrobial, anticancer, and platelet antiaggregatical activities.[1] In the 1990s, Feelisch and Gasco reported that furoxans with certain substituent patterns release a gaseous transmitter nitric oxide (NO) under physiological conditions,[2] a unique characteristic that makes them distinct from other heteroaromatic compounds. Since then, furoxans have gained more research attention. Thus far, various furoxan molecules endowed with spontaneous NO-releasing ability under physiological conditions have been developed, including hybrid molecules composed of covalently linked furoxan and existing drug architectures.[3] Our group has recently developed photo-induced NO-releasing furoxans,[4] which allowed the spatiotemporal control of NO release. Furoxans also serve as versatile intermediates in organic synthesis. Because of its weak aromatic stabilization, the furoxan ring is susceptible to ring opening under various reaction conditions.[1a] By utilizing this feature, our group developed a methodology for the transformation of carboxylic acids into various functional groups via sequential introduction and decomposition of the furoxan ring.[5] Thus, the utility of furoxan has been increasing in the fields of pharmaceuticals, biology, and synthetic chemistry.

To date, furoxans bearing various substituents such as alkyl, aryl, alkenyl, alkynyl, carbonyl, CN, OR, $NR_2$, SR, $NO_2$, $SO_2R$, and halogen have been synthesized. However, to the best of our knowledge, a furoxan bearing a substituent whose electronegativity is less than that of hydrogen, such as metal or metalloidal atoms, remains unknown (Figure 1A). This fact is ascribed to the known fast irreversible ring opening upon the localization of electron density at the 3- or 4-carbon atom of the furoxan ring (Figure 1B). This lack of metalated furoxans has limited further exploration of furoxan chemistry. Herein we report the first synthesis of borylfuroxans. As a synthetic application, the transformation of borylfuroxans into a diverse range of 1,2-dioximes and their derivatives is demonstrated.

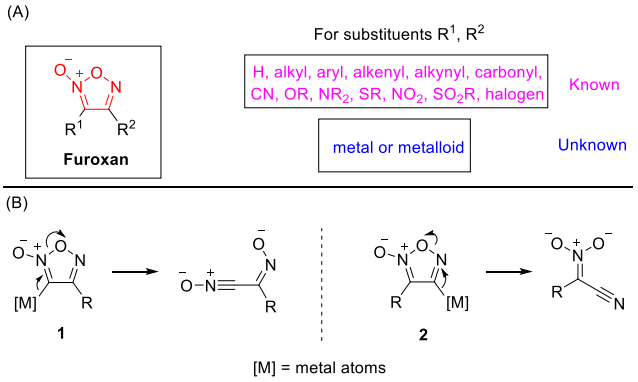
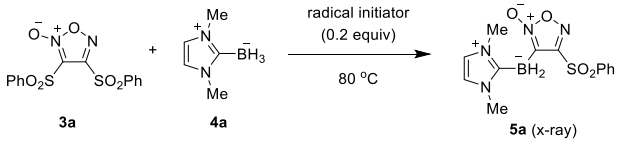



**Figure 1.** (A) Substituents on a furoxan ring. (B) Fast decomposition of metalated furoxans

Previously, we discovered that 3-sulfonylfuroxans function as radical acceptors and react with carbon radicals, enabling rare C-C bond forming reactions on the furoxan ring.[5] Inspired by the pioneering studies on *N*-heterocyclic carbene (NHC)-ligated boryl radical chemistry by Curran Lacôte, Malacria, Fensterbank, Taniguchi, and Wang,[6] we envisioned that the boryl radical may react with 3-sulfonylfuroxans and thus began our investigation using disulfonyl furoxan **3a** and NHC-borane **4a** (Table 1). To our delight, the reaction proceeded at 80 °C in the presence of a common radical initiator, 2,2-azobisisobutyronitrile (AIBN) to afford the expected product NHC-borylated furoxan **5a** (entry 1). The structure of **5a** was unambiguously determined by single-crystal X-ray diffraction analysis. Contrary to our initial concern about the stability against the ring opening, **5a** was stable enough to be isolable. Notably, excellent regioselectivity toward 3-position attack was observed, leaving the 4-sulfonyl group untouched; this regioselectivity has also been previously discussed.[5] Solvent screening revealed that benzene was the best choice for this reaction (entries 1-4). The increase in the molarity of **4a** improved the yield of **5a** up

to 42% (entries 1, 5, and 6). In entry 6, starting material **3a** was consumed and structure-unknown byproducts were observed, which explains the observed moderate yield. The same reaction conditions as entry 6, except using 0.1 or 0.3 equiv of AIBN, led to the inferior product yields (27% and 36%, respectively). The borylation of furoxan did not proceed in the absence of a radical initiator (entry 7). The other tested radical initiators were inferior to AIBN at the examined temperature (80 °C) (entries 8–11 vs. entry 6).

**Table 1.** Optimization of reaction conditions for 3-borylfuroxan synthesis




| entry | **4a** (equiv) | radical initiator | solvent | time /h | yield /%[a] |
|---|---|---|---|---|---|
| 1 | 1.2 | AIBN | benzene | 8 | 26 |
| 2 | 1.2 | AIBN | $CH_3CN$ | 8 | 12 |
| 3 | 1.2 | AIBN | THF | 6 | 22 |
| 4 | 1.2 | AIBN | $CCl_4$ | 7 | 20 |
| 5 | 2.0 | AIBN | benzene | 3 | 35 |
| 6 | 2.5 | AIBN | benzene | 1 | 42 |
| 7 | 2.5 | – | benzene | 6 | trace |
| 8 | 2.5 | TBHP | benzene | 1 | 33 |
| 9 | 2.5 | BPO | benzene | 1 | 26 |
| 10 | 2.5 | TBPB | benzene | 1 | 18 |
| 11 | 2.5 | DTBP | benzene | 1 | 8 |

[a] Isolated yield. AIBN: azobisisobutyronitrile, TBHP: *tert*-butyl hydroperoxide, BPO: benzoyl peroxide, TBPB: *tert*-butyl peroxybenzoate, DTBP: di-*tert*-butyl peroxide.

With the optimized conditions in hand, we next investigated the scope of the borylation of 3-sulfonylfuroxans (Figure 2). The substituents at the 4-position were first examined. Not only disulfonyl furoxan **3a** (Table 1) but also 3-sulfonylfuroxans bearing alkoxy, alkylsulfanyl, aryl, and alkyl substituents at the 4-position smoothly underwent the radical addition reaction to furnish the desired products in good yields (**5b**–**e**). As an alternative approach, heteroatom substituents (OR and SR) at the 4-position could also be installed by the $S_NAr$ reaction of **5a** (Scheme 1). Next, we investigated the scope of boryl radical precursors using 3-benzenesulfonyl-4-ethoxyfuroxan (**3b**) as the radical acceptor. Not only imidazole-type NHC-boryl furoxans (**5f**–**j**) but also benzimidazole- and triazole-type NHC-boryl furoxans (**5k**–**m**) were compatible with the reaction conditions. It should be noted that only in the case of **5j**, 1:2 adduct **5jb** of NHC-borane and furoxan was obtained. In addition to NHC-boranes, a pyridine-borane derivative also afforded the desired adduct under standard conditions in moderate yield (**5n**). NHC-$BH_2CN$ uneventfully participated in the radical reaction to give product **5o**. To our disappointment, NHC-$BF_2H$[7] did not afford adduct **5p**.

To further broaden the borylfuroxan chemical library, B–H functionalization of borylfuroxans with the furoxan ring retained was examined (Scheme 2). Treatment of **5b** with acetic acid in the presence of Pd/C catalyst resulted in the mono-acetoxylation of the boron atom to afford **6** (Scheme 2a). In this transformation, no reaction occurred in the absence of Pd/C catalyst. *B*-Fluorination of **5k** using selectfluor (2.1 equiv) proceeded (Scheme 2b); *B*-mono- and *B*,*B*-difluoroboryl furoxans **7** and **8** were isolated along with NHC-$BF_3$ **9**.[6k]

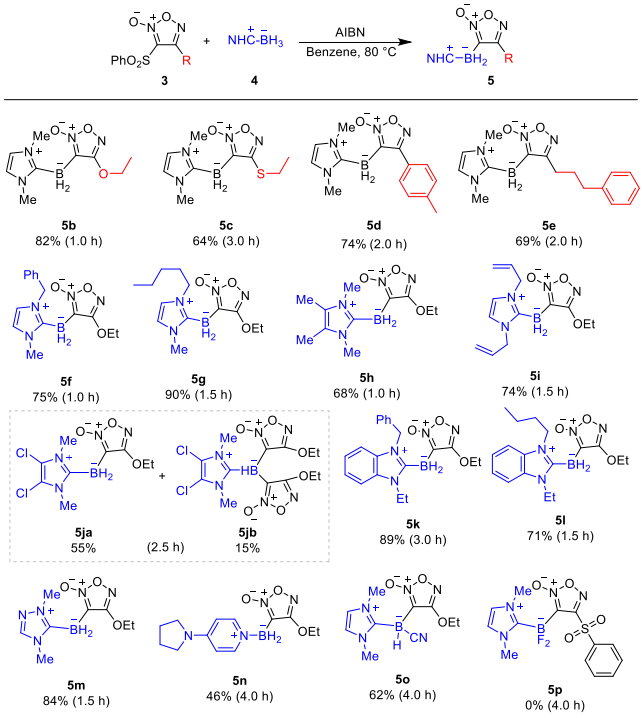
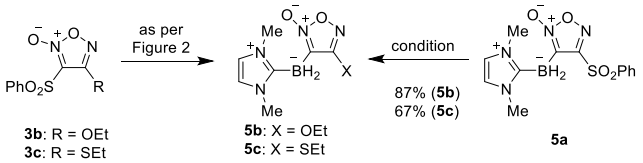


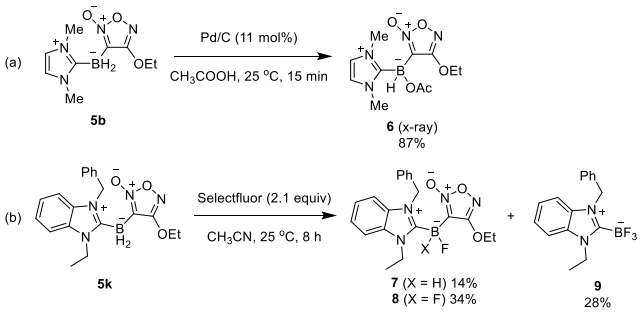

**Figure 2.** Substrate scope for 3-borylfuroxan synthesis (product structures are shown). Condition: **3** (1.0 equiv), **4** (2.5 equiv), AIBN (0.2 equiv), benzene, 80 °C.

**Scheme 1.** Binary pathways to 4-alkoxy- and 4-alkylsulfanyl-3-borylfuroxans




Conditions: For **5b**, **5a** (1 equiv), 50% NaOH aq. (2.2 equiv), EtOH, 65 °C, 31 h; For **5c**, **5a** (1 equiv), EtSH (1.5 equiv), 50% NaOH aq. (2.2 equiv), THF, 65 °C, 48 h.

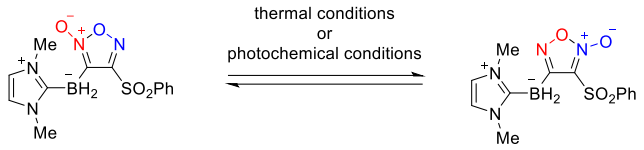
**Scheme 2.** B–H bond functionalization of borylfuroxans




Thermal and photochemical isomerization of furoxans from one regioisomer to the other provides easy access to both regioisomers, contributing to broadening of the synthetic scope.[8]

The equilibrated regioisomeric ratio is dependent on the isomerization conditions.[9] We attempted the isomerization of **5a** (Scheme 3). Under both thermal and photochemical conditions, the isomerization proceeded with acceptable mass balance to afford the corresponding regioisomer, 4-borylfuroxan **10**. Insoluble byproducts appeared during the reaction, which could account for the moderate mass balance.

**Scheme 3.** Isomerization of borylfuroxans[a]

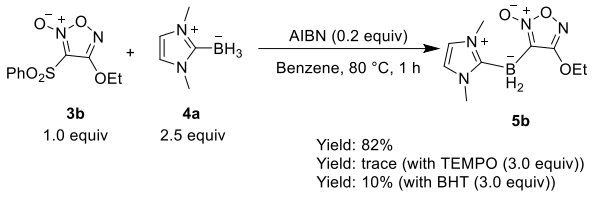



| Condition | 5a : 10 | mass balance |
|---|---|---|
| thermal (110 °C, toluene, 3 h) | 84 : 16 | 74% |
| photochemical (light (λ = 400 nm), 25 °C, benzene-$d_6$, 1 h) | 56 : 44 | 75% |

[a] Mass balance is the sum of the yields of **5a** and **10**. The **5a**:**10** ratio and mass balance were determined by $^1$H NMR spectroscopic analysis.

To gain insight into the mechanism, radical trap experiments were performed (Scheme 4). The product yields decreased when a radical scavenger, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or 2,6-di-*tert*-butyl-*p*-cresol (BHT), was used along with the standard reaction conditions,[10] suggesting that a radical process is involved during the course of the reaction.

**Scheme 4.** Radical trap experiments




Based on the above observations and our previous studies on carbon radical addition to 3-sulfonylfuroxans, a reaction mechanism for boryl-furoxan formation is proposed (Figure 3). The formation of NHC-boryl radical **12** from NHC-borane **11** (BDE (NHC-$BH_2$–H) = 80–82 kcal mol$^{-1}$)[11] is initiated by hydrogen atom abstraction by the 2-cyanoprop-2-yl radical (BDE (C–H) = 92 kcal mol$^{-1}$)[12] generated from AIBN under heating conditions. Radical **12** undergoes an addition reaction with 3-sulfonylfuroxan **13** to form radical intermediate **14**, which is a resonance structure of nitroxyl radical **15**, a well-known stable radical. Boryl furoxan product **16** is generated from **14**, with the liberation of sulfonyl radical **17**. In view of the requirement of only catalytic AIBN, **17** (BDE (O–H) = 78 kcal mol$^{-1}$)[13] should abstract the hydrogen atom of the next molecule **11** to form **12**; thus, the radical chain reaction ensues. With regard to the hydrogen atom transfer from **11** to **17**, $\Delta G^{\neq}$ and $\Delta G^0$ are computationally calculated to be +19.9 and +3.4 kcal mol$^{-1}$, respectively, implying an energetic barrier that can be overcome under heating conditions (Figure S4). Alternative initiation pathway, in which the 2-cyanoprop-2-yl radical reacts with **13** to give **17**, is also possible.

Oximes are an important class of molecules because of their rich reaction patterns and coordination ability, and are therefore, widely seen in bioorganic systems, medicine, and electrochemical and electrooptical sensors.[14] 1,2-Dioximes are of particular interest because of their chelating ability to form stable metal complexes relevant to metallo-enzymes, as exemplified by cobaloximes known as vitamin $B_{12}$ mimics.[15] The furoxan framework includes the atomic sequence of the 1,2-dioxime structure and can be regarded as a synthetic intermediate of 1,2-dioximes. In fact, we could convert the prepared borylfuroxans into a spectrum of 1,2-dioximes and its derivatives, some of which are otherwise difficult to access, in a stereospecific manner. Upon treatment with 1 equiv of $Br_2$, borylfuroxan **5a** provided a single stereoisomer of sulfonylglyoxime **18**, though the related mechanism remains elusive (Figure 4a).[16] When borylfuroxan **5e** was treated with 2 equiv of $Br_2$, bromoglyoxime **19** was selectively formed with a C=N bond geometric pattern different from that in **18** (Figure 4b).[16] Treatment of **5a** with trityl chloride in the presence of $HBF_4$ afforded chloroglyoxime derivative **20** (Figure 4c).[16] Pd/C-catalyzed hydrogenation of **5a** furnished the rare boryl-substituted 1,2-dioxime **21** as a single stereoisomer along with its cyclized form **22** (Figure 4d). On the other hand, hydrogenation of 3-borylfuroxan **5b** under the same conditions did not proceed, probably because the electron-donating 4-ethoxy group made the furoxan ring insensitive to reduction. Further investigation revealed that hydrogenation of **5b** proceeded in the presence of $Pd(OH)_2$ catalyst in MeOH; under these conditions, cyclization and methoxylation subsequently occurred, and boracycle **23** was obtained in high yield (Figure 4e). 1,2-Dioximes are generally accessible via the reaction of 1,2-dicarbonyl compounds with $NH_2OH$ or α-oximation of the carbonyl with $NO^+$ reagents, followed by oximation using $NH_2OH$; however, most of the 1,2-dioximes synthesized in this study are difficult to access using such methods. Thus, the developed synthetic methods for 1,2-dioximes via furoxans can be regarded as complementary to conventional methods.

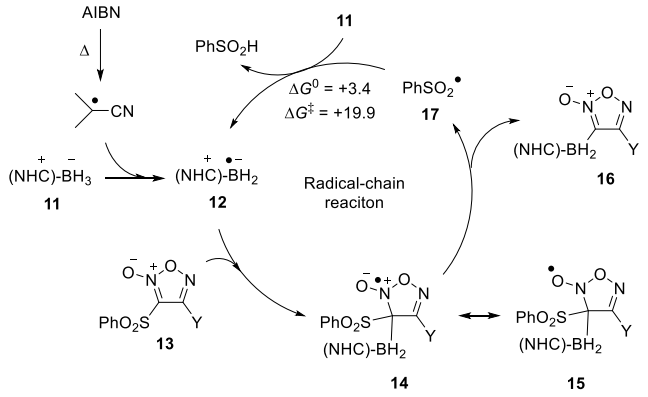



**Figure 3.** Proposed reaction mechanism for boryl-furoxan formation. Energy values calculated by DFT are shown in kcal mol$^{-1}$.

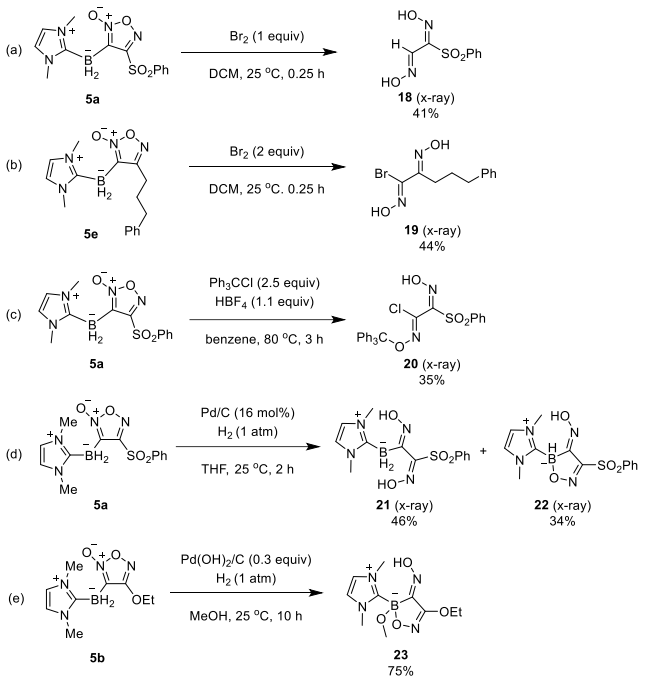



**Figure 4.** Transformation of borylfuroxans into various types of 1,2-dioximes and their derivatives.

In conclusion, we report the synthesis of borylfuroxans as the first example of metalloid-containing furoxans. The NHC-boryl radicals generated *in situ* reacted with sufonylfuroxans to forge C–B bond formation on the furoxan ring. As a demonstration of the synthetic application of this protocol, borylfuroxans were converted into various 1,2-dioximes and their derivatives. Studies aimed at identifying the further utility of borylfuroxans in organic synthesis and materials science are ongoing in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

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

Experimental procedures, NMR spectra, proposed mechanism, DFT calculations, sc-XRD analysis, and characterization data of compounds (PDF).

CCDC 2077149−2077155 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Author Contributions

The manuscript was written through contributions of all authors.

### Notes

The authors declare no competing financial interest.

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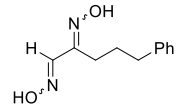
(16) The proposed mechanism is shown in the Supporting Information. When 2 equiv of $Br_2$ was treated with **5a**, a complex mixture was obtained and neither **18** nor its bromoglyoxime derivative was observed. When 1 equiv of $Br_2$ was treated with **5e**, the $^1$H NMR analysis of the crude material implied the formation of compounds which were thought to be an isomeric mixture of **19'** (59% yield) along with **19** (17% yield). In the HRMS chart of the crude material, the peaks corresponding to **19'** were observed. However, the attempts to isolate and fully characterize **19'** failed, probably due to its lack of stability under chromatographic conditions on silica gel.




**19'**
(mixture of *E*/*Z* isomers)