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An Unprecedented Formal [5 + 2] Cycloaddition of Nitrones with *o*-Carboryne via Tandem [3 + 2] Cycloaddition/Oxygen Migration/Aromatization Sequence

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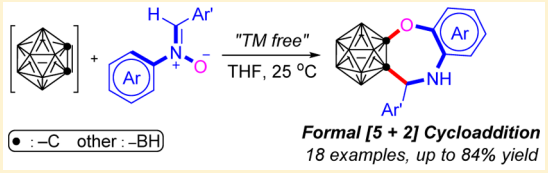
Supporting Information

ABSTRACT: Heterocyclic skeletons are widespread among natural products as well as bioactive molecules. Cycloaddition reaction has created new opportunities to access heterocycles of great complexity due to its advantage of multiple bond formation in a single step. Here, we describe an unprecedented formal [5 + 2] cycloaddition of nitrone with *o*-carboryne to afford carborane-fused seven-membered heterocycles. Experimental and theoretical data suggest that a sequence of [3 + 2] cycloaddition, N−O bond cleavage, oxygen migration and rearomatization is involved in this unprecedented reaction. In this process, the nitrone moieties serve as five-atom coupling partners with both heteroatoms being incorporated into the framework of the final products. This new methodology also offers new insight into the chemistry of nitrones.



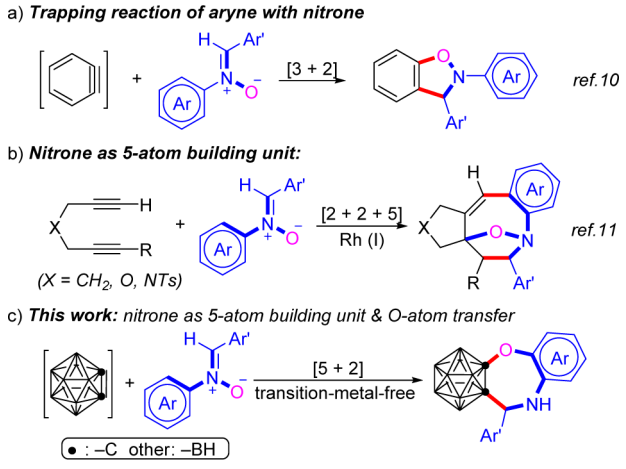
INTRODUCTION

Heterocyclic skeletons are widespread among natural products as well as bioactive molecules. Cycloaddition reaction has created new opportunities to access heterocycles of great complexity due to its advantage of multiple bond formation in a single step.[1] As a result, developing cycloaddition-based synthetic methods for the efficient construction of heterocyclic compounds is becoming a very attractive strategy in modern organic synthesis.[1a−c]

Nitrones have been known for more than a century for their main reactivities as electrophiles toward organometallic reagents and as versatile 1,3-dipolarophiles.[2] Cycloadditions involving nitrones, which allow the incorporation of two heteroatoms into the frameworks in a single step, have maintained a place of prominence in the toolbox of the synthetic chemists and proven to be an efficient approach to various nitrogen-containing heterocycles.[1a,c,3] It has been documented that nitrones can readily undergo [3 + 2],[1c,3a−c,4] [3 + 3],[5,6] [4 + 3],[7] [2 + 2 + 3][8] cycloaddition reactions with a wide range of dipolarophiles. In these studies, nitrones serve exclusively as three-atom building blocks. Moreover, 1,3-diploar cycloadditions of nitrones are also widely used as a trapping reaction for arynes or other related intermediates (Scheme 1a).[9,10] Very recently, a Rh(I)-catalyzed cyclization of diynes with nitrones was reported, in which the nitrone group serves as a five-atom coupling partner to afford bridged eight-membered heterocycles (Scheme 1b).[11] This reaction is initiated by Rh-mediated C−H activation of the *N*-aryl group. To the best of our knowledge, nitrone moieties serve as five-atom building blocks followed by oxygen migration have not been known (Scheme 1c).

On the other hand, carborane (o-$C_2B_{10}H_{12}$), a 3-dimensional relative of benzene, is a class of boron hydride clusters in which one or more BH vertices are replaced by CH units.[12] Owing to their unique properties, functional carboranes are now finding a broad range of applications encompassing organic synthesis, drug design, polymers, cancer therapy, catalysis, metal−organic frameworks, electronic devices and more.[13] 1,2-Dehydro-*o*-carborane or *o*-carboryne (**2**),[14] a 3-dimensional relative of benzyne, has been used as a useful synthon for generating a wide range of functional carboranes over the past 20 years.[15] It can undergo cycloadditions,[16] ene reaction[17] and C−H bond insertion reaction[16a,18] with a variety of organic molecules to

Scheme 1. Cycloadditions Involving Nitrones, Benzyne, and *o*-Carboryne



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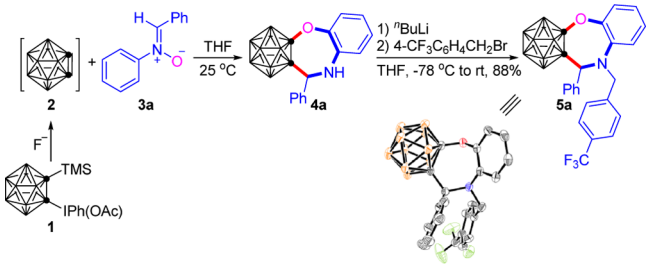
afford a large class of functional carboranes. Cycloadditions involving *o*-carboryne intermediate have been developed to enable the synthesis of various carbocyclic carborane derivatives. However, they are limited to [4 + 2] and [2 + 2] fashions.[15a,b] Dipolar cycloaddition of *o*-carboryne for the synthesis of carborane-fused heterocycles still remains elusive. Herein, we report an unprecedented formal [5 + 2] cycloaddition of nitrones with *o*-carboryne via a sequence of tandem [3 + 2] cycloaddition/oxygen migration/rearomatization to address carborane-fused seven-membered heterocycles (Scheme 1c). Such carborane-fused dihydrobenzo[1,4]-oxazepines may exhibit similar biological activities to those of physiologically active dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives.[19]

RESULTS AND DISCUSSION

Reaction Design and Synthesis of 5a. In our initial investigation, a THF solution of phenyl[*o*-(trimethylsiyl)-carboranyl]iodonium acetate (**1**)[14b,20] was treated with *N*,*α*-diphenyl nitrone (**3a**) in the presence of CsF. After workup, an oily compound **4a** was isolated in 72% yield as the major product with the loss of one aromatic proton, which was indicated by the ^{1}H NMR spectrum. The ^{1}H NMR also suggested that this compound features an active hydrogen (e.g., NH or OH), which can undergo H/D exchange with D_2O.

To gain some structural information on the product, attempts were made to further functionalize this compound. Fortunately, single-crystals suitable for X-ray analysis were obtained from the benzylation reaction of this compound with 4-(trifluoromethyl)benzyl bromide and the corresponding benzylated product was structurally characterized as carborane-fused dihydrobenzo[1,4]oxazepine **5a** (Scheme 2).[21]

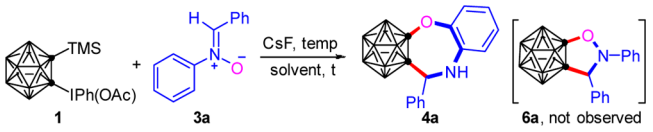
Scheme 2. Synthesis of 5a



Optimization of the reaction conditions showed that both temperature and reaction time were crucial to the yield of **4a**. Higher temperatures or prolonged reaction time dramatically decreased the yields, due to the cage deboronation of the product by fluoride (Table 1, entries 1−4).[22] The solvents also displayed significant influence on the outcome of this reaction. *o*-Carborane (*o*-$C_2B_{10}H_{12}$) was produced quantitatively when acetonitrile was employed as solvent and a complex mixture was obtained if the reaction was performed in dichloromethane (Table 1, entries 5 and 6). Lowering the amount of CsF to 1.0 or 1.5 equiv led to the incomplete conversion of precursor **1** (Table 1, entries 7 and 8). A lower yield was obtained when increasing the amount of nitrone **3a** to 2.0 equiv (Table 1, entry 9).

Substrate Scope. Under the optimal conditions shown in Table 1, entry 1, the scope of this [5 + 2] cycloaddition reaction of *o*-carboryne with various nitrones was examined and the desired cycloadducts were isolated in moderate to high yields (Table 2). Both electron-withdrawing groups (Cl, Br, F, CF_3, NO_2) and electron-donating groups (Me, OMe) on the

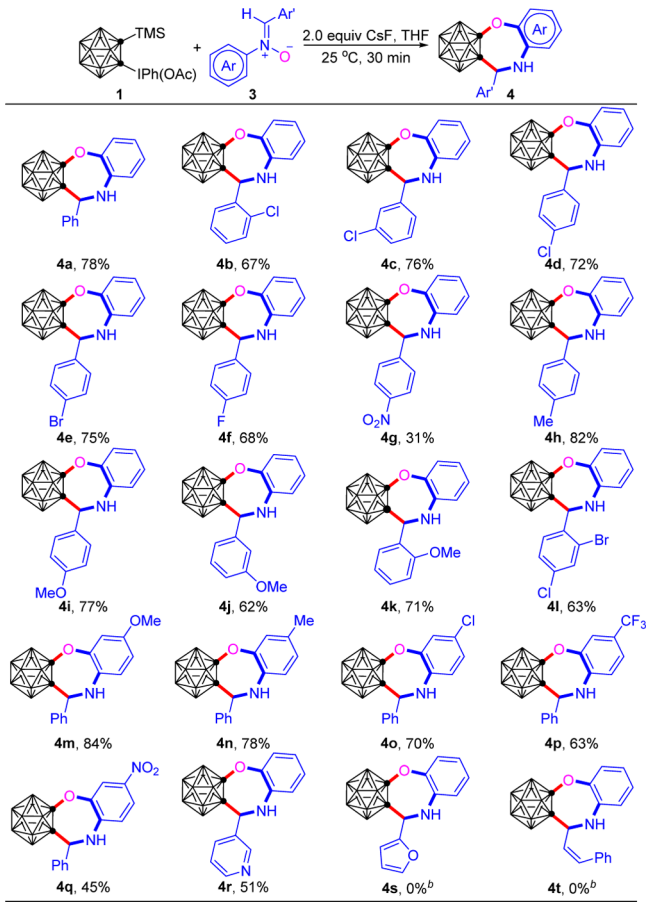
Table 1. Optimization of Reaction Conditions[a]



entry	3a (equiv)	CsF (equiv)	solvent	temp (°C)	t (min)	4a (%)[b]
1	1.1	2.0	THF	25	30	78
2	1.1	2.0	THF	25	120	73
3	1.1	2.0	THF	60	120	50
4	1.1	2.0	THF	60	720	15
5	1.1	2.0	CH_3CN	25	30	-[c]
6	1.1	2.0	CH_2Cl_2	25	30	-[d]
7	1.1	1.0	THF	25	30	45[e]
8	1.1	1.5	THF	25	30	69[e]
9	2.0	2.0	THF	25	30	57
10	1.1	2.0	DME	25	30	75

[a]Reaction conditions: **1** (0.1 mmol), **3a** (0.11 or 0.2 mmol), CsF (0.1, 0.15, or 0.2 mmol), solvent (3 mL). DME = dimethoxyethane. [b]Isolated yields. [c]*o*-Carborane was recovered. [d]Complex mixture. [e]**1** was not completely consumed.

Table 2. Substrate Scope for [5 + 2] Cycloaddition of Nitrones with *o*-Carboryne[a]



[a]Reaction conditions: **1** (0.1 mmol), **3** (0.11 mmol), CsF (0.2 mmol), THF (3 mL); yields of isolated products. [b]Inseparable mixture of products.

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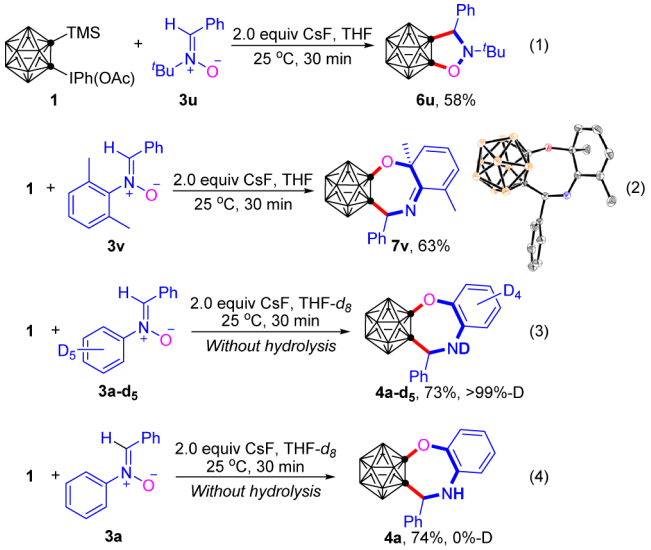
C− and N−aryl rings were well tolerated. In general, nitrones with electron-donating groups tend to result in higher yields than those with electron-withdrawing groups (**4d−g** vs **4h−i**; **4m−n** vs **4o−q**). For instance, reactions of nitrone **3h** and **3m** proceeded smoothly to afford the cycloadducts **4h** and **4m** in >80% yields, whereas only 31% or 45% of the desired product was isolated for nitrone **3g** or **3q** that bears a nitro group, respectively. For nitrone **3r** bearing a 3-pyridyl group, the desired cycloadduct **4r** was obtained in 51% isolated yield. Unfortunately, nitrones **3s** and **3t**, which feature a 2-furyl or a styryl group, respectively, gave inseparable mixtures of products, probably due to the side reaction of the furan[14a] and alkene[17b,23] moieties with *o*-carboryne.

Mechanistic Study. The formation of **4** reveals that an unprecedented rearrangement involving N−O bond cleavage and O atom migration has occurred. To understand the reaction mechanism of this formal [5 + 2] cycloaddition reaction, several control experiments were conducted (Scheme 3). When the *N*-aryl ring is replaced by an alkyl group, for

Scheme 3. Control Experiments



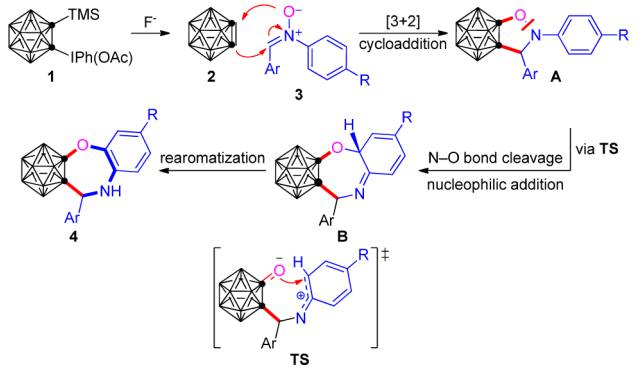
instance, a *tert*-butyl group in **3u**, the desired [5 + 2] cycloadduct was not observed. Instead, a 1,3-dipolar cycloaddition took place to give the corresponding [3 + 2] cycloadduct **6u** in 58% isolated yield, which is similar to the reaction of benzyne[10] with nitrones (Scheme 3, eq 1).

A single compound was isolated from the reaction of *α*-phenyl-*N*-2,6-dimethylphenylnitrone **3v** with **1**, in which the *ortho* positions of the *N*-phenyl ring are blocked by two methyl groups. To our surprise, the ^{1}H NMR spectrum of this compound indicated a single compound with the loss of aromaticity of the original *N*-2,6-dimethylphenyl group and new olefinic protons suggestive of a diene (δ 6.35 (d, J = 6.0 Hz, 1H), 6.11 (dd, J = 9.6 and 6.0 Hz, 1H), 5.98 (d, J = 9.2 Hz, 1H)). These data clearly ruled out the formation of the [3 + 2] cycloadduct. Finally, the structural confirmation of this compound as imine **7v** was obtained by single-crystal X-ray analyses (Scheme 3, eq 2).[21]

The reaction of **1** with deuterium-labeled nitrone **3a−d$_5$** in THF-d_8 was also investigated. The desired product **4a−d$_5$** was obtained with more than 99% deuterium incorporation into the N−H bond (Scheme 3, eq 3). On the other hand, the reaction of **1** with **3a** in THF-d_8 did not afford any deuterated product, suggesting that the D (H) incorporated into the N−H bond of the product comes from the nitrone substrate (Scheme 3, eq 4).

On the basis of these control experiments, we believe that this reaction occurs through a three-step sequential [3 + 2] cycloaddition/oxygen migration/rearomatization mechanism (Scheme 4). A [3 + 2] cycloaddition reaction between

Scheme 4. Proposed Reaction Pathway



diarylnitrone **3** and *o*-carboryne **2**, generated in situ from the precursor **1** in the presence of fluoride, affords the [3 + 2] cycloadduct **A**. Heterolytic cleavage of the N−O bond[6c] gives another intermediate **B** through transition state **TS** in which the nitrenium ion[24] is stabilized by the aryl unit via π conjugation and the oxide is stabilized by the carborane cage via exo π-bonding interaction.[25] Rearomatization of **B** affords the final product **4**.

Computational Analysis of Reaction Pathways. To examine the validity of the above proposed reaction mechanism for this formal [5 + 2] cycloaddition, DFT calculations were conducted (Figure 1). Starting from the [3 + 2] cycloadduct, our calculations show that the proposed N−O bond cleavage/oxygen migration sequence is actually a concomitant (concerted one-step) process. The barrier calculated for this step is only 11.0 kcal/mol, which is consistent with the fact that this reaction is performed at room temperature. The resulting seven-membered ring intermediate **IM-2** is more stable than the [3 + 2] cycloadduct by 11.2 kcal/mol, which agrees well with the experimental isolation of compound **7v**. Starting from the intermediate **IM-2**, the rearomatization process to afford the final product is also calculated. The results show that the H shift process via either [1,3]-H shift or sequential [1,5]-H shift/[1,3]-H shift is very unfavorable due to the high energy barrier. Instead, a CsF assisted deprotonation/protonation process[26] is more favorable, which may also explain why additional base is needed in this reaction (Table 1, entry 1 vs entries 7−8).

The aforementioned results suggest the origin of this new reaction to be that the electron-deficient carborane cage induces the heterolytic cleavage of the N−O bond, in which the resultant oxygen anion is stabilized by the carborane cage[12a,c] via *exo* π-bonding interaction,[25] and the generated nitrenium ion is stabilized by the aryl group through π conjugation.[27] If the carboranyl is replaced by less electron-deficient phenyl, DFT calculations suggest a different rearrangement pathway with the first activation energy being 21.4 kcal mol^{-1}, leading to the formation of 4-oxazoline derivative (see Figure S6 in the Supporting Information).[28]

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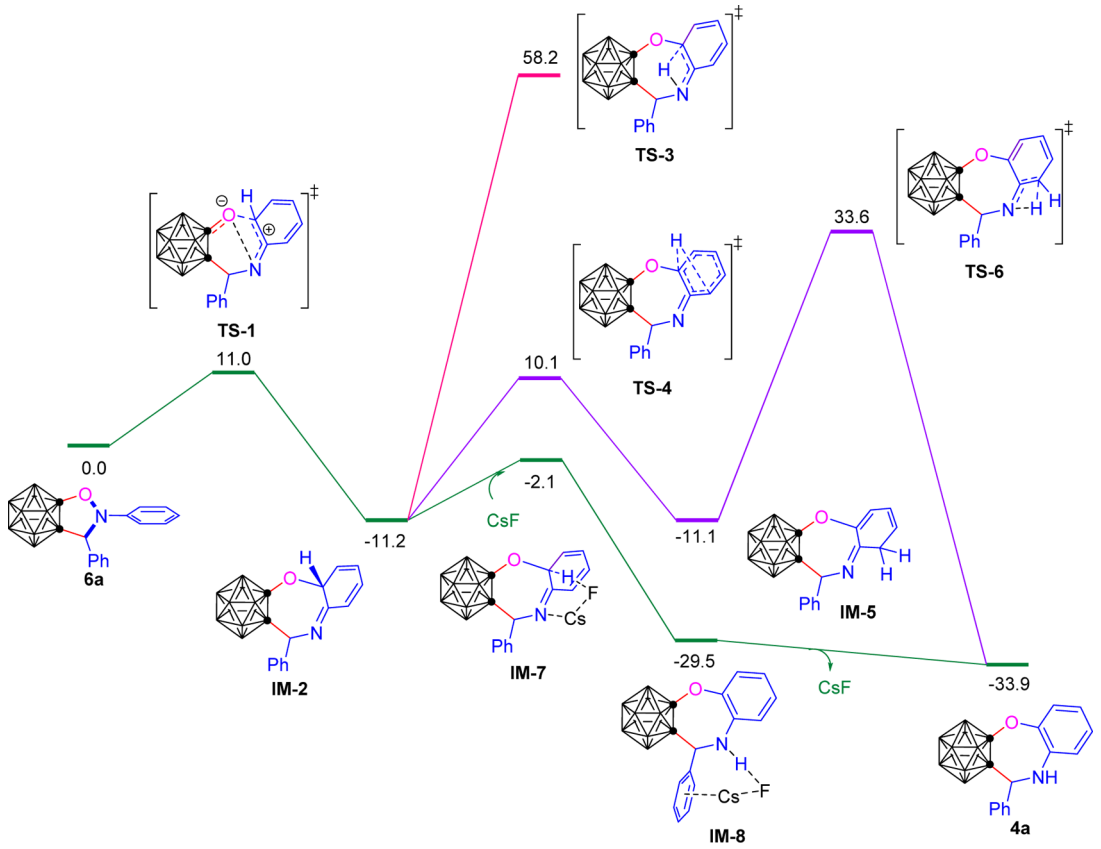

Figure 1. Energy profiles (ΔG_{sol}, kal/mol) calculated for the proposed reaction pathways with relative solvation-corrected free energies in kcal/mol (estimated by optimization at B3LYP level with LANL2DZ basis set used for Cs and 6-31+G(d,p) basis set used for all other atoms, and subsequent single point energy calculation at the same level of theory with consideration of entropy contribution and solvent effect of THF (CPCM model/UAKS radii)).

CONCLUSIONS

In summary, we have described a formal [5 + 2] cycloaddition of nitrone with *o*-carboryne to access carborane-fused seven-membered heterocycles. In this process, nitrones serve as five-atom building units, which is very rare in the literature. Mechanistic studies as well as DFT calculations suggest that a sequence of [3 + 2] cycloaddition/N−O bond cleavage/oxygen migration/rearomatization leads to the final products. Such unprecedented reactivity pattern of nitrones may also be found in other aromatic systems, which can stabilize both the resultant oxide anion and nitrenium ion. This study provides new insight into the chemistry of nitrones. The resultant carborane-fused dihydrobenzo[1,4]oxazepines may exhibit similar biological activities to their benzene analogues.[19]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09074.

Detailed experimental procedures, complete characterization data (PDF)

X-ray data for **5a** and **7v** (CIF)

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Notes

The authors declare no competing financial interest.

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