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RESEARCH ARTICLE

Desulfurdioxidative N-N Coupling of *N*-Arylhydroxylamines and *N*-Sulfinylanilines: Reaction Development and Mechanism

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Abstract: A highly efficient and chemoselective approach for the divergent assembling of unsymmetrical hydrazines through an unprecedented intermolecular desulfurdioxidative N-N coupling is developed. This metal free protocol employs readily accessible *N*-arylhydroxylamines and *N*-sulfinylanilines to provide highly valuable hydrazine products with good reaction yields and excellent functional group tolerance under simple conditions. Computational studies suggest that the *in situ* generated *O*-sulfenylated arylhydroxylamine intermediate undergoes a retro-[2π+2σ] cycloaddition via a stepwise diradical mechanism to form the N-N bond and release SO_2.

Introduction

N-N bond containing compounds, in particular hydrazines, are widely found in a number of pharmaceuticals,[1] natural products,[2] as well as in functional materials (Figure 1a).[3] In addition, hydrazine and its derivatives are key precursors for the preparation of a series of nitrogen-containing heterocycles, such as indoles,[4] indazoles,[5] pyrazoles[6] and triazoles.[7] Due to this, various synthetic strategies for the construction of hydrazine motifs have been developed in the past few decades. The conventional approaches to hydrazine scaffolds include: (1) direct reduction/hydrogenation of azo compounds[8] (Figure 1b, Eq. 1); (2) modification of N-N precursors via C-N bond formation reactions,[9] which often suffered from the generation of metal salt waste, low functional group tolerance or the employment of expensive reagent (Figure 1b, Eq. 2); (3) the catalytic intermolecular N-N bond formation, which remains challenging because most existing methods in this catalog are limited to the assembling of symmetrical tetra-substituted hydrazines or N-N linked bicarbazoles[2b, 10] (Figure 1b, Eq. 3); (4) nitrene-involved intermolecular N-N coupling of *N*-alkylanilines with dioxazolones in the presence of iridium or iron catalysis[11], and Ni-catalyzed N-N cross-coupling of hydroxamates with aryl and aliphatic amines (Figure 1b, Eq. 4);[12] (5) a highly strained P(III)/P(V)-catalyzed intermolecular reductive N-N bond formation of electron-deficient nitroarenes and anilines through a cascade nitro deoxygenation, dehydrative condensation and azoarene reduction process (Figure 1b, Eq. 5).[13] It is highly desired to develop new methods,

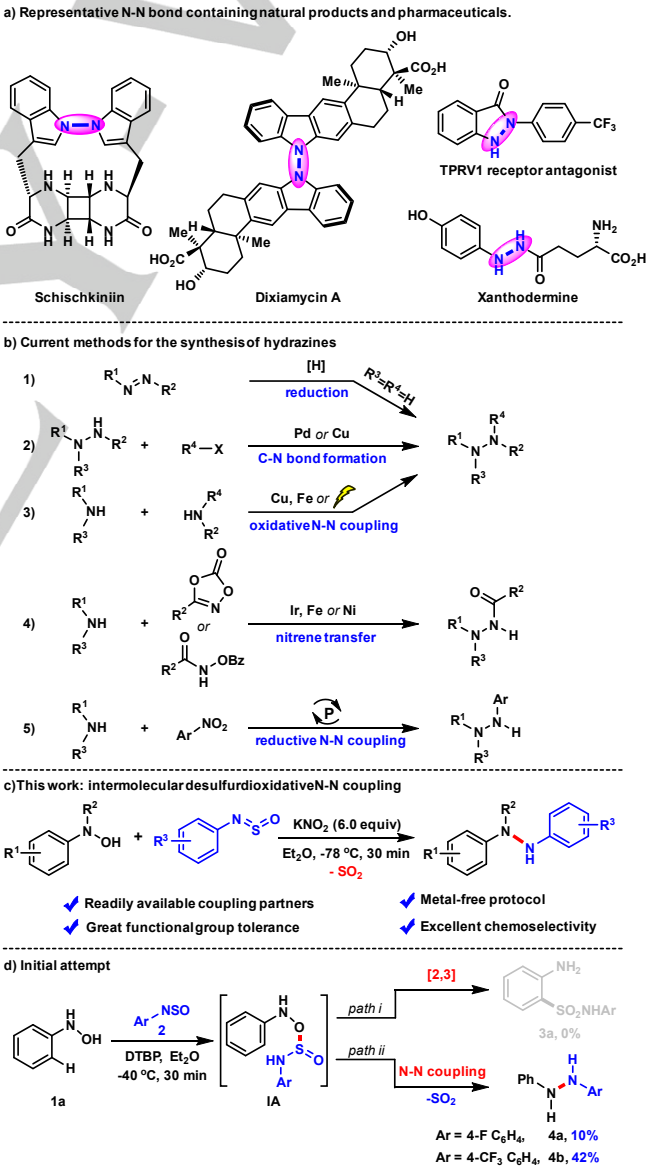

Figure 1. a) Representative N-N bond containing natural products and pharmaceuticals; b) Current methods for the synthesis of hydrazine; c) This

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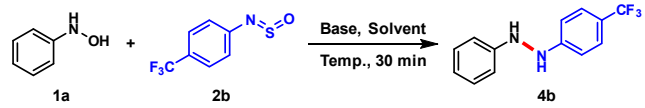
work: intermolecular desulfurdioxidative N-N coupling; d) Initial attempt. DTBP = 2,6-di-*tert*-butylpyridine.

in particular, the direct N-N coupling strategies from readily available materials, for the synthesis of N-N bond embedded molecules, that can avoid the drawbacks in the previous ones (such as using transition-metal catalysts, specialized organocatalysts, stoichiometric excess oxidants or additives, and low functional group tolerance). We present herein a highly selective and efficient metal-free intermolecular desulfurdioxidative N-N coupling of *N*-arylhydroxylamines and *N*-sulfinylanilines for the preparation of highly valuable hydrazine products under very simple conditions (Figure 1c). We have also carried out DFT study of the reaction mechanism, showing that this is an unprecedented retro-[2π+2σ] reaction with loss of SO_2 via a stepwise diradical mechanism.

Results and Discussion

Table 1. Optimization study[a]



Entry	Base	Solvent	Temp.	Yield (%)[b]
1	DTBP	Et_2O	-40 °C	42
2	DTBP	Et_2O	-60 °C	63
3	DTBP	Et_2O	-78 °C	75
4	-	Et_2O	-78 °C	28
5	DTBP	Hexane	-78 °C	34
6	DTBP	CH_2Cl_2	-78 °C	39
7	DTBP	Toluene	-78 °C	29
8	DTBP	THF	-78 °C	27
9	pyridine	Et_2O	-78 °C	28
10	DMAP	Et_2O	-78 °C	48
11	Et_3N	Et_2O	-78 °C	20
12	K_2CO_3	Et_2O	-78 °C	40
13	K_2HPO_4	Et_2O	-78 °C	70
14	KNO_2	Et_2O	-78 °C	80
15	$NaNO_2$	Et_2O	-78 °C	63
16[c]	KNO_2	Et_2O	-78 °C	58
17[d]	KNO_2	Et_2O	-78 °C	55

[a]Reaction conditions: **1a** (0.6 mmol, 3.0 equiv), **2b** (0.2 mmol, 1.0 equiv), base (1.2 mmol, 6.0 equiv), solvent (2.0 mL), N_2. [b]Isolated yield. [c]2.0 equivalents of KNO_2 was employed. [d]2.0 equivalents of **1a** was employed. DMAP: 4-Dimethylaminopyridine.

The present reaction was discovered serendipitously because we initially wanted to achieve the preparation of *ortho*-sulfonylated aniline **3a** through the cascade *O*-sulfinylation and concerted [2,3]-sigmatropic rearrangement between phenylhydroxylamine **1a** and *N*-sulfinylaniline **2a** in the presence of DTBP (Figure 1d, path i).[14] Instead of obtaining the expected product **3a**, 10% yield of diarylhydrazine **4a**, which might be furnished through a desulfurdioxidative N-N coupling process, was isolated (Figure 1d, path ii). Increasing the electrophilicity of *N*-sulfinylaniline by employing the *para*-CF_3 substituted substrate **2b** resulted in the higher yield (42%) of the corresponding *N,N'*-diarylhydrazine product **4b** (Figure 1d, path ii).

Encouraged by the aforementioned results, we started the optimization study by choosing phenylhydroxylamine **1a** and *N*-sulfinylaniline **2b** as model substrates to evaluate this noncanonical desulfurdioxidative N-N coupling (Table 1, for more detailed optimization results, see the Supporting Information.). After systematic screening of temperatures, solvents and bases, we serendipitously found that the employment of KNO_2 could furnish the desired product **4b** in 80% yield in Et_2O at -78 °C for 30 minutes (Table 1, entries 1-14). Switching to $NaNO_2$, reducing the loading of KNO_2 or hydroxylamine **1a** resulted in lower yields of the corresponding product (Table 1, entries 15-17). Thus, the combination of 3.0 equivalents of arylhydroxylamine **1a** with 0.2 mmol of *N*-sulfinylaniline **2b** in the presence of 6.0 equivalents of KNO_2 in Et_2O solution at -78 °C for 30 minutes was selected as the optimal reaction conditions for this cascade transformation (Table 1, entry 14).

With the optimized conditions in hand, the generality of this metal-free desulfurdioxidative N-N coupling to give *N,N'*-diarylhydrazine products was examined. A wide array of *N*-arylhydroxylamines with diverse substituents was investigated at the outset. As shown in Figure 2, *para*-, *meta*-, and *ortho*-substituted *N*-phenylhydroxylamines bearing both electron-donating and electron-withdrawing groups react smoothly with CF_3-substituted *N*-sulfinylaniline **2b** to deliver *N,N'*-diarylhydrazines **4b**-**4p** in moderate to excellent yields. 2,5-di, 3,5-di and 2,3,5-trisubstituted *N*-phenylhydroxylamines were amenable to this cascade protocol to afford the corresponding products **4q**-**4x** under standard conditions. In addition, *N*-naphthylhydroxylamine and *N*-heteroaryl, such as *N*-isoquinolinyl, *N*-pyridyl and *N*-dibenzofuranyl hydroxylamine could also be tolerated albeit with relatively lower yields (**4y**-**4ab**). Interestingly, when *N*-alkyl, *N*-phenylhydroxylamine was subjected to the reaction conditions, 71% yield of the expected *N,N,N'*-trisubstituted hydrazine product **4ac** was obtained. It is worth noting that *N*-phenylhydroxylamines tethered natural product or pharmaceutical-relevant scaffold, including fenchol, adamantanol, menthol and diacetonefructose, could also be efficiently converted into the corresponding *N,N'*-diarylhydrazine products **4ad**-**4ag** in moderate to good yields. The X-ray diffraction was conducted to confirm the structure of compound **4af** (For details, see the Supporting Information).[15]

Next, we turned our attention to the generality and limitation of *N*-sulfinylaniline with *N*-phenylhydroxylamines under standard reaction conditions. The results showed that *N*-sulfinylaniline bearing electron-neutral group (**4ah**) and moderate electron-withdrawing groups, such as halogens, ester, cyano group and CF_3, could proceed well to generate the corresponding products **4a** and **4ai**-**4au** in moderate to good yields. To our surprise, *N*-sulfinylamine bearing other electron-withdrawing groups, such as benzoyl (**2n**), sulfonyl (**2o**) and ester (**2p**-**2q**) groups, were not amenable to this protocol under the standard conditions (For details, see the Supporting Information).

For the sake of completing the two steps of aniline *N*-sulfinylation and the subsequent desulfurdioxidative N-N coupling process in one-pot, we tried to prepare several *N,N'*-diarylhydrazine products from more readily available anilines and thionyl chloride. We were pleased to find that this one-pot, two-

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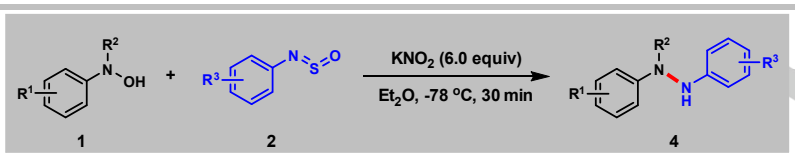
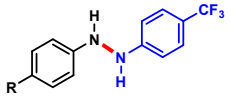


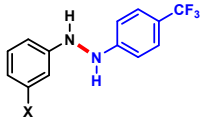
Variation of arylhydroxylamine coupling partner



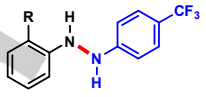
4b, R = H, 80%

4c, R = Me, 66%
4d, R = Et, 89%
4e, R = Ph, 53%
4f, R = F, 57%

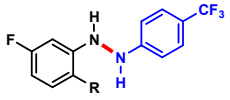
4g, R = Cl, 48%
4h, R = Br, 54%
4i, R = I, 61%
4j, R = CF_3, 58%



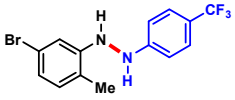
4k, X = Me, 56%
4l, X = F, 50%
4m, X = Cl, 70%
4n, X = Br, 71%



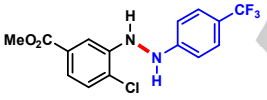
4o, R = Cl, 89%
4p, R = CO_2Et, 55%



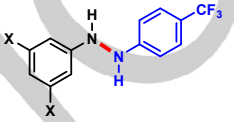
4q, R = F, 42%
4r, R = Me, 52%
4s, R = OMe, 40%



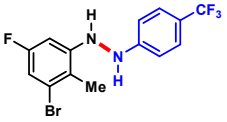
4t, 51%



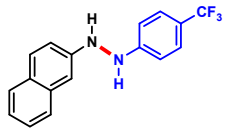
4u, 66%



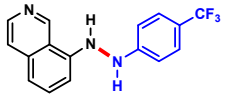
4v, X = Cl, 79%
4w, X = Br, 44%



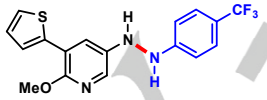
4x, 50%



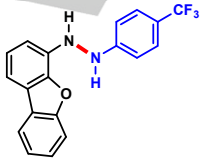
4y, 71%



4z, 51%

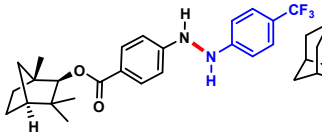


4aa, 44%

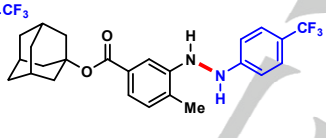


4ab, 54%

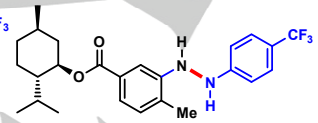
4ac, 71%



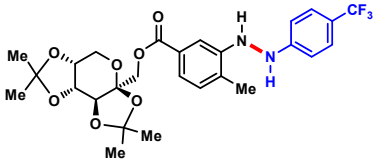
4ad, 53%



4ae, 52%

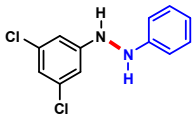


4af, 40%
X-ray CCDC: 2236222

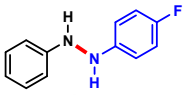


4ag 67%

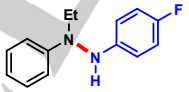
Variation of sulfinylaniline coupling partner



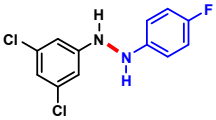
4ah, 42%



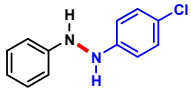
4a, 52%



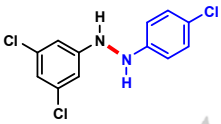
4ai, 67%



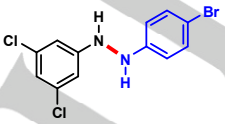
4aj, 42%



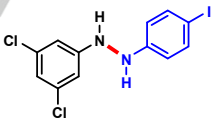
4ak, 61%



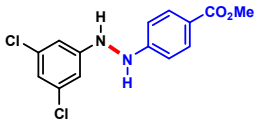
4al, 57%



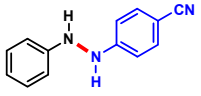
4am, 42%



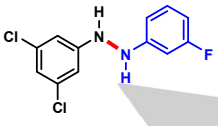
4an, 49%



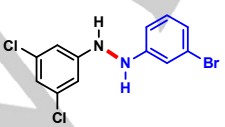
4ao, 54%



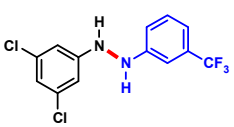
4ap, 59%



4aq, 41%



4ar, 64%



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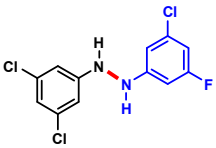
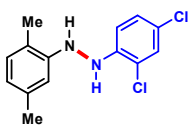


4at, 57%



4au, 42%

Figure 2. Substrate scope. Reaction conditions: **1** (0.6 mmol, 3.0 equiv), **2** (0.2 mmol, 1.0 equiv), KNO_2 (1.2 mmol, 6.0 equiv), Et_2O (2.0 mL), -78 °C, N_2, 30 minutes. Yields of isolated products

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step strategy could be successfully achieved without the purification of moisture-sensitive *N*-sulfinylanilines **2** and afford the corresponding *N,N'*-diarylhydrazine products **4** in reasonable yields and excellent chemoselectivity under standard conditions (Figure 3).

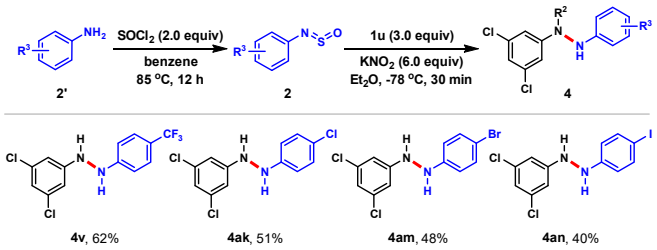

Figure 3. One-pot, two-step protocol for the synthesis of hydrazine **4**. Reaction conditions for step one: **2'** (0.2 mmol, 1.0 equiv), $SOCl_2$ (0.4 mmol, 2.0 equiv), benzene (2.0 mL), 85 °C, N_2, 12 h. Reaction conditions for step two: **1u** (0.6 mmol, 3.0 equiv), KNO_2 (1.2 mmol, 6.0 equiv), Et_2O (2.0 mL), -78 °C, N_2, 30 minutes. Yields of isolated products.

To gain some mechanistic insights into this novel transformation, several control experiments were carried out (Figure 4). Firstly, the competing experiment of phenylhydroxylamines **1b** and **1i** with *para*-CF_3 substituted *N*-sulfinylaniline **2b** was conducted, and the result revealed that the more nucleophilic phenylhydroxylamine **1b** was more reactive to generate the corresponding *N,N'*-diarylhydrazine **4c** in a higher yield [Figure 4, Eq. (1)]. The competition experiment of phenylhydroxylamine **1u** with two different *N*-sulfinylanilines **2a** and **2b** was also set up, 4% of *N,N'*-diarylhydrazine **4ah** and 31% of *N,N'*-diarylhydrazine **4v** could be isolated, indicating the more electrophilic *para*-CF_3 substituted *N*-sulfinylaniline **2b** was much more reactive than *N*-sulfinylaniline **2a** [Figure 4, Eq. (2)]. In addition, we found that the desired product **4b** could still be obtained in a good yield in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), illustrating the free radical pathway might not be involved in this transformation [Figure 4, Eq. (3)].

Based on the aforementioned experimental results, we studied the mechanism of this unique cascade transformation through computational chemistry. Experimentally, 6 equivalents of KNO_2 were used, leading us to hypothesize that the solvated KNO_2 helps the formation of **A** (Figure 5). We further proposed that, NO_2 anion and the substrates can form various complexes through hydrogen bonding before reaching **A**.[16] These complexes could be in equilibrium. Here we just considered one possible pathway to form **A**, with a reasonable assumption that various alternative and similar pathways could also easily reach **A**. Without KNO_2, formation of **A** was slow and the reaction yield was not satisfactory, supporting the proposed pathway shown below.

Figure 5 details the possible way for the formation of the key intermediate **A** assisted by base. The reaction starts from the formation of the complex **Int1**, which has hydrogen bonding and π-π stacking between **1a** and **2b**. Then, a NO_2 anion enters, giving complex **Int2**. Subsequently, deprotonation of **1a** accompanied with a nucleophilic attack occurs to afford **Int3** via a concerted transition state **TS1,** requiring an activation free energy of 3.0 kcal/mol. Finally, proton transfer through **Int4** forms intermediate **A**, which has a π-π stacking in its structure. The whole process to form **A** is easy and is slightly exergonic by 2.5 kcal/mol.

Then we studied the mechanism of N-N coupling from **A**. DFT calculations found that **A** could undergo a retro-[2π+2σ] reaction via a stepwise diradical mechanism or a $6e^-$ pseudo-pericyclic reaction via a concerted transition state, to give the N-N coupling product (Figure 5). First, the σ-bond homolysis of **A** takes place through an open-shell diradical transition state **TS2** (<S^2>=0.54), requiring an activation free energy of 7.9 kcal/mol, giving the diradical intermediate **Int5** (<S^2>=0.91). Then **Int5** undergoes N-N coupling easily via **TS3** (<S^2>=0.88), requiring an activation free energy of 1.3 kcal/mol, giving product **4b**. In the first step, the spin density in **TS2** shows that the diradicals are distributed in the two anilines and oxygen atoms, indicating that both N-O bond and N-S bond are breaking and the S=O π bond is forming. Analysing the spin densities in **Int5** and **TS3** in the subsequent step shows that the diradicals are concentrated within the two anilines. This indicates that the N-S bond is completely broken after the first step, allowing the coupling of two aniline radicals to form the N-N σ bond. Thus, we named this reaction as a stepwise retro-[2π+2σ] reaction since the backward reaction of **4b** with SO_2 can be envisioned as the π bond of S=O in SO_2 reacted with the σ-bond of N-N in **4b**. Many [2π+2σ] reactions (through a stepwise mechanism) have been documented in the literature.[17]

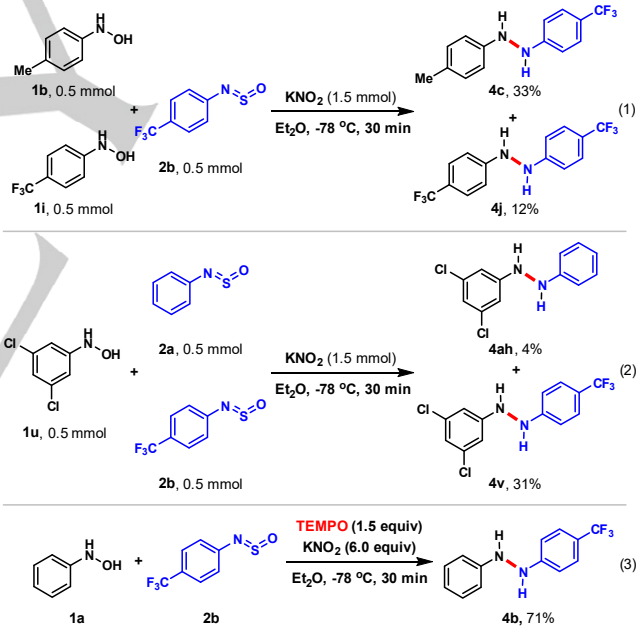

Figure 4. Control experiments.

On the other hand, we can locate a close-shell concerted transition state **TS2'** with π-π stacking, which requires an activation free energy of 13.5 kcal/mol to reach **4b** from **A**. IRC calculations demonstrate that **TS2'** lead directly to the product **4b**, and IBO analysis along IRC shows the electron flow from σ(N-O) orbital to π(S=0) orbital, σ(N-S) orbital to the n(N) orbital, and the n(N) orbital to σ(N-N) orbital (see SI for the IBO analysis[18]). Thus, **TS2'** could be regarded as a $6e^-$ pseudo-pericyclic reaction.[19] However, **TS2'** is higher in terms of free energy than **TS2** by 5.6 kcal/mol and is disfavored. We attribute this to the tight transition state that is not entropically favoured

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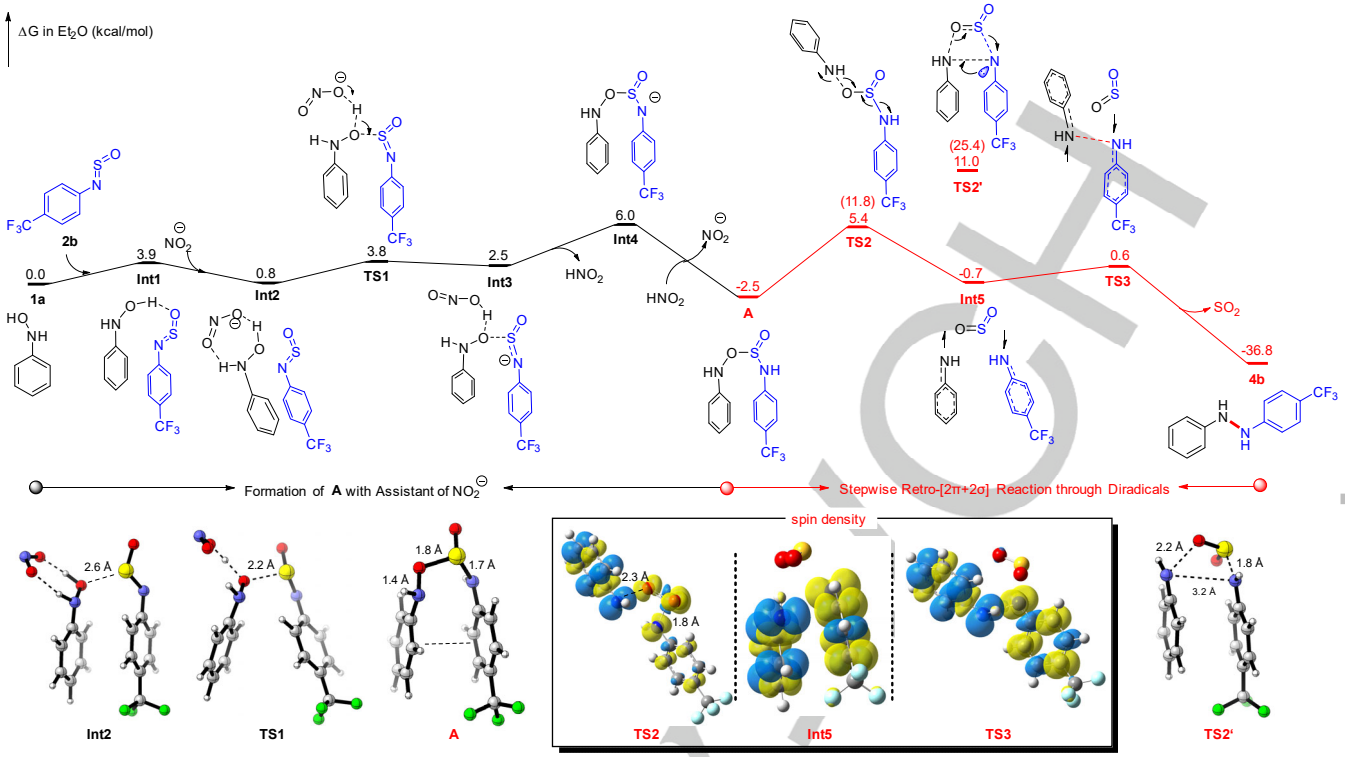

Figure 5. The proposed Gibbs free energy surface for the *N-N* coupling reactions between *N*-arylhydroxylamines and *N*-sulfinylanilines. The formation of **A** (black line) was computed at the SMD(Et_2O)/ωB97M-V/ma-def2-QZVP//B3LYP-D3(BJ)/6-311+G(d,p) level. The retro-[2π+2σ] reactions (red line) was computed at the SMD(Et_2O)/(U)B3LYP-D3(BJ)/ma-def2-QZVP and SMD(Et_2O)/DMRG-PDFT/cc-PVTZ with a (22e, 19o) active space (shown in parentheses) based on the optimized structures at (U)B3LYP-D3(BJ)/6-311+G(d,p). The box shows the spin density distributions (isovalue=0.002).

($\Delta\Delta E^{\ddagger}$=0.6 kcal/mol while $\Delta\Delta G^{\ddagger}$=5.6 kcal/mol for **TS2** and **TS2'**). The concerted four-member ring transition state without π-π stacking does not have a stable wavefunction and can be ruled out. Thus, this N-N coupling reaction takes place through a stepwise diradical mechanism, named retro-[2π+2σ] reaction.

As shown in Figure 5, σ-bond homolysis in this retro-[2π+2σ] reaction is the rate-determining step. We used different methods to study the activation free energy of this step, which is very sensitive (see SI for the details of benchmark study). This could be understood because the single-reference method (U)DFT has shortcomings on the open-shell singlet diradicals.[18a] The hybrid functional (U)B3LYP has been shown to perform well for open shell species[20] and gives a very low activation free energy of this σ-bond homolysis of 7.9 kcal/mol. The multi-reference method DMRG-PDFT[21] with a (22e, 19o) active space was also carried out, suggesting a 14.3 kcal/mol of activation free energy of **TS2** ($t_{1/2}$=0.18 hour at -78 °C with 14 kcal/mol of activation free energy). Thus, the retro-[2π+2σ] reaction through σ-bond homolysis could take place fast at -78 °C. As shown in Figure 5 (spin density), the aniline-type substrates are really required, because both aromatic rings can stabilize the formed nitrogen radicals in retro-[2π+2σ] reaction through conjugation effect. Our calculation also found that the σ-bond homolysis using a *N*-alkylhydroxylamine **12** and *N*-arylsulfinylaniline **2b** through **TS2-Bn** (<S^2>=0.68) requires an activation free energy of 21.5 kcal/mol, which can explain why other species failed at -78 °C (see SI for details). We have also considered the expulsions of CO_2 and SO_3 instead of SO_2 from hypothesized substrates through DFT calculations and experiments, suggesting that expulsions of SO_2 from **A** is crucial for this retro-[2π+2σ] reaction (see SI for details).

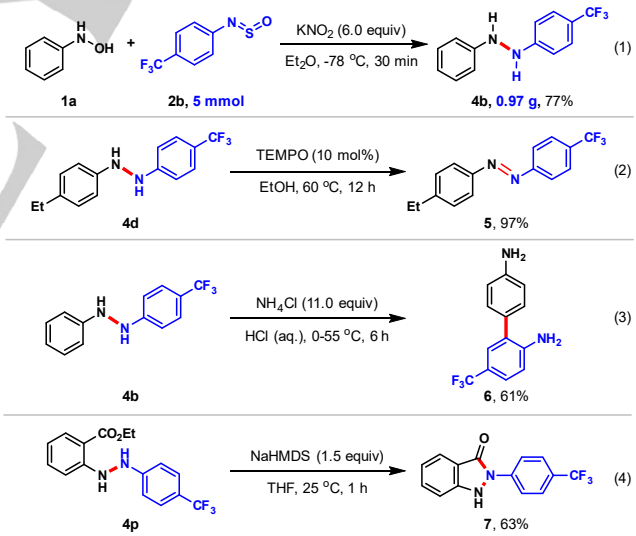

Figure 6. Gram-scale reaction and synthetic applications. TEMPO = 2,2,6,6-tetramethylpiperidoxyl; NaHMDS = sodium bis(trimethylsilyl)amide.

To evaluate the synthetic practicability of this novel cascade transformation, a large scale reaction of phenylhydroxylamine **1a** with *N*-sulfinylaniline **2b** was successfully carried out, furnishing the corresponding *N,N'*-diarylhydrazine **4b** in 77% yield under standard conditions [Figure 6, Eq. (1)]. To demonstrate the synthetic application of the newly formed *N,N'*-diarylhydrazine products, **4b**, **4d** and **4p** were selected as representatives to be manipulated into other useful functional molecules under different conditions as presented in Figure 6. For instance, *N,N'*-diarylhydrazine **4d** could be readily converted into the corresponding diazo compound **5** in excellent yield in the presence of TEMPO [Figure 6, Eq. (2)];[22] biaryl compound **6**, was

generated in 61% yield through the acid-promoted benzidine rearrangement of **4b** [Figure 6, Eq. (3)].[23] Fortunately, indazolone **7**, which was a bioactive TPRV1 receptor antagonist,[1a] could be directly prepared in 63% yield through the intramolecular cyclization of *N,N′*-diarylhydrazine **4p** in the presence of NaHMDS [Figure 6, Eq. (4)].[13]

Conclusion

In summary, we have described a novel and practical strategy for N-N bond construction through an unprecedented intermolecular cascade *O*-sulfination and desulfurdioxidative N-N coupling pathway under metal and oxidant free conditions. This method offers an efficient synthetic route to access structurally diverse *N,N′*-diaryl hydrazine scaffolds from readily available *N*-arylhydroxylamines and *N*-sulfinylanilines with excellent chemoselectivity and great functional group tolerance. The newly synthesized hydrazine motif could be efficiently converted into various functional molecules under different reaction conditions. Theoretical study suggests that the *in situ* generated *O*-sulfenylated arylhydroxylamine intermediate, which is promoted by KNO_2, undergoes a stepwise diradical pathway with the extrusion of SO_2 and forms the N-N bond, named as a stepwise retro-[2π+2σ] reaction here. Further potential application in medicinal chemistry and evaluation of other utility of the current method are undergoing in this laboratory.

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Conflict of interest

The authors declare no competing financial interest.

Keywords: *N*-arylhydroxylamines • *N*-sulfinylanilines • N-N coupling • retro-[2π+2σ] cycloaddition • *N,N′*-diaryl hydrazines

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[15] Deposition Numbers 2236222 (for **4af**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures

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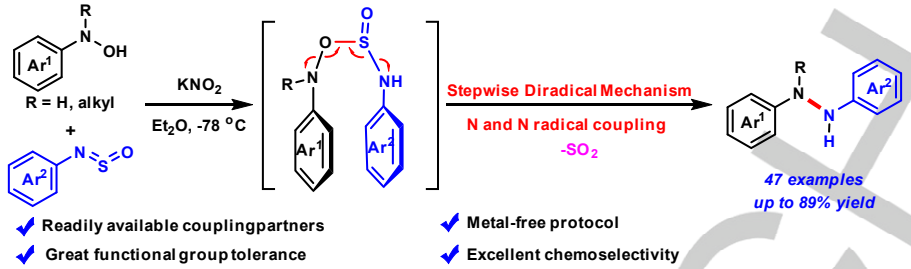
Desulfurdioxidative N-N Coupling of *N*-Arylhydroxylamines and *N*-Sulfinylanilines: Reaction Development and Mechanism



This article describes a novel and practical strategy for N-N bond construction. The strategy involves an unprecedented intermolecular cascade *O*-sulfination and desulfurdioxidative N-N coupling (via stepwise retro-[2π+2σ] cycloaddition, supported by quantum chemistry calculations) from readily available *N*-arylhydroxylamines and *N*-sulfinylanilines under metal and oxidant free conditions.