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(Citation)
Organic & Biomolecular Chemistry,15(9):1965-1969

(Issue Date)
2017-03-07

(Resource Type)
journal article

(Version)
Accepted Manuscript

Journal Name

COMMUNICATION

Synthesis of alkynyl furoxans. Rare carbon–carbon bond-forming reaction on a furoxan ring

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Received 00th January 20xx,
Accepted 00th January 20xx

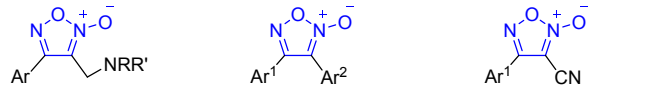
DOI: 10.1039/x0xx00000x

www.rsc.org/

A rare carbon-carbon-bond forming reaction on a furoxan ring has been developed. The nucleophilic aromatic substitution (S_NAr) reaction of 4-nitrofuroxans with alkynyl lithium proceeded with high yields, which enabled the first practical synthesis of both alkynyl furoxan regioisomers. Due to the versatility of the alkyne functional group, various derivatizations of the carbon–carbon triple bond in the afforded products were possible. Thus, this developed method is a convergent approach to a wide spectrum of carbon-substituted furoxans.

Furoxans (1,2,5-oxadiazole-2-oxides) have been reported to exhibit various significant biological activities such as platelet antiaggregatory properties, and antibacterial and antifungal activities.[1] Moreover, their ability to release nitric oxide (NO) has rendered them a distinctive class of heteroaromatic compounds; NO, a bioactive signaling molecule, plays an important role in a wide range of biological systems including, vasodilation, neurotransmission, and regulation of hormone secretion.[2] Thus, furoxan has been applied as a building block in hybrid pharmaceutical candidates[3] and switchable NO donors.[4]

Most biologically active furoxans reported to date bear one or two carbon substituents on the furoxan ring (Figure 1).[5] Conventionally, carbon-substituted furoxans were synthesized via the pre-installation of the required carbon substituent on the precursor (e.g. dioxime, alkene), followed by furoxan ring-formation (Figure 2a).[6] However, to construct a library of



- neuroprotective
- COX-2 inhibitor
- photo-induced NO-donor
- platelet antiaggregatory

Figure 1 Existing biologically active carbon-substituted furoxans

furoxan derivatives by this method, one needs to tediously synthesize precursors with different carbon substituents. Instead, a convergent strategy, where a carbon substituent is installed after furoxan ring formation, would represent an attractive manifold for the synthesis of a variety of furoxan-based molecules (Figure 2b). Unfortunately, furoxans readily undergo ring-opening degradation by strong carbon nucleophiles.[7] To the best of our knowledge, only two specific examples of carbon–carbon bond-forming reactions on the furoxan ring have been reported to date (Gasco et al., Figure 2c).[5b] They reacted (phenylsulfonyl)furoxans, synthesized from the corresponding ketone in six steps, with a Grignard reagent to introduce an aromatic substituent on the furoxan ring. In these reactions, low-to-moderate yields were afforded and the scope

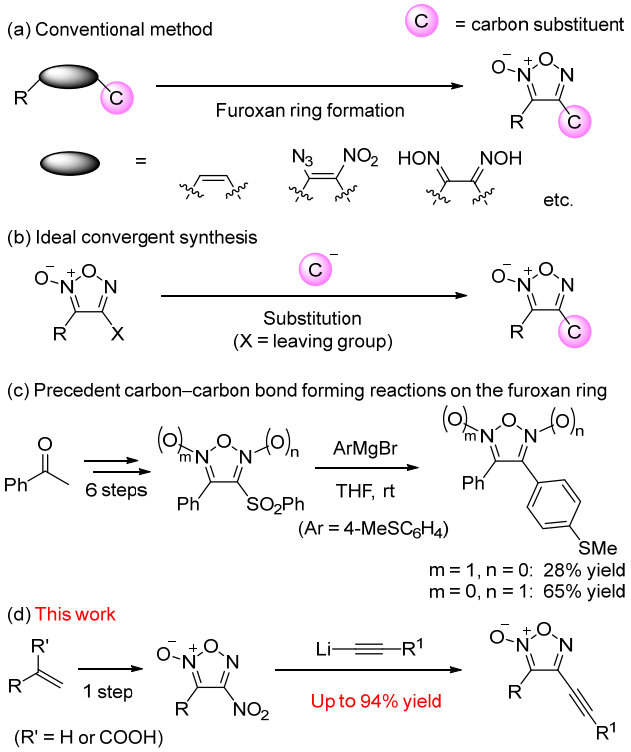


Figure 2 Synthesis of carbon-substituted furoxans.

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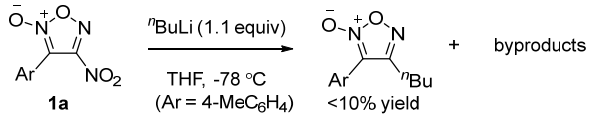
† Electronic Supplementary Information (ESI) available: typical experimental procedures, characterization of new compounds, copies of ^{1}H and ^{13}C NMR. See DOI: 10.1039/x0xx00000x

was not further investigated.

Recently, we discovered that 4-nitrofuroxans, synthesized in one step from commonly accessible alkenes,[8] reacted smoothly with alkynyl lithium reagents. This aromatic substitution-type (S_NAr) reaction afforded 4-alkynyl furoxans, stereospecifically, in high yields (Figure 2d). The 3-alkynyl furoxan isomers were also synthesized by isomerization of 4-alkynyl furoxans. Thus, a general and direct access to both alkynyl furoxan isomers has been established. Various functionalization reactions of the afforded alkyne were conducted, demonstrating that furoxans bearing different carbon substituents can be accessible using the developed method reported herein.

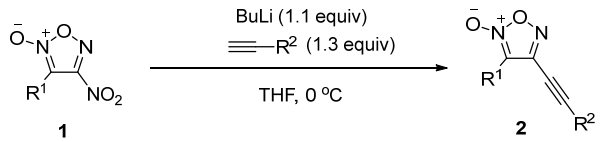
Aiming for a high-yielding carbon–carbon bond forming reaction on the furoxan ring, we conducted extensive screening of the conditions (carbon nucleophiles, leaving group on the furoxan ring, base employed, and solvent). However, most of the tested conditions afforded the products, in low yield, together with a significant amount of by-products. One typical failed example was the reaction of 4-nitrofuroxans with an alkyl lithium reagent (Scheme 1). A negligible yield of the desired adduct was isolated and various by-products were afforded, even when the reaction was conducted at a low temperature (-78 ºC). One of the identified by-products proved to be 4-butoxyfuroxan (mechanism in Figure S1). Various unidentified polar by-products, probably derived from ring opening of the furoxan moiety, were also formed.



Scheme 1 Reaction of 4-nitrofuroxan **1a** (Ar = 4-MeC_6H_4) with BuLi

Finally, a combination of an alkynyl lithium compound with 4-nitrofuroxan **1** was discovered to affect the carbon–carbon bond forming reaction on the furoxan ring, affording 4-alkylnyl furoxan in high yield (Table 1, entry 1).[9] In this reaction the regioisomer 3-alkynyl furoxan was not detected, implying that this reaction is stereospecific. This is the first practical synthesis of an alkynyl furoxan[10] and one of the rare examples of C–C bond-forming reactions on the furoxan ring (*vide supra*). 3-(4-Methylphenyl)-4-(phenylsulfonyl)furoxan (**3**) was used as a substrate (Table 1, entry 2) and the adduct was formed, albeit in moderate yield, with accompanying unidentified by-products. This suggests that under the employed conditions, 4-nitrofuroxan is a better substrate for alkynylation than 4-(arylsulfonyl)furoxan. Both phenylacetylene and silylacetylene afforded the products in high yield (Table 1, entries 3 and 4). Conversely, propiolate afforded the product in low yield (Table 1, entry 5). This was attributed to the incompatibility of the ester group under this condition. The scope of the substituent at C3 was also investigated (Table 1, entries 6–11). The reactions of 4-nitrofuroxans bearing electron-rich and electron-deficient aromatic rings provided the products uneventfully (Table 1,

Table 1 Synthesis of 4-alkynyl furoxans **2**



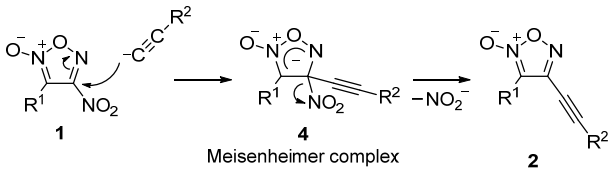
Entry	R^1	R^2	Time /h	Yield /%	**2**
1	4-MeC_6H_4	$^nC_6H_{13}$	1	94	**2a**
2[a]	4-MeC_6H_4	$^nC_6H_{13}$	1	56	**2a**
3	4-MeC_6H_4	Ph	1	87	**2b**
4	4-MeC_6H_4	$SiMe_2{}^tBu$	0.5	80	**2c**
5[b]	4-MeC_6H_4	CO_2Et	3	16	**2d**
6	4-$MeOC_6H_4$	$^nC_6H_{13}$	1	76	**2e**
7	4-FC_6H_4	$^nC_6H_{13}$	0.5	76	**2f**
8	4-$CF_3C_6H_4$	$^nC_6H_{13}$	2	80	**2g**
9	3-BrC_6H_4	$^nC_6H_{13}$	1	76	**2h**
10	2,4,6-$Me_3C_6H_2$	$^nC_6H_{13}$	3	67	**2i**
11	2,6-$Cl_2C_6H_3$	$^nC_6H_{13}$	1.5	79	**2j**
12	*N*-Ts-indol-3-yl	$^nC_6H_{13}$	6	72	**2k**
13	pyridin-2-yl	$^nC_6H_{13}$	2	77	**2l**
14[c]	^iPr	$^nC_6H_{13}$	4	85	**2m**
15[c]	$^nC_5H_{11}$	$^nC_6H_{13}$	4	75	**2n**
16[c]	$^cC_6H_{11}$	$^nC_6H_{13}$	4	77	**2o**

[a] 3-(4-Methylphenyl)-4-(phenylsulfonyl)furoxan (**3**) was used as a substrate instead of 4-nitrofuroxan (**1**); [b] at -78 ºC; [c] at -60 ºC.

entries 6–8). Bulky substituents and nitrogen-containing heteroaromatic rings at the C3 position of the furoxan ring were tolerated (Table 1, entries 10–11, and 12–13, respectively). Notably, under the same conditions, 3-alkyl-4-nitrofuroxans also underwent alkynylation to afford the products in high yield (Table 1, entries 14–16). In all cases, the reactions afforded 4-alkynyl furoxans stereospecifically; the formation of 3-alkynyl furoxans was not observed.

The proposed alkynylation mechanism (Scheme 2) is as follows: the alkynyl anion nucleophilically attacks the C4 atom in 4-nitrofuroxan to afford **4** (Meisenheimer complex).[11] Denitration of **4** results in the stereospecific formation of 4-alkynyl furoxan. Moreover, since 3-alkyl-4-nitrofuroxans (R^1 = alkyl in Scheme 2) also afforded the product in high yield (Table 1, entries 14–16), stabilization of the Meisenheimer complex by an R^1 substituent is not required. This underscores the generality and applicability of the developed methodology.

With the facile synthetic route for 4-alkynyl furoxans in hand, the synthesis of 3-alkynyl furoxans was next investigated. Treatment of 3-nitro-4-phenylfuroxan (**5**) with an alkynyl lithium reagent, using the same conditions developed for the synthesis of 4-alkynyl furoxan, failed to afford the desired



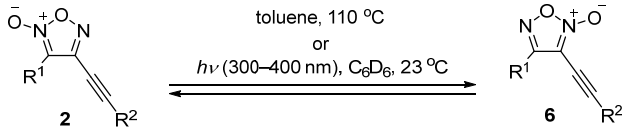
Scheme 2 Proposed mechanism for the alkynylation of 4-nitrofuroxan.

adduct. This was attributed to the insufficient electrophilicity of the C3 atom in **5**.[12]

We then chose to examine another strategy, namely, the isomerization of 4-alkynyl furoxans **2**. Both thermal (toluene, 110 °C)[13] and photochemical[14] (λ = 300–400 nm) isomerization proceeded well (Table 2; see Figures S3 and S4 for more details). In all cases, no significant formation of by-products was observed until equilibrium was reached. Moreover, the afforded mixture of 3- and 4-alkynyl furoxans was mostly separable by chromatography. Thus, 3-alkynyl furoxans **6** could be synthesized in pure form and characterized. Generally, the thermal stability of 3-alkynyl furoxan is slightly higher than that of 4-alkynyl furoxan. The product ratio at the photostationary state varies depending on the other substituent on the furoxan ring. For example, the photochemical isomerization of **2a** provided a 17:83 mixture in favor of **6a** (entry 1, Table 2). The integration of the molar absorption coefficient of **2a** at wavelengths ranging between 300 and 400 nm is even smaller than that of **6a** (Figure S2). This suggests that the light absorption efficiency is not the main factor that determines the product ratio at the photostationary state.

Once the synthetic routes to both alkynyl furoxan isomers were established, we next focused on the derivatization of the afforded products to showcase the utility of the developed method. The silyl protective group in **2c** could be removed; terminal alkyne **7** was produced in high yield (Figure 3A). Ethyl cyanoformate affected the alkoxycarbonylation reaction to afford **2d**. This could not be directly formed from the

Table 2 Thermal and photochemical isomerization of 4-alkynyl furoxans **2**[a]



	Substrate			Ratio (**2**:**6**)[b]	
Entry	**2**	R^1	R^2	*thermal*	*photo*
1	**2a**	4-MeC_6H_4	$^nC_6H_{13}$	44:56	17:83
2	**2b**	4-MeC_6H_4	Ph	44:56	32:68
3	**2c**	4-MeC_6H_4	$SiMe_2{}^tBu$	41:59	8:92
4	**2d**	4-MeC_6H_4	CO_2Et	0:100	10:90
5	**2e**	4-$MeOC_6H_4$	$^nC_6H_{13}$	38:62	10:90
6	**2f**	4-FC_6H_4	$^nC_6H_{13}$	33:67	29:71
7	**2g**	4-$CF_3C_6H_4$	$^nC_6H_{13}$	40:60	53:47
8	**2h**	3-BrC_6H_4	$^nC_6H_{13}$	40:60	40:60
9	**2i**	2,4,6-$Me_3C_6H_2$	$^nC_6H_{13}$	48:52	64:36
10	**2j**	2,6-$Cl_2C_6H_3$	$^nC_6H_{13}$	42:58	90:10
11	**2k**	*N*-Ts-indol-3-yl	$^nC_6H_{13}$	28:72	22:78
12	**2l**	pyridin-2-yl	$^nC_6H_{13}$	46:54	56:44
13	**2m**	^iPr	$^nC_6H_{13}$	20:80	62:38
14	**2n**	$^nC_5H_{11}$	$^nC_6H_{13}$	38:62	76:24
15	**2o**	$^cC_6H_{11}$	$^nC_6H_{13}$	30:70	50:50

[a] Thermal conditions: at 110 °C in toluene. Photochemical condition: irradiated with light (λ = 300–400 nm) at 23 °C in C_6D_6; [b] Product ratio in equilibrium (thermal condition) or at photostationary state (photochemical condition). Determined by ^1H NMR analysis.

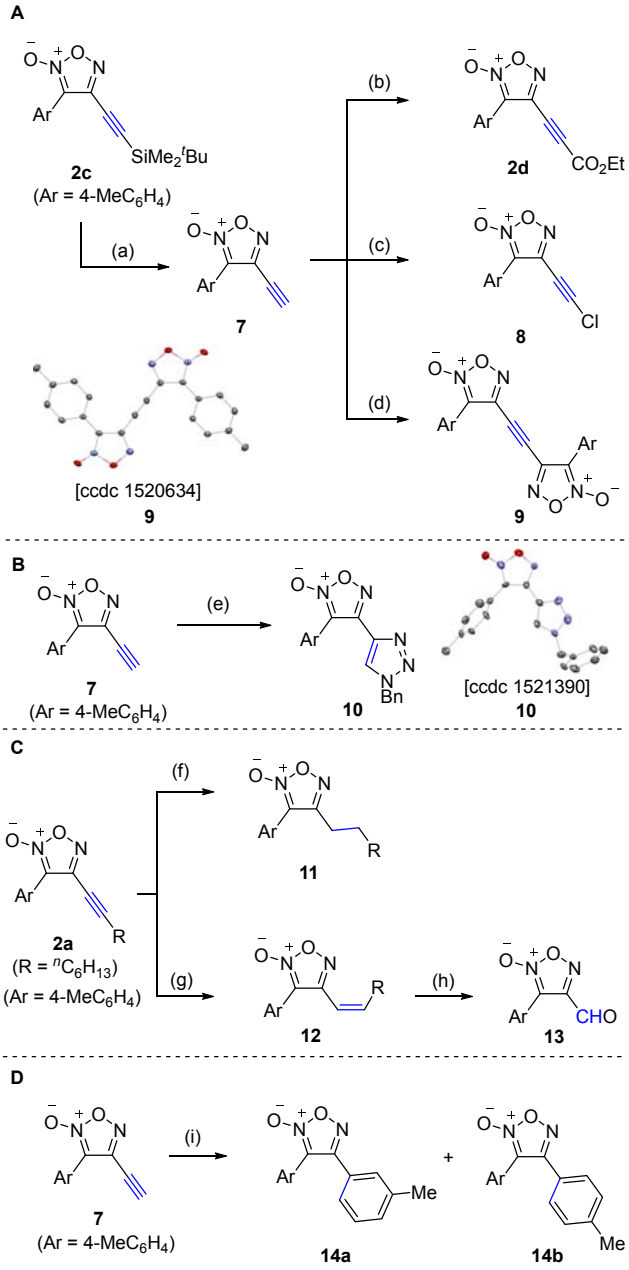


Figure 3 Derivatization of alkynyl furoxans. Reaction conditions: (a) TBAF (1.1 equiv), CH_2Cl_2 , 18 °C (99%); (b) *n*-BuLi (1.1 equiv), THF, -78 °C; $NCCO_2Et$ (1.3 equiv), -78 °C (76%); (c) *n*-BuLi (1.05 equiv), THF, -78 °C; $PhSO_2Cl$ (1.2 equiv), -78 °C (92%); (d) **7** (1.3 equiv), *n*-BuLi (1.1 equiv), THF, -78 °C; **1a** (1 equiv), -78 °C (80%); (e) $PhCH_2N_3$ (1.5 equiv), CuO (5 mol %), H_2O:*t*-BuOH = 2:1, 23 °C (92%) (f) H_2 (1 atm), Pd/Fib (0.45 mol %), 18 °C, 3 h (73%); (g) H_2 (1 atm), Pd/Fib (0.45 mol %), 18 °C, 10 min (88%); (h) O_3, MeOH:CH_2Cl_2 = 3:7, -78 °C; SMe_2, 20 °C (80%); (i) [(naphthalene)Rh(cod)]BF_4 (2 mol%), isoprene (2 equiv), CH_2Cl_2, 23 °C (87%); DDQ (1.5 equiv), 24 °C (97%, **14a**:**14b** = 81:19). TBAF = tetrabutylammonium fluoride, Pd/Fib = palladium-fibroin, DDQ = 2,3-dichloro-4,5-dicyano-*p*-benzoquinone

alkynylation of 4-nitrofuroxan in an acceptable yield (entry 5, Table 1). Potentially, chloroacetylene **8** can be further

derivatized by a cross-coupling reaction; it was synthesized by the reaction of lithium acetylide (derived from **7)** with benzenesulfonyl chloride.[15] Symmetrical bisfuroxanylacetylene **9** was synthesized by the reaction of terminal alkyne **7** with 4-nitrofuroxan **1a**.

Notably, the developed alkylation reaction provides a method to access furoxans, bearing other carbon substituents, by means of derivatization of the alkynyl group. Copper-catalyzed Huisgen's cyclization (click chemistry) proceeded smoothly to afford triazole **10** (Figure 3B). This demonstrates the utility of the developed method to readily synthesize furoxans with an arbitrary functional moiety (such as hybrid molecules).[3] Careful tuning of the reaction conditions for the palladium-catalyzed hydrogenation of **2a** enabled selective reduction to both alkyl- and alkenyl furoxan moieties in good yield (Figure 3C).[16] Alkenyl furoxan **12** could be converted by ozonolysis to aldehyde **13**, an important precursor of the well-studied NO-donor cyanofuroxan.[17,5d] Finally, a two-step benzannulation reaction of **7** provided diarylfuroxans **14** (Figure 3D).[18] These are known as COX-2 inhibitors[5b] and potential thiol-independent photo-induced NO-donors.[5c]

In conclusion, a novel, versatile carbon–carbon bond-forming reaction on furoxan rings is reported. The S_NAr reaction of 4-nitrofuroxans with alkynyl lithium reported herein provided the first practical and general procedure for the synthesis of alkynyl furoxans. The afforded alkynyl furoxans can be extensively derivatized, leading to a series of carbon-substituted furoxans, which makes this method a convergent approach to various carbon-substituted furoxans. We believe that this developed synthetic method shows great potential in application to studies using furoxan-based molecules in the fields of material and medical sciences.

We thank JSPS KAKENHI Grant Number JP16K18844, the Naito Foundation, Inoue Science Research Award, NOVARTIS Foundation (Japan) for the Promotion of Science, TOBE MAKI Scholarship Foundation, Kawanishi Memorial ShinMaywa Education Foundation, and Daiichi Sankyo Foundation of Life Science for financial support.

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