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Synthesis of sulfonyloxy furoxans via hydroxyfuroxan ammonium salts

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ABSTRACT

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

1. Introduction

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

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

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

2. Results and discussion

An ideal precursor for sulfonyloxy furoxans is the corresponding hydroxyfuroxan. A literature survey showed that nitrofuroxans were transformed into corresponding hydroxyfuroxans upon basic hydrolysis.[9] However, under the previously reported conditions, we could not obtain the desired hydroxyfuroxans in yields higher than

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30%. Furthermore, the yields were not reproducible.[10] During the course of our investigation, Makhova et al. have also pointed out the difficulty in obtaining 4-hydroxyfuroxans in high yields using the previously reported procedures.[11] These authors have reported that the product yield is significantly sensitive to the base molar ratio and the nature of the co-solvent.

In our study, we found that the treatment of 4-nitrofuroxan **1a** with tetrabutylammonium (TBA) hydroxide 30-hydrate in THF afforded the 4-hydroxyfuroxan TBA salt **2a** (Table 1, entry 1). The TBA salt (**2a**) moved to the organic phase in the usual phase separation (H_2O/CH_2Cl_2) and subsequent concentration of the organic phase gave compound **2a** in high yield and sufficient purity as a white solid (Fig. 1). In the phase separation step, the excess NBu_4OH was transferred to the water phase. It is worth noting that TBA salt **2a** stayed in the salt form even on the standard SiO_2 chromatography column.[12] In contrast to the reaction conditions reported by Makhova et al. (NaOH was used as a base), the excess of base did not have any adverse effect on the product yield (entries 1–3). Furthermore, commercially available aqueous solution of NBu_4OH could also be used for the transformation (entry 4). Thus, the simplicity of the reaction and the insensitivity of the product yield to the base molar ratio ensured a reliable formation of hydroxyfuroxan salts. The structure of **2a** was unambiguously determined by X-ray diffraction analysis (Fig. 1) and showed that all non-hydrogen atoms in the anion were almost coplanar. This observation suggested that the negative charge was delocalized over the entire anion. No significant hydrogen-bonding between the anion and cation fragments was observed.

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

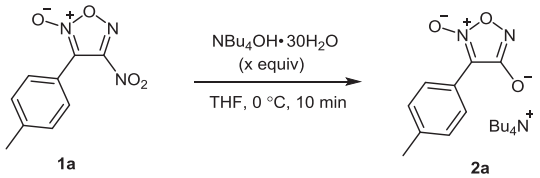
The facile isolation of the hydroxyfuroxan salt eliminated the need for acidification and base treatment for further sulfonylation. TBA salt **2a** was treated with triflic anhydride (Tf_2O) without the addition of a base in CH_2Cl_2 at 0 °C, and led to the formation of 4-(triflyloxy)furoxan **3a** in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

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

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

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

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



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

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