Radical Cyclization

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Transition from π Radicals to σ Radicals: Substituent-Tuned Cyclization of Hydrazonyl Radicals**

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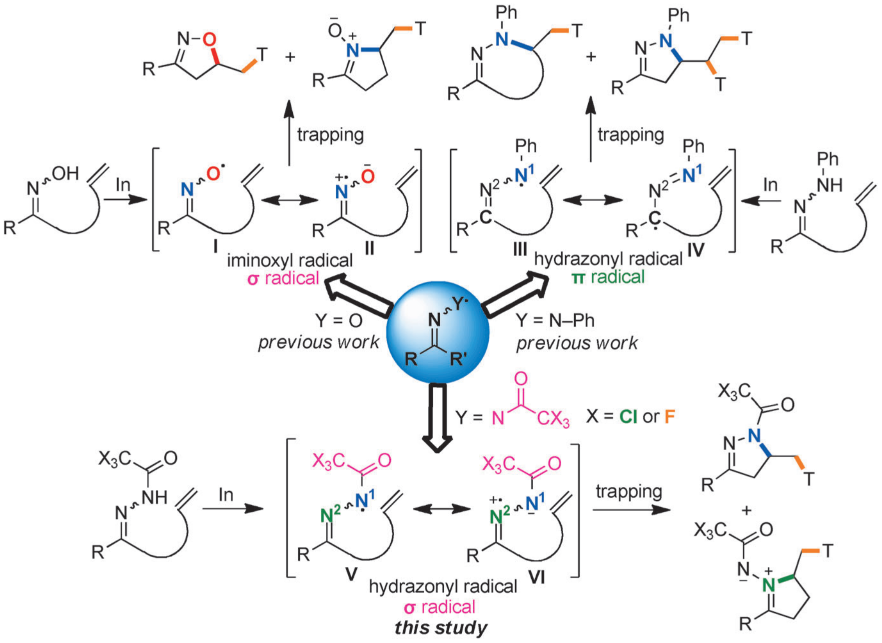
Abstract: *Hydrazonyl radicals are known for their π-electronic structures; however, their σ-electronic structures have not been reported as yet. Herein, we show that readily accessible β,γ- and γ,δ-unsaturated N-trichloroacetyl and N-trifluoroacetyl hydrazones can be conveniently converted into hydrazonyl σ radicals, which subsequently undergo 5-exo-trig radical cyclization at the N*^{1} *or N*^{2} *atom to form pyrazolines and azomethine imines, respectively.*

Hydrazonyl and iminoxyl radicals have been known for a long time. Although they have similar molecular structures, the electronic properties of these two kinds of radicals are totally different. Iminoxyl radicals are σ radicals with the single-electron spin delocalized on both the O and the N atom.[1] In other words, two resonance structures **I** and **II** can be drawn for iminoxyl radicals (Scheme 1, top left). On the other hand, hydrazonyl radicals are ordinarily referred to as π radicals, which means that the spin density is delocalized on the π orbital of the N^{1} atom and conjugated C atom, but not on the N^{2} atom.[2] Thus, hydrazonyl radicals are represented with resonance structures **III** and **IV**, different from those of iminoxyl radicals (Scheme 1, top right).

Recently, we confirmed the electronic properties of these two kinds of radicals by computational and experimental studies.[3] We demonstrated that β,γ- and γ,δ-unsaturated ketoximes can be converted into the corresponding iminoxyl radicals, which behave as oxygen-centered radicals as well as nitrogen-centered radicals. Consequently, 5-*exo*-trig radical cyclizations[4] can take place at both the O and the N atom, depending on the position of the carbon–carbon double bond (Scheme 1, top left).[3a] On the other hand, the hydrazonyl radicals derived from *N*-phenyl-substituted β,γ- and γ,δ-unsaturated hydrazones under similar conditions only undergo the respective 5-*exo*-trig, 6-*exo*-trig, and (or) tandem 1,5-H shift/5-*exo*-trig cyclization at the N^{1} atom, thus indicating that these *N*-phenyl-substituted hydrazonyl radicals are π radicals (Scheme 1, top right).[3b,5]



Scheme 1. Top left: Cyclizations of iminoxyl radicals, and their two resonance structures **I** and **II**. Top, right: Cyclizations of hydrazonyl radicals, and their two resonance structures **III** and **IV**. Bottom: Cyclizations described herein of hydrazonyl σ radicals, and their two resonance structures **V** and **VI**. In = initiation, T = radical-trapping moiety.

As free radicals containing two heteroatoms, iminoxyl radicals have been studied extensively.[6] However, studies on hydrazonyl radicals have rarely been reported. Could hydrazonyl radicals also behave like iminoxyl radicals? Could the N^{2} atom also be tuned as a radical center to undergo radical cyclizations? To answer these questions, we conducted studies to further explore the nature and diverse reactivity of hydrazonyl radicals. We anticipated that the substituent might affect the delocalization of spin density and thus change the hydrazonyl radical from a π radical to a σ radical. Indeed, our theoretical and experimental studies both confirm that the electronic structure of hydrazonyl radicals can

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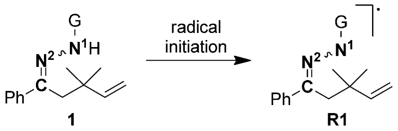
be adjusted by varying the substituent on the N^1 atom. Thus, *N*-trichloroacetyl and *N*-trifluoroacetyl hydrazonyl radicals behave as σ radicals: for these radicals incorporating β,γ-unsaturation, 5-*exo*-trig cyclization at the N^1 atom was found to take place, whereas their γ,δ-unsaturated counterparts underwent 5-*exo*-trig cyclization at the N^2 atom (Scheme 1, bottom). These radicals can be conveniently generated from the corresponding hydrazones by using TEMPO$^+$BF$_4^-$ as the oxidant and Cs$_2$CO$_3$ as the base. Our results demonstrate for the first time that hydrazonyl radicals can be tuned to behave as σ radicals by changing the substituent at the N^1 atom.[7]

At the beginning of this study, variously N-substituted γ,δ-unsaturated hydrazones **1** were used as model compounds to calculate (Gaussian 09, DFT calculations at the B3LYP/6-31+G(d) level) the spin density delocalized on their corresponding hydrazonyl radicals **R1**.[8] The results are summarized in Table 1. It is clear that the phenyl-substituted hydrazonyl radical **R1a** is a typical π radical (Table 1, entry 1, and Figure 1), which is consistent with our previous observation.[3b] However, as the strength of the electron-withdrawing capacity of the substituent increased, the spin density located on the C atom decreased dramatically from 0.29 to −0.05; at the same time, the spin density on the N^2 atom increased significantly from 0.04 to 0.38 (Table 1, entries 2–9). The mesyl group is an exception, probably as a result of its steric effect. In particular, when trichloroacetyl and trifluoroacetyl groups were incorporated in the hydrazone, the corresponding radicals became σ radicals because the single-electron spin density was located on both the N^1 atom (0.44; 0.41) and N^2 atom (0.35; 0.38), rather than the C atom (Table 1, entries 8 and 9, and Figure 1).[9] The observed transition from π radicals to σ radicals might be attributed to the negative charge on the N^1 atom in the resonance structure **VI**. This negative charge can be delocalized onto the carbonyl oxygen atom and can spread further owing to the inductive effect of the CX$_3$ group (Scheme 1, bottom). Therefore, on the basis of the computational studies, hydrazonyl radicals can be divided into three types: 1) π radicals (**R1a–c**); 2) σ radicals (**R1g–i**); 3) σ+π mixed radicals (**R1d–f**).

Table 1: Substituent-tuned spin-density delocalization on the N^1, N^2, and C atoms of γ,δ-unsaturated hydrazonyl radicals.[a]



Entry	G	Spin density on **R1**				Radical type
		N^1	N^2	C	Δ[b]	
1	Ph (**1a**)	0.56	−0.01	0.23	0.57	π
2	Me (**1b**)	0.61	0.04	0.29	0.57	π
3	*t*Bu (**1c**)	0.59	0.10	0.20	0.49	π
4	H (**1d**)	0.62	0.16	0.17	0.46	σ+π
5	CF$_3$ (**1e**)	0.55	0.17	0.23	0.38	σ+π
6	mesyl (**1f**)	0.56	0.18	0.19	0.38	σ+π
7	benzoyl (**1g**)	0.52	0.28	0.04	0.24	σ[c]
8	trichloroacetyl (**1h**)	0.44	0.35	−0.04	0.09	σ[c]
9	trifluoroacetyl (**1i**)	0.41	0.38	−0.05	0.03	σ[c]

[a] Calculated Mulliken spin-density values. [b] Δ is the difference in spin density between N^1 and N^2. [c] This denotation indicates that the spin-bearing orbital is orthogonal to the adjacent C=N double bond.

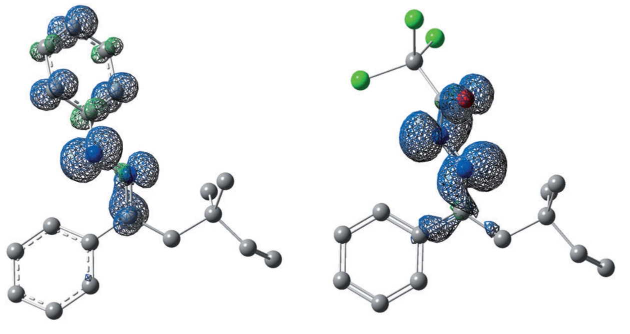
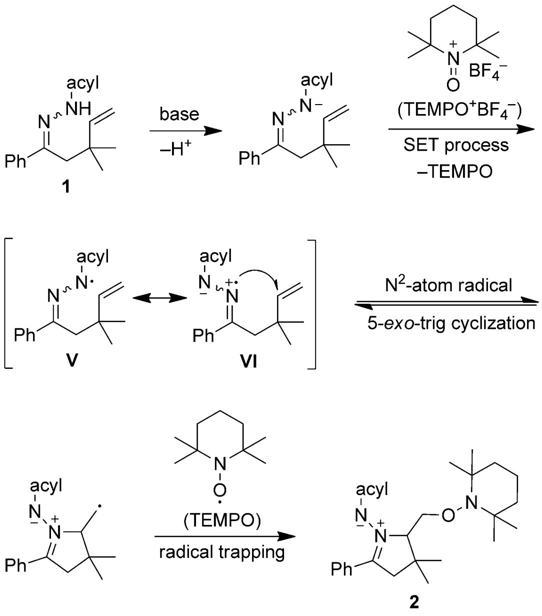
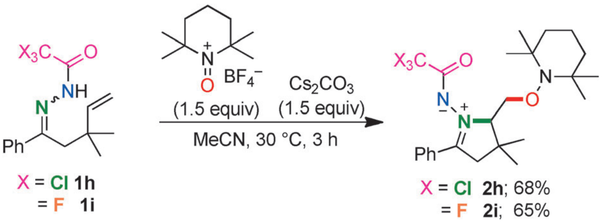


Figure 1. Calculated Mulliken spin-density maps of hydrazonyl π radical **R1a** (left) and σ radical **R1h** (right). Blue grid lines indicate regions of positive spin density, and green grid lines indicate regions of negative spin density.

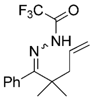
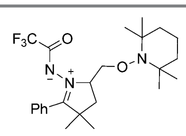
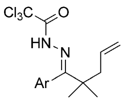
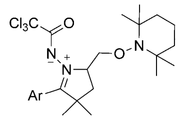
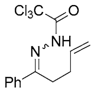
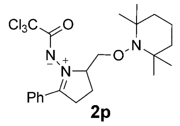
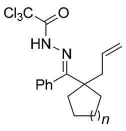
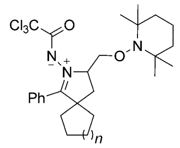
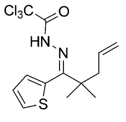
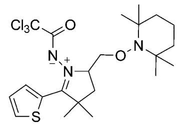
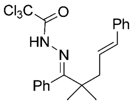
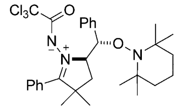
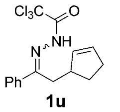
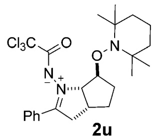
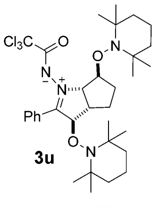
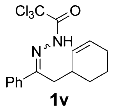
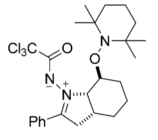
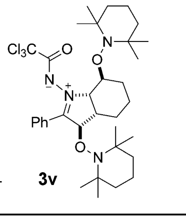


Scheme 2. Proposed mechanism for 5-*exo*-trig cyclizations at the N^2 atom of hydrazonyl σ radicals



Scheme 3. Hydrazonyl-σ-radical-promoted 5-*exo*-trig cyclizations at the N^2 atom.

Table 2: Hydrazonyl-σ-radical-promoted N^2-atom 5-*exo*-trig cyclization for the synthesis of azomethine imines.[a]

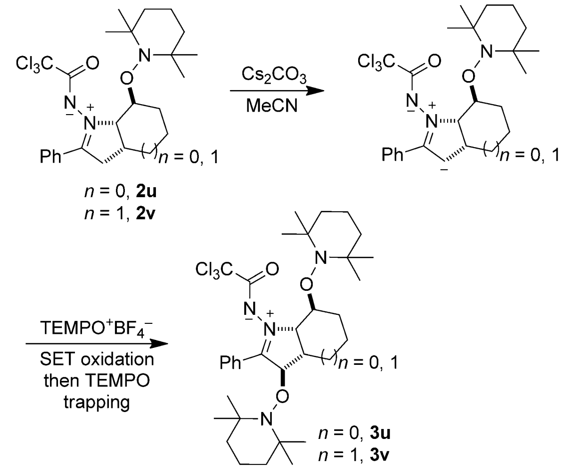
Entry	Substrate	Products	Yield [%][b]
1	 **1j**	 **2j**	83
			
2	Ar = Ph **1k**	Ar = Ph **2k**	88
3	Ar = *p*-MeOC$_6$H$_4$ **1l**	Ar = *p*-MeOC$_6$H$_4$ **2l**	82
4	Ar = *p*-MeC$_6$H$_4$ **1m**	Ar = *p*-MeC$_6$H$_4$ **2m**	81
5	Ar = *p*-ClC$_6$H$_4$ **1n**	Ar = *p*-ClC$_6$H$_4$ **2n**	85
6	Ar = *m*-BrC$_6$H$_4$ **1o**	Ar = *m*-BrC$_6$H$_4$ **2o**	78
7	 **1p**	 **2p**	68
			
8	*n* = 1 **1q**	*n* = 1 **2q**	82
9	*n* = 2 **1r**	*n* = 2 **2r**	87
10	 **1s**	 **2s**	72
11	 **1t**	 **2t**	91 95:5[c,d]
12[e]	 **1u**	 **2u** +  **3u**	3 (**2u**) >99:1[c,d] 68 (**3u**) >99:1[c,d]
13[e]	 **1v**	 **2v** +  **3v**	14 (**2v**) >99:1[c,d] 63 (**3v**) >99:1[c,d]

[a] All reactions were carried with a hydrazone **1** (0.5 mmol), TEMPO$^+$BF$_4^-$ (0.75 mmol), and Cs$_2$CO$_3$ (0.75 mmol) at a 0.5 M concentration in MeCN at 30 °C for 3–6 h. [b] Yield of the isolated product. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The configuration of the major diastereomer was confirmed by ^{1}H NMR spectroscopy on the basis of coupling constants or by X-ray crystal-structure analysis. [e] The reaction was carried out with TEMPO$^+$BF$_4^-$ (3 equiv) and Cs$_2$CO$_3$ (3 equiv).

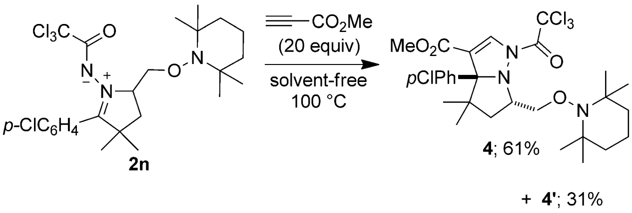
Encouraged by the results of the theoretical calculations, we prepared compounds **1g–i** to see if they could be converted into the corresponding σ radicals to undergo 5-*exo*-trig radical cyclization at the N^2 atom. It was expected that if γ,δ-unsaturated *N*-acyl hydrazones were deprotonated with a base, the corresponding hydrazonyl anions would react with TEMPO cation (2,2,6,6-tetramethyl-1-oxopiperidin-1-ium) through a single-electron-transfer (SET) process to produce hydrazonyl radicals and TEMPO.[10] The hydrazonyl radicals would then undergo a 5-*exo*-trig cyclization at the N^2 atom to give carbon-centered radicals, which could be trapped immediately by TEMPO to produce azomethine imine derivatives **2** (Scheme 2). Indeed, when *N*-trichloroacetyl- and *N*-trifluoroacetyl-substituted hydrazones **1h** and **1i** were treated with TEMPO$^+$BF$_4^-$ (1.5 equiv) and Cs$_2$CO$_3$ (1.5 equiv) in CH$_3$CN at 30 °C, the desired 5-*exo*-trig cyclization at the N^2 atom took place smoothly to afford **2h** and **2i** in 68 and 65 % yield, respectively (Scheme 3). The reaction hardly took place at all in the absence of Cs$_2$CO$_3$, thus indicating that a base is necessary for this efficient process.[11] The potential 6-*exo*-trig radical cyclization at the N^1 atom was not observed, as the 6-*exo*-trig cyclization is generally much less favored than its 5-*exo*-trig counterpart. Our computational studies also proved this point.[8] When the *N*-benzoyl hydrazone **1g** was used as the substrate under the same conditions, the reaction did not take place, and only **1g** was recovered. Apparently, the formation of **2h** and **2i** cannot be the result of initial oxidation of the carbon–carbon double bond.

To examine the scope of the present reaction, a variety of γ,δ-unsaturated *N*-trichloroacetyl and *N*-trifluoroacetyl hydrazones were subjected to the reaction conditions shown in Scheme 3. The results are summarized in Table 2. Compounds **1j–t** reacted very well under the reaction conditions to give the corresponding aminooxygenation products **2** in good-to-excellent yields. Notably, the formation of compounds **2** involves the aminooxygenation of unactivated alkenes: a type of reaction of synthetic significance.[12] When a *gem*-dimethyl group was present at the α position, as in **1j** and **1k**, the yields of products **2j** and **2k** of 5-*exo*-trig cyclization at the N^2 atom were increased to 83 and 88 % (Table 2, entries 1 and 2). The structures of compounds **2j** and **2k** were confirmed by single-crystal X-ray diffraction studies.[13] On the other hand, the 1,5-H shift involving the N^1 atom, which occurs under other circumstances,[3b,14] was not observed in the present case, because it is much less favored than the 5-*exo*-trig cyclization at the N^2 atom. When hydrazones **1q** and **1r** were utilized in the reaction, azomethine imines were formed as spiro compounds in excellent yields (Table 2, entries 8 and 9). Hydrazone **1s** incorporating a thiophene moiety was also transformed into the desired product **2s** in good yield (Table 2, entry 10), and the reaction of compound **1t**, which incorporates a styrenyl moiety, afforded **2t** in 91 % yield with high *trans* stereoselectivity (Table 2, entry 11). The configuration of **2t** was also identified by a single-crystal X-ray diffraction study.[13] When the alkene moiety was incorporated in a ring, as in the case of **1u**, the reaction afforded only a small amount of the expected product **2u**; the major product became the doubly TEMPO trapped azomethine imine **3u** as a single diastereomer. A similar result was obtained for the reaction of **1v**. The structure of **3u** was unambiguously identified by a single-crystal X-ray diffraction study.[13] By the use of 3 equivalents of TEMPO$^+$BF$_4^-$ and 3 equivalents of Cs$_2$CO$_3$, **3u** and **3v** were obtained in yields of 68 and 63 %, respectively (Table 2, entries 12 and 13). Evidently, these two products were generated by the further oxidation of **2u** and **2v** by TEMPO$^+$BF$_4^-$ (Scheme 4). The observed high stereoselectivity can be accounted for by the preferential trapping of the cyclization-derived carbon radicals and the oxidized carbon radicals from the less-hindered *exo* side.

Azomethine imines are valuable synthetic intermediates that have attracted great attention because of their multiple uses as 1,3-dipoles[15] and electrophiles[16] in organic synthesis. In this context, **2n** reacted with the dipolarophile methyl propiolate through [3+2] cycloaddition to form **4** and its diastereomer **4′** in a combined yield of 92 % (Scheme 5).



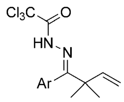
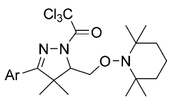
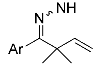
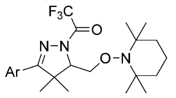
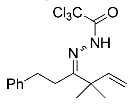
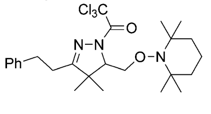
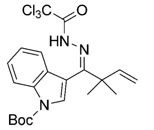
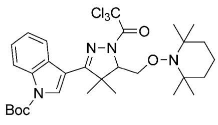
Scheme 4. Transformation of **2u** and **2v** into **3u** and **3v**, respectively.



Scheme 5. Transformation of azomethine imine **2n** by a [3+2] cycloaddition with methyl propiolate.

As revealed by the aforementioned calculations, *N*-trifluoroacetyl and *N*-trichloroacetyl hydrazonyl radicals can be viewed as σ radicals with spin density located on both the N^1 atom and the N^2 atom. However, γ,δ-unsaturated hydrazonyl radicals were shown to undergo exclusively 5-*exo*-trig cyclization, and 6-*exo*-trig cyclization at the N^1 atom was not detected. We anticipated that if β,γ-unsaturated hydrazones were used as the radical precursors, 5-*exo*-trig cyclization at the N^1 atom would take place to form pyrazolines. Indeed, when we subjected β,γ-unsaturated hydrazones **5** to the present conditions, pyrazolines **6** were formed in excellent yields (Table 3). Pyrazolines are known to possess diverse biological activity, including antimicrobial, analgesic, and anticancer activity.[17] The present protocol provides a convenient method for the preparation of these valuable compounds.

Table 3: Hydrazonyl-σ-radical-promoted N^1-atom 5-*exo*-trig cyclization for the synthesis of pyrazolines.[a]

Entry	Substrate	Product	Yield [%][b]
			
1	Ar = Ph **5a**	Ar = Ph **6a**	93
2	Ar = *p*-MeC$_6$H$_4$ **5b**	Ar = *p*-MeC$_6$H$_4$ **6b**	85
3	Ar = *p*-ClC$_6$H$_4$ **5c**	Ar = *p*-ClC$_6$H$_4$ **6c**	77
			
4	Ar = Ph **5d**	Ar = Ph **6d**	91
5	Ar = *p*-MeC$_6$H$_4$ **5e**	Ar = *p*-MeC$_6$H$_4$ **6e**	83
6	 **5f**	 **6f**	66
7	 **5g**	 **6g**	75

[a,b] See Table 2. Boc = *tert*-butoxycarbonyl.

In conclusion, we have demonstrated for the first time that hydrazonyl radicals, which generally exhibit π-electronic structures, can be tuned to σ radicals by attaching a trifluoroacetyl or trichloroacetyl group to the N^1 atom. In this way, both the N^1 and the N^2 atom become reactive radical centers.[18] These hydrazonyl σ radicals can be generated simply from *N*-trichloroacetyl and *N*-trifluoroacetyl hydrazones by using $TEMPO^+BF_4^-$ as the oxidant and Cs_2CO_3 as the base. This protocol has great synthetic implications. Under the indicated reaction conditions, β,γ- and γ,δ-unsaturated *N*-trifluoroacetyl and *N*-trichloroacetyl hydrazones readily underwent the corresponding $C-N^1$ and $C-N^2$ bond-forming 5-*exo*-trig cyclization to afford structurally important pyrazolines and azomethine imines in high yields. Further studies on the hydrazonyl-radical-promoted reactions are in progress in our laboratory.

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