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Modular synthesis of carbon-substituted furoxans via radical addition pathway. Useful tool for transformation of aliphatic carboxylic acids based on “build-and-scrap” strategy

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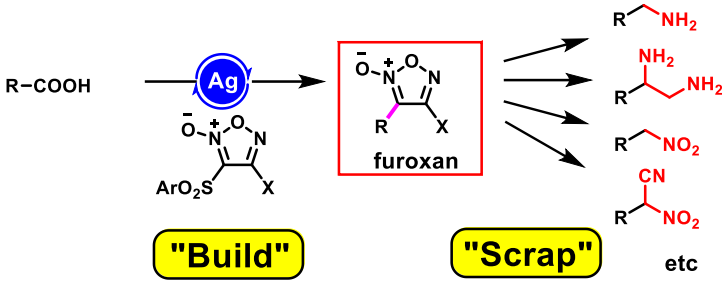
Supporting Information Placeholder



ABSTRACT: Utilizing radical chemistry, a new general C–C bond formation on the furoxan ring was developed. By taking advantage of the lability of furoxans, a wide variety of transformation of the synthesized furoxans have been demonstrated. Thus, this developed methodology enabled not only the modular synthesis of furoxans but also short-step transformations of carboxylic acids to a broad range of functional groups.

Heterocyclic compounds unarguably play a central role in the research and development of functional molecules, such as pharmaceuticals and device materials.[1] One of these heterocyclic compounds is furoxan (1,2,5-oxadiazole-2-oxide),[2-8] which has a long history of more than 150 years since its first synthesis by Kekulé.[9-10] Furoxan has a unique heteroatom-rich structure, consisting of a five-membered ring with the exocyclic oxygen connected to the 2-position nitrogen atom. The 3- and 4-positions of the furoxan ring are open to arbitrary substituents, which brings forth the diversity of furoxan-based molecules. At research level, furoxan-containing molecules have been reported to show several biological activities typical to heterocyclic compounds.[6, 8] Furthermore, certain classes of furoxans exhibit nitric oxide-releasing ability under physiological conditions,[11-14] which makes furoxan distinct from other heterocyclic compounds. Despite its drug-like structure, as well as the potential biological activities, furoxan has been connected with very limited practical applications so far.[15] This phenomenon could partially be attributed to the scarcity of general and facile synthesis methods for furoxans with diverse carbon substituents. With regard to organic reactions of furoxans, they often suffer ring opening, especially in presence of strong nucleophiles or reductive conditions,[7] due to their highly oxidized, thereby electron-deficient nature; therefore, conventionally, carbon substituents had to be installed prior to the furoxan ring formation (Figure 1A).[5] However, this method is not divergent and therefore inappropriate for establishing a furoxan-based chemical library. Very recently, our group reported the first general C–C bond forming reactions on the furoxan ring, which allowed the divergent synthesis of carbon-substituted furoxans from a common precursor (Figure 1B).[16-17] The key for success was the application of soft carbon nucleophiles in order to avoid the furoxan ring decomposition. However, even with this method, the introduced carbon substituents were limited to alkynyl and cyanide groups. The sequential installation of both substituents in a modular fashion has not yet been realized.

We recently developed carbon radical addition to sulfonyl furoxans using carboxylic acids as a radical source; the details of this research are presented in this article. The developed method is a rare example of successful and elusive C–C bond formation on the furoxan ring.[18] The sequential introduction of two different substituents to the pre-formed furoxan ring was feasible, which represents the first example of a fully divergent furoxan synthesis (Figure 1C). In addition, the

synthesized furoxans ("build" step) were subjected to ring-opening ("scrap" step) and could be transformed to a variety of other functional groups. As a result, our work could offer a unique strategy for late-stage transformation of carboxylic acids to other functional groups via "build-and-scrap" processing of furoxan (Figure 1D).

Initial investigation for divergent furoxan synthesis began with disulfonyl furoxan **2**, which is readily synthesized from α-arylsulfonyl acetic acids in one step[19-20] and is not of potentially explosive nature.[21] Inspired by reports of carbon radical addition reactions with a sulfonyl moiety serving as a radical leaving group,[22-28] we investigated C–C bond forming reactions of disulfonyl furoxans **2** with carbon radicals (Table S1). To our delight, desired adduct **3a** was obtained in high yield using a combination of $AgNO_3$ and $K_2S_2O_8$ (Figure 2)[29-33]. The distinctive feature of this reaction is its unconventional regioselectivity; C–C bond formation occurred exclusively at the 3-position, which is in sharp contrast to the ionic reactions, where reversed selectivity in favor of the more electrophilic 4-position is generally observed.[2, 5, 34] Various $ArSO_2$ groups are tolerated; products **3b**–**e** were obtained in good yields. Similar yield could also be obtained in a gram-scale reaction (**3a**). A wide range of carboxylic acids have proven to perform well as a radical donor (**3f**–**z**). Unfortunately, α-ketocarboxylic acid and aryl carboxylic acid performed poorly (**3aa**–**b**). Late-stage furoxan introduction to natural products and medicinal agents was also successful (**3ac**–**e**).

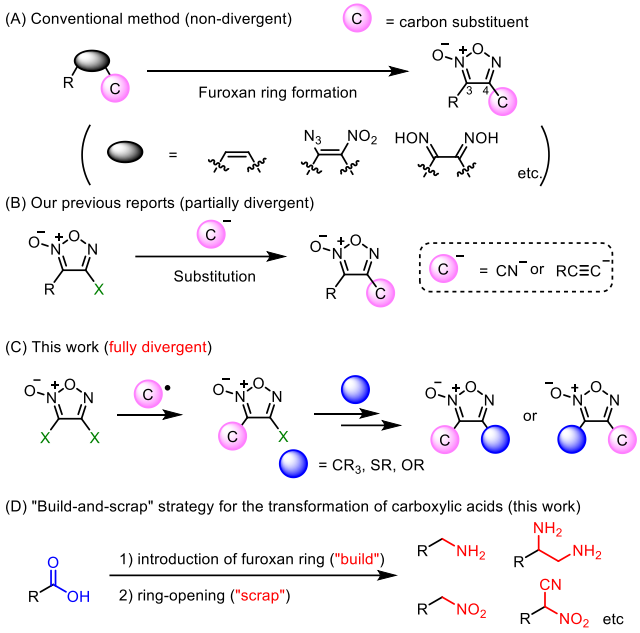


Figure 1. Comparison of synthetic strategies of carbon-substituted furoxan.(A–C) and "build-and scrap" strategy developed in this work (D)

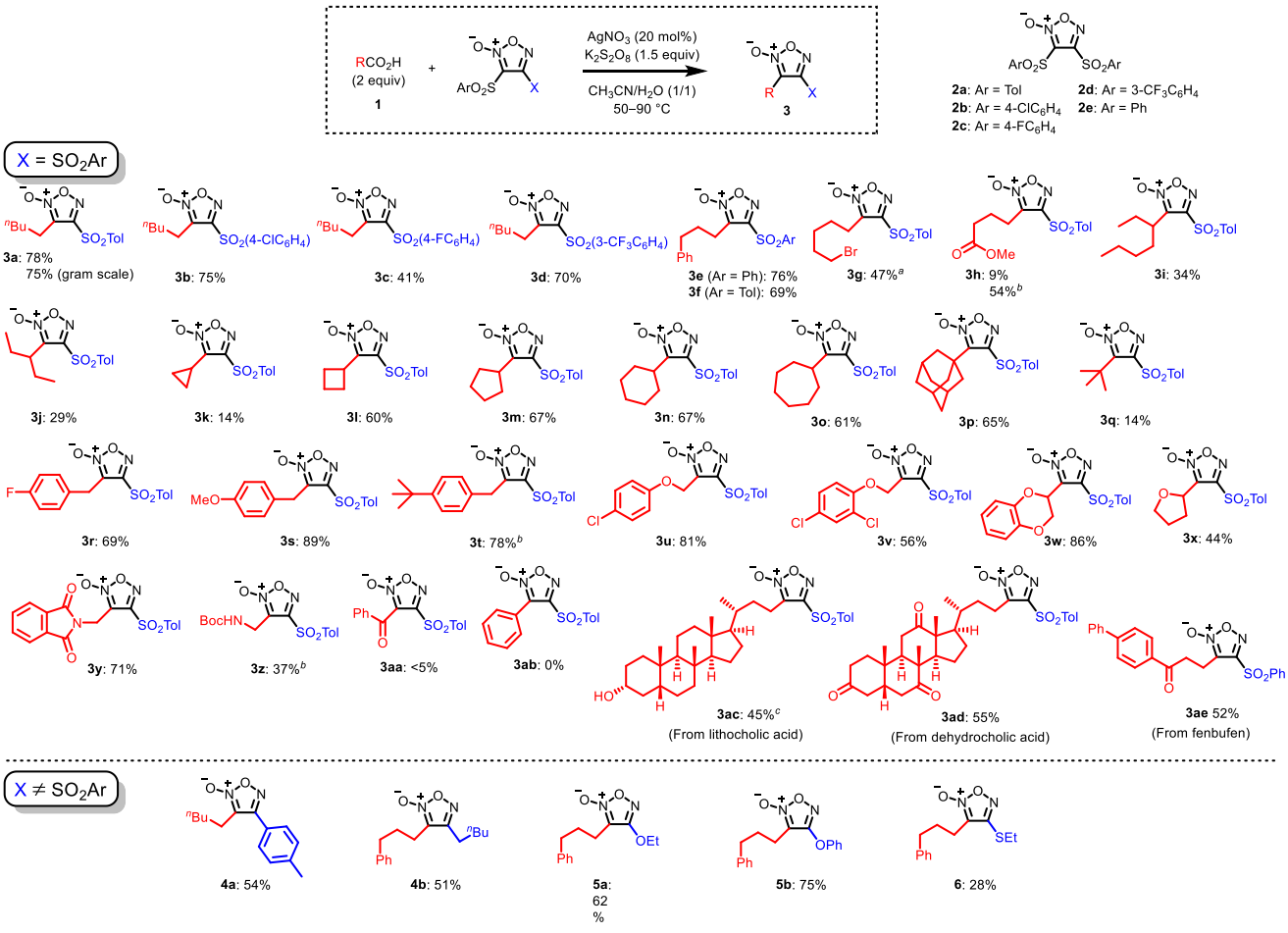
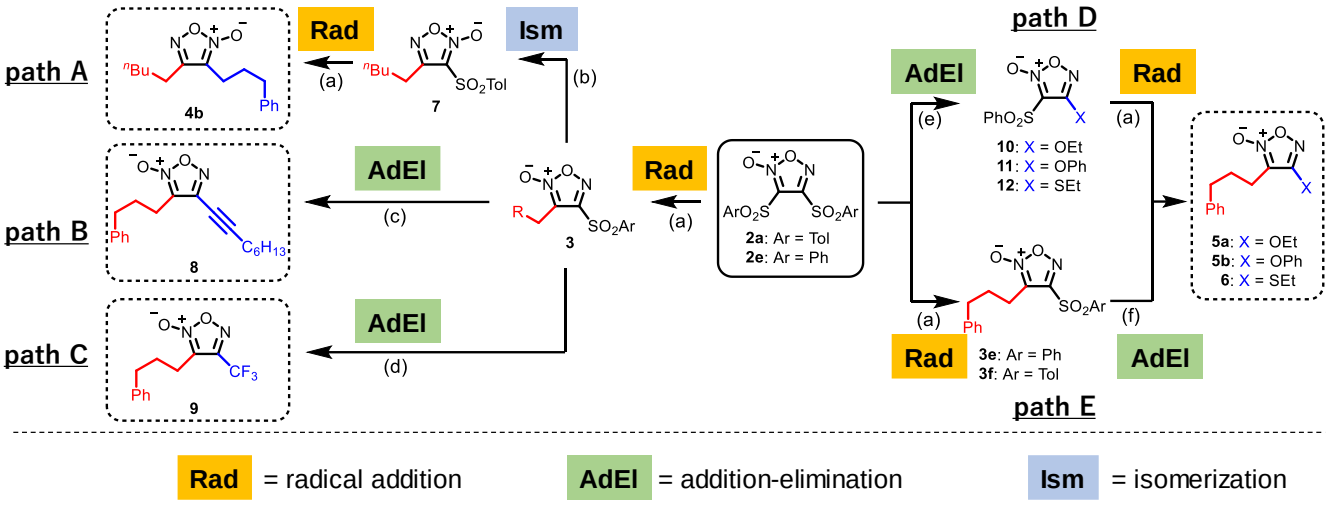


Figure 2. Scope and limitation for radical addition reaction of sulfonyl furoxans. Experimental details are provided in the Supporting Information. [a] $AgNO_3$ (0.4 equiv). [b] K_2CO_3 (1.5 equiv) was added. [c] $AgNO_3$ (0.4 equiv), $K_2S_2O_8$ (3.0 equiv).

Scheme 1. Modular synthesis of carbon-substituted furoxans by utilizing radical reaction.[a]



[a] Reaction conditions: (a) Figure 2. (b) **3a**, toluene, 140 °C, 33%. (c) **3e**, BuLi (1.1 equiv), oct-1-yne (1.3 equiv), THF, 0 °C, 44%. (d) **3e**, CsF (2.5 equiv), Me_3SiCF_3 (2.0 equiv), THF, –20 °C, 53%. (e) ref. 34, 37. (f) For **5a** and **6**: **3f**, NaOH (2.3 equiv), EtXH (2.0 equiv), THF, rt, 84% (**5a**), 49% (**6**). For **5b**; **3e**, NaOH (6.0 equiv), PhOH (6.0 equiv), DMF, 38 °C, 30%.

To our delight, the sulfonyl group at the 4-position proved not to be a necessity for the radical addition reaction. Not only 3,4-disulfonyl furoxans, but also 3-sulfonyl furoxans having 4-position substituents other than a sulfonyl group performed well as a radical acceptor (Figure 2, bottom).

The developed reactions of sulfonyl furoxans with alkyl radicals enabled the sequential installation of the two substituents to furoxans in a modular fashion,[21] which is summarized in Scheme 1. 3-Alkyl-4-sulfonyl furoxan **3**, synthesized from disulfonyl furoxan using the developed radical reaction pathway, was isomerized thermally to **7**, which served as the substrate for the second radical addition reaction to give 3,4-dialkyl furoxan **4b** as a single regioisomer (path A). The alkynylation of **3** was performed using the previously developed conditions to afford **8** in good yield (path B).[16] Unprecedented trifluoromethylation of sulfonyl furoxan using Me_3SiCF_3 and CsF granted **9** in good yield (path C). 3-Alkyl furoxan with oxygen or sulfur substituents at the 4-position were synthesized through alkoxylation or alkylthionylation of disulfonyl furoxan,[34-35] followed by radical-mediated alkylation (path D). The same products can also be synthesized in reverse reaction order: thus, disulfonyl furoxan **2** was subjected to radical reaction to give 3-alkyl-4-sulfonyl furoxan **3**, which then was subjected to addition-elimination reaction to give the adducts bearing heteroatom substituents (**5a**, **5b**, and **6**) (path E). Although both routes provide the same product in comparable yields, one or the other is preferred under certain conditions, when it comes to creating a furoxan-based chemical library. When diversity in the alkyl group is required, the radical addition should follow the addition-elimination reaction. However, when diversity in the heteroatom is desired, the addition-elimination reaction should follow the radical addition.

Based on literature precedents,[24, 33] a plausible mechanism is depicted in Figure 3. A noteworthy feature of the developed reaction is the exclusive site-selectivity in favor of the addition at the 3-position of disulfonyl furoxan. To clarify the origin of this selectivity, we performed long-range corrected (LC) density functional theory (DFT) calculations[36-38] for the radical addition and elimination steps, using the simplified substrates (**RT1**) (Figure 4a). The free-energy barriers of the alkyl radical addition step for the 3- and 4-position attacks are calculated to be 13.3 and 18.6 kcal mol^{-1}, respectively. These results could account for the observed site-selectivity in favor of 3-position attack. The origin of the energy difference between **3-TS1** and **4-TS1** can be explained by considering the stabilization effect derived from spin delocalization (Figure 4b). The spin density analysis revealed that the alpha spin (blue color) on the furoxan ring of **3-TS1** is delocalized over N2 and O1' atoms, while that of **4-TS1** is localized on the N5 atom. This energy difference between the 3- and 4-position attacks becomes more prominent at the stage of intermediates, **3-INT** and **4-INT** (ΔG = 15.1 kcal mol^{-1}). The stabilized nature of **3-INT** is readily understandable by the fact that the resonance form of **3-INT** is a nitroxyl radical **16**, a well-known stable radical, as exemplified by 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).[39]

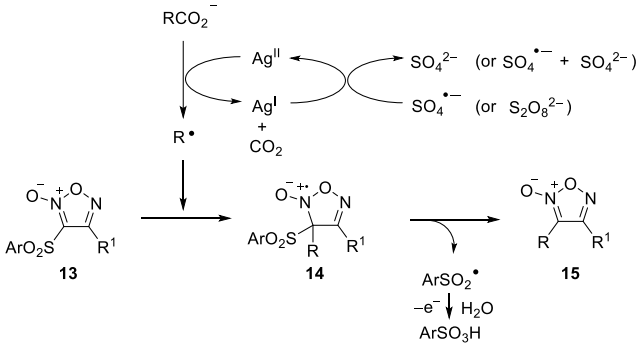


Figure 3. Proposed reaction mechanism.

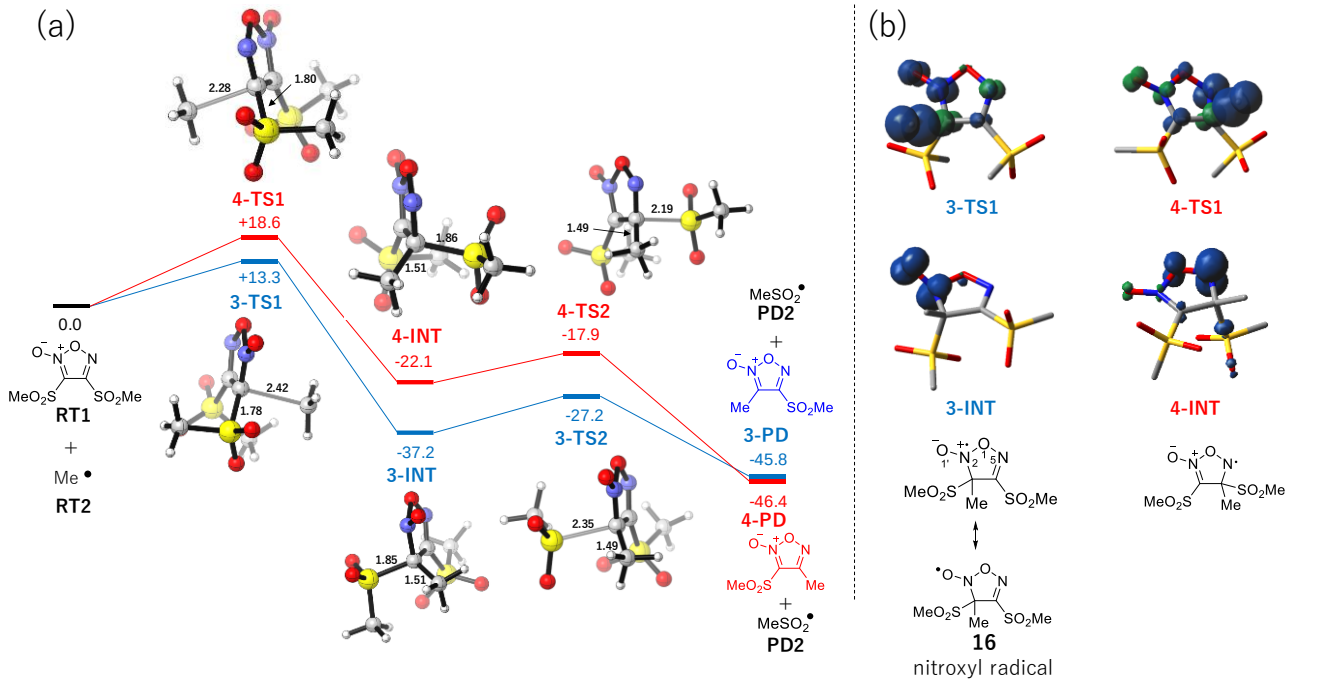


Figure 4. (a) The computed potential energy surface and relative Gibbs free energies in radical addition reaction to furoxan at the (u)LC-BLYP/6-31G(d) level with the polarizable continuum solvation model of SMD and DMSO. All energies are indicated in kcal mol^{-1}, and interatomic distances are shown in angstroms. (b) Spin density analysis of transition states (**3-TS1** and **4-TS1**) and intermediates (**3-INT** and **4-INT**) revealed the distribution of alpha (blue) and beta (green) spin. The hydrogen atoms are omitted for clarity.

In recent years, the transformation of common functional groups under mild conditions has proven effective for the late-stage molecule functionalization.[40] A carboxylic acid group, which is prevalent in natural products and non-natural pharmaceuticals, is one of the targets for late-stage modification. Based on the expectation that furoxans are prone to a variety of ring-degradation, due to their weak aromaticity and electron-deficient nature, we propose that furoxans could serve as synthetically versatile intermediates for late-stage transformation of carboxylic acids. This so-called "build-and-scrap" strategy was found feasible (Figure 5). Sulfonylfurazan **17** could be generated from **3e** in one step.[41] The sulfonyl group of **17** can be a useful synthetic tool to introduce other substituents to the furazan.[42-43] (*E*,*E*)-Dioximes **18**[44] and **19** were stereospecifically obtained by hydrogenation of the starting furoxans.[45] Dioxime **20** with a CF_3 substituent was obtained, although as a regioisomeric mixture. (*Z*,*Z*)-Dioxime **21**,[44] a regioisomer of **18**, could also be synthesized in a pure form from the regioisomer of **3e,** generated by photochemical isomerization of **3e**. The reduction of **3e** by excess amount of $LiAlH_4$ provided monoamine **22**.[46] In contrast, 1,2-diamine **23** could be obtained by sequential reduction protocol, i.e. hydrogenation using Pd/C catalyst followed by $LiAlH_4$. Interestingly, the reduction of **3e** using 2 equivalent of tributyltin hydride was found to afford nitroalkane **24**, the mechanism of which remains a question to be explored. Meanwhile, oxime **25** was obtained selectively by using increased amount of tributyltin hydride. Simple treatment of **3e** with KOH induced an unprecedented transformation to afford nitrile **26**. Under the same conditions with a slight modification, α-hydroxyimino carboxylic acid **27**[44] could be generated as the main product. In contrast to the reaction using KOH, the use of Bu_4NOH provided the corresponding hydroxide furoxan Bu_4N salt.[47] The following

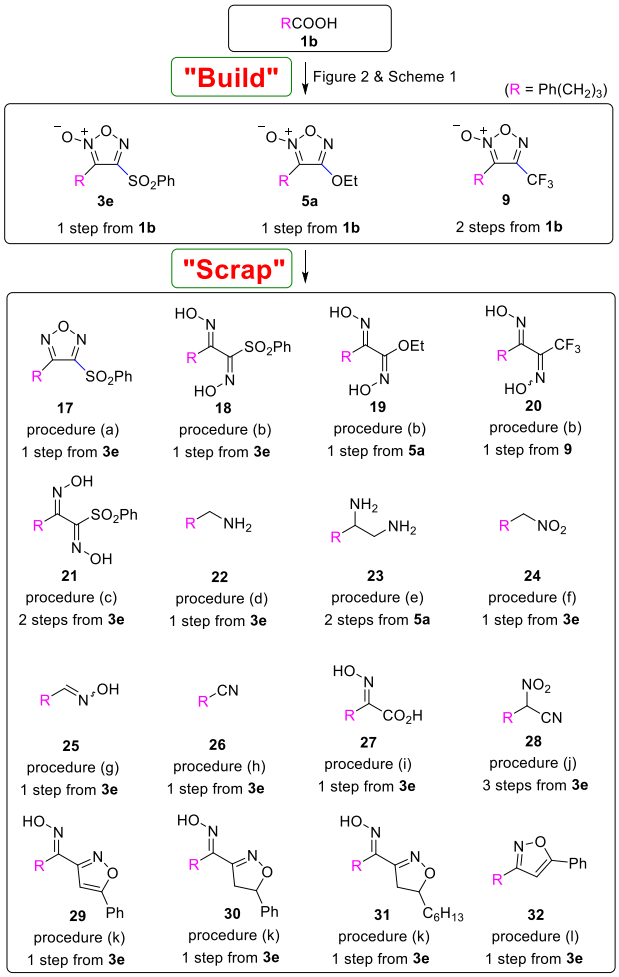


Figure 5. "Build-and-scrap" of furoxans leading to a variety of functional groups. (a) $P(OEt)_3$ (3 equiv), 100 °C, 54 h, 74%. (b) Pd/C (10 mol%), H_2 (1 atm), MeOH, rt, 100% (**18**, 2 h), 82% (**19**, 3 h), 81% (**20**, 19 h, dr = 3:1). (c) (1) hν (λ = 300–400 nm), C_6D_6, rt, 2.5 h, 55%. (2) Pd/C (10 mol%), H_2 (1 atm), MeOH, rt, 0.5 h, 100%. (d) $LiAlH_4$ (5 equiv), THF, 0 °C, 7 h, 39%. (e) (1) procedure (b). (2) $LiAlH_4$ (5 equiv), THF, 0 °C, 3.5 h, 57%. (f) Bu_3SnH (2 equiv), benzene, 40 °C, 5 d, 41%. (g) Bu_3SnH (5 equiv), benzene, 40 °C, 5 d, 43%. (h) KOH (2.3 equiv), THF, rt, 3 d, 46%. (i) KOH (5.0 equiv), THF, rt, 16 h, 18%. (j) (1) Bu_4NOH (2 equiv), THF, rt, 1 h. (2) Tf_2O (1.1 equiv), CH_2Cl_2, 0 °C, 15 min, 21% (2 step). (3) $Pd(PPh_3)_4$ (1 equiv), benzene, rt, 10 min, 52%. (k) 1,3-dipolarophile (3 equiv), DMF, 130–150 °C, 33% (**29**, using phenylacetylene), 12% (**30**, using styrene), 18% (**31**, using oct-1-yne). (l) phenylacetylene (3 equiv), toluene, 130 °C, 89 h, 8%.

trifluoromethylsulfonylation gave the 4-(triflyloxy)furoxan, which was converted to α-nitrocyano compound **28** upon treatment with $Pd(PPh_3)_4$. Although multisteps are required, the mild reaction parameters enable the access to a nitrocyanomethyl group, a relatively rare functional group in literatures[48-49]. Compounds **29**–**32**,[44] a molecule class of isoxazole and isoxazoline with an adjacent oxime moiety, could be synthesized by heating a mixture of **3e** and 1,3-dipolarophile, alkyne and alkene, according to the relevant literature.[50] Isoxazole **32**, lacking the oxime group versus **29**, could be generated from the same starting furoxan **3e** by changing the solvent.[51] Thus, functional groups with a diverse range of size, electronic nature, and hydrogen bonding ability are easily installed using a carboxylic acid as a synthetic handle.

In conclusion, we have developed radical addition reactions to furoxans, in which the carbon radical is generated from carboxylic acids in the presence of a silver catalyst and persulfate salt. The present strategy enables a rare C–C bond formation on the furoxan ring. Furthermore, we demonstrated that the generated furoxans can be transformed to a variety of functional groups by taking advantage of the lability of the furoxan ring. Hence, furoxan "build-and-scrap" strategy provides a powerful method to convert carboxylic acids to a variety of functional groups in short steps. The expansion of this strategy to other common functional groups and the development of other "scrap" methods of furoxans are in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, characterization data, DFT calculations, crystallographic data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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