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Radical and Nitrenoid Reactivity of 3-Halo-3-phenyldiazirines

Rafael Navrátil,[†] Ján Tarábek,[‡] Igor Linhart,[†] and Tomáš Martinů*[,†]

[†]Department of Organic Chemistry, University of Chemistry and Technology, Technická 5, 166 28 Prague, Czech Republic

[‡]Institute of Organic Chemistry and Biochemistry CAS, v.v.i., Flemingovo náměstí 542/2, 166 10 Prague, Czech Republic

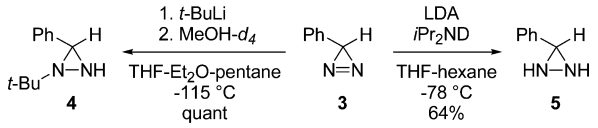
Supporting Information

ABSTRACT: 3-Halo-3-phenyl-3*H*-diazirines (halogen = Br or Cl) undergo a dissociative single-electron transfer from alkyllithiums (RLi) in THF-based solvent mixtures. The resulting 3-phenyldiazirinyl radical, observed by EPR spectroscopy, is eventually transformed to benzonitrile. In Et_2O, 2 equiv of RLi add to both nitrogens of halodiazirine N═N bond, affording *N,N′*-dialkylbenzamidines. The nitrenoid reactivity of some *N*-alkyl-1*H*-diazirine intermediates is manifested by their insertion into the α-C−H bond of THF or Et_2O.

The chemistry of 3*H*-diazirines is dominated by denitrogenation of their CN_2 cycles affording carbenes,[1] but other reactive intermediates, e.g. diazirinyl radicals,[2−5] diazirinyl anions,[5−7] or imidoylnitrenes,[3b,8,9,10a,11] have also been observed or implicated in reactions of diazirines under specific conditions. Here, we report the solvent-dependent radical and nitrenoid reactions of 3-halo-3-phenyldiazirines (**1**) with alkyllithiums that have resulted from our search for the 3-phenyldiazirinyl anion Phc-CN_2^- (**2**) in solution. Our observations shed new light on the reactivity of halodiazirines with electron donors and nucleophiles, with high relevance to the diazirine halogen exchange reactions.[1,12]

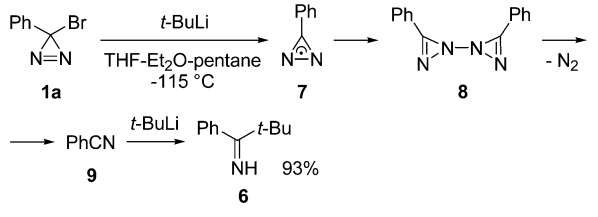
Ab initio calculations have indicated that the nonaromatic 4π-electron cycle of 3-unsubstituted diazirinyl anion Hc-CN_2^- is stabilized by the inductive effect of two nitrogen atoms and by cyclic conjugation.[13] In accordance with theory, several diazirinyl anions (including **2**) have been generated in the gas phase by deprotonation of the corresponding diazirines;[6] however, these species have remained elusive in solution. Anion **2** was considered as an intermediate in superoxide-initiated radical dehalogenation of 3-bromo-3-phenyldiazirine (**1a**),[5] and 3-alkoxydiazirinyl anions were suggested as intermediates in anionic fragmentation of 3-halodiazirine-3-carboxylic esters.[7] To the best of our knowledge, no attempt at deprotonation of a diazirine ring in solution has been reported despite its relatively favorable predicted acidity ($pK_a \approx 34-39$ for the 3,3-unsubstituted diazirine in DMSO).[13] Other reactions can, however, be expected to occur when diazirines are exposed to the usual strong bases. We have indeed observed that, instead of the diazirine ring lithiation (followed by attempted deuteration), *t*-BuLi adds to the N═N bond[14] of 3-phenyldiazirine (**3**) even at −115 °C to form *tert*-butyldiaziridine **4** in quantitative yield after quenching with MeOH-d_4 and aqueous workup (Scheme 1). Similarly, LDA/iPr_2ND does not accomplish the CN_2 ring H/D exchange with **3**, but it reduces the N═N bond, affording diaziridine **5** in 64% yield.[15] NOTE: All reactions reported here have been carried out by the addition of a diazirine to a solution of organolithium, and the product yields have been determined by ^1H NMR spectroscopy.

Scheme 1. Attempted H/D Exchange with Diazirine 3



After these initial observations we turned our attention to the lithium−halogen exchange reactions of bromodiazirine **1a** (the potentially more suitable iododiazirines are not synthetically available). The reaction of **1a** with 3 equiv of *t*-BuLi in 5:1:1 THF−Et_2O−pentane at −115 °C followed by quenching with MeOH afforded *tert*-butyl ketimine **6** as the only product in 93% yield (Scheme 2). The formation of **6** can be explained by one-electron reduction of **1a** to nitrogen-centered radical **7** with the first equivalent of *tert*-BuLi, dimerization of **7** to bis-1*H*-diazirine **8**, and its denitrogenation to benzonitrile (**9**) which reacts with the second equivalent of the lithium reagent; a mixture of **6** and **9** is indeed obtained if only 1 equiv of *t*-BuLi is used. The irreversible reduction of **1a** to **9** had been previously described using electrochemistry on platinum[14] and reactions with trialkylstannyl or trialkylsilyl radicals,[2] superoxide ion, or lithium naphtalenide.[5] We have also found a good

Scheme 2. Reaction of Diazirine 1a with *t*-BuLi



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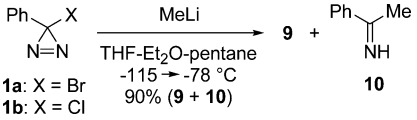
agreement between the yield of **6** and the volume of gas, assumed to be N_2, evolved in the reaction of **1a** with 5 equiv of *t*-BuLi at −60 °C (75% of **6** and 70% of N_2 by ideal gas law; the reaction temperature was increased to facilitate the liberation of gas).

In an effort to minimize the undesired single-electron transfer (SET) from the organolithium to the halodiazirine, we chose to replace *t*-BuLi with MeLi. The reactions of bromodiazirine **1a** or chlorodiazirine **1b** with MeLi, however, afforded nitrile **9** at −115 °C again, and mixtures of **9** and methyl ketimine **10** at −78 °C (Scheme 3). Unlike **6**, imine **10**

Scheme 3. Reaction of Diazirines 1 with MeLi



is prone to hydrolysis and it is accompanied by varying amounts of acetophenone. Since **1a** always reacts faster than **1b** (typically 100% vs 70% conversion in 20 min at −115 °C in 2:1 THF−Et_2O), it is likely that the irreversible SET from MeLi is concerted with the dissociation of the halide ion, the bromide being a better leaving group than the chloride ion. We have eventually confirmed the intermediacy of the diazirinyl radical **7**, expected to be involved in the formation of **9**, by EPR spectroscopy at room temperature. The spectrum of the nitrogen-centered radical **7**, corresponding to literature data[2a] and our DFT calculations, was obtained upon mixing **1a** with MeLi in a flow cell EPR cavity (Figures 1 and 2).

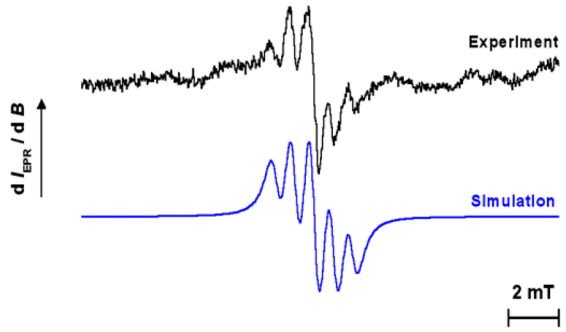


Figure 1. EPR spectrum of 3-phenyldiazirinyl radical (**7**), centered at g = 2.0039, $a(^{14}N)$ = 0.749 mT; generated from THF solutions of diazirine **1a** (8.5×10^{-2} M) and MeLi (5.1×10^{-1} M) at room temperature.

At very low temperatures (down to −120 °C), the reactions of **1a** with MeLi also yielded small amounts of dehalogenated diazirine **3**; no such reaction was observed with **1b**. The lack of reaction progress with time much beyond the conversion reached immediately after all of **1a** had been syringe-pumped to the reaction mixture indicates that the reaction may actually occur in hotspots created during the addition process. The overall yield of **3** was maximized to 20% (at 75% conversion) when a low total concentration of **1a** (ca. 5×10^{-3} M) and a sufficient concentration of MeLi (ca. 5×10^{-1} M) were used, the reagent thus being in a 100-fold excess relative to **1a** (Scheme 4). No improvement in the yield of **3** resulted from the use of common additives such as LiCl, LiBr, or HMPA. Complete deuteration of **3** on the CN_2 ring after quenching the

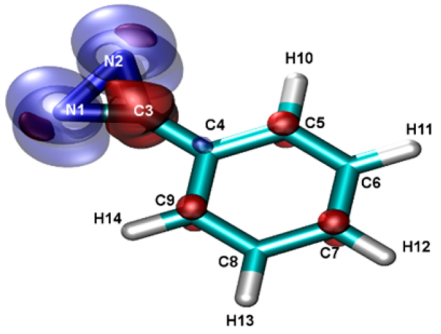
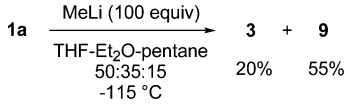


Figure 2. Spin density (iso value = 2.4×10^{-3} e/Å^3) of radical **7** calculated at the B3LYP/EPR-III//B3LYP/6-311+G(d,p)/CPCM-(THF) level. Blue surfaces: positive values (α spins). Red surfaces: negative values (β spins).

Scheme 4. Dehalogenation of Diazirine 1a to 3



reaction with MeOH-d_4 suggests the intermediacy of an anionic species, potentially the lithiated diazirine **2-Li** or the hypervalent bromine ate complex **11-Li** (Figure 3). The latter

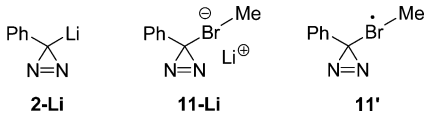


Figure 3. Possible intermediates in dehalogenation of diazirine **1a**.

possibility is consistent with no observed favorable effect of the electron-withdrawing CF_3 or NO_2 groups in the *para* position of the substrate's phenyl ring on the yield of the dehalogenated product. The formation of the anionic intermediate appears to be kinetically preferred to the SET process leading to nitrile **9**, as the **3**:**9** ratio tends to be higher at lower conversions (1:1 vs 1:2.8 at 40% vs 75% conversion). The intermediate is unstable at −78 °C; brief warming of the reaction mixture to this temperature followed by recooling to −115 °C and quenching with MeOH resulted in quantitative conversion of **1a** to the mixture of **9** and **10** with no **3** observed (cf. Scheme 3). The lability of the ate complex **11-Li** can be explained by its dissociation back to **1a** and MeLi, or by its loss of an electron resulting in the formation of radical **7** via a bromine-centered radical **11′** eliminating MeBr (such a process has been described for iodine ate complexes[16]). Alternatively, if the intermediate corresponds to **2-Li**, radical **7** could be formed directly by the loss of an electron.

While MeLi or *t*-BuLi brought about the reduction of bromodiazirine **1a** to nitrile **9** in THF−Et_2O−(pentane) mixtures above −115 °C, the reaction of **1a** with *n*-BuLi under similar conditions afforded only traces of **9**, the major product being *N*,*N*′-di-*n*-butylbenzamidine (**12**). Moreover, we identified minor amounts (up to 10%) of *N*,*N*′-dimethylbenzamidine (**13**) in the reaction products of MeLi with chlorodiazirine **1b**. In further experiments using Et_2O in the absence of THF, the reaction of **1a** with *n*-BuLi afforded **12** in 78% yield, and **1a** or **1b** with MeLi gave **13** in 53% or 70% yields, respectively (Table 1); all reactions proceeded with virtually no reduction to **9**. Under similar conditions, *t*-BuLi

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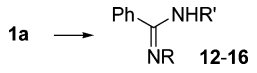
Table 1. Formation of *N,N′*-Disubstituted Amidines



R, R′	reagent	equiv	solvent	*t* (°C)	yield (%)
n-Bu (**12**)	*n*-BuLi	2	Et_2O/hexane 3:1	0	78
Me (**13**)	MeLi	20 (5)[a]	Et_2O	−110 (−78)[b]	53 (70)
t-Bu (**14**) [*t*-Bu,H (**15**)]	*t*-BuLi	5	Et_2O/pentane 3:1	−110	20 [15]
*i*Pr (**16**)	*i*PrMgCl·LiCl	3	THF	−78	65

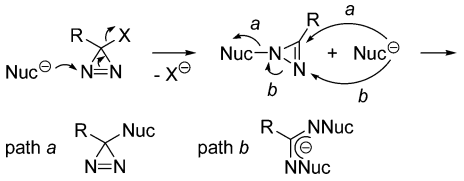
[a]Using chlorodiazirine **1b**. [b]No reaction at −110 °C.

and **1a** afforded *N,N′*-di-*tert*-butyl- and *N*-*tert*-butylamidines **14** and **15** in 20% and 15% yields, respectively, with traces of imine **6**. Our results are in agreement with the previously known addition of PhLi to **1b** in Et_2O affording *N,N′*-diphenylbenzamidine in a high yield.[9] We note in passing that *N,N′*-diisopropylamidine **16** can be prepared in 65% yield from **1a** and the Turbo Grignard reagent *i*PrMgCl·LiCl in THF, instead of the much less readily available *i*PrLi.

From the above-mentioned observations, the following mechanistic scheme can be drawn: (i) Alkyllithium transfers one electron to a halodiazirine in an irreversible dissociative SET generating a diazirinyl radical, eventually affording a nitrile. This pathway appears to be promoted by solvents based on THF. With **1a** and MeLi, SET may be preceded by the formation of an anionic intermediate, stable only at very low temperatures and affording the dehalogenated diazirine **3** upon protonation. (ii) Competing with SET is the nucleophilic addition of organolithium to the halodiazirine N=N bond. Upon a loss of the halide ion, the resulting N1-substituted 1*H*-diazirine undergoes the addition of the second equivalent of organolithium to position N2.

Apart from phenyl- and alkyllithiums in Et_2O, trisubstituted phosphines in CH_2Cl_2 have also been reported to add to both nitrogen atoms of halodiazirines **1**, affording various *N,N′*-bis(phosphine)benzamidinium salts.[10] It is important to note that this reactivity differs substantially from the "signature" reaction of halodiazirines—the halogen exchange by the fluoride, alkoxide, or cyanide ions or by primary and secondary amines.[1,12] According to the generally accepted "double S_N2'" mechanism, the 1*H*-diazirine intermediate undergoes a second nucleophilic attack at C3, releasing the first equivalent of a nucleophile from N1 (path *a* in Scheme 5). The amidine-

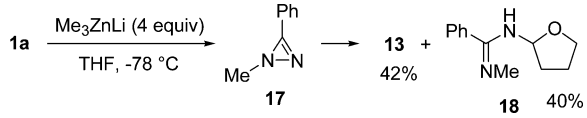
Scheme 5. Reactions of 3*H*- and 1*H*-Diazirines with Nucleophiles



forming and the halogen exchange pathways have not been known to occur simultaneously, with the exception of the reaction of **1a** with tetrabutylammonium cyanide, affording 3-phenyldiazirine-3-carbonitrile[17] and traces of *N,N′*-dicyanobenzamidine.[11] In light of the above-mentioned facts, it will be necessary to analyze the effect of various nucleophiles, solvents, and other conditions on the reactivity of 1*H*-diazirines. The suggestion that the second step of the diazirine halogen exchange may not involve an S_N2'-like process but a [1,3]-sigmatropic rearrangement[10] should be reconsidered; examples of such a rearrangement have been reported.[18]

Remarkably, in a reaction of **1a** with 3:1 MeLi/$ZnCl_2$ (the resulting Me_3ZnLi was tested for the improvement of the yield of **3** in the dehalogenation of **1a**), we observed a formal insertion of the putative 1*H*-diazirine intermediate **17** into the α-C−H bond of THF. *N*-Methyl-*N′*-(2-oxolanyl)amidine **18** was obtained along with dimethylamidine **13** in 40% and 42% yields, respectively (Scheme 6). We had previously reported a

Scheme 6. Formation of C−H Insertion Product 18



similar diazirine−nitrogen insertion into the α-C−H bond of Et_2O in a reaction of a 3-bromo-3*H*-diazirine-3-carboxylic ester with phenylmagnesium bromide, affording dihydrooxazole **21** via 1*H*-diazirine **19** (Figure 4).[11] The mechanism of these

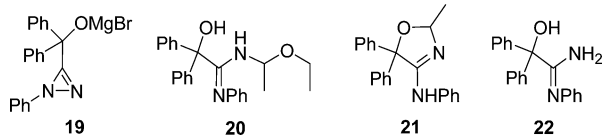


Figure 4. 1*H*-Diazirine **19** and its follow-up products in Et_2O (ref 11).

insertions is unclear at present, and we remain focused on its elucidation. A question also arises whether the intermediacy and subsequent hydrolysis of the corresponding *O*-ethyl hemiaminal may explain the observed formation of monosubstituted amidine **15** (cf the previously reported **20** → **22**).

In the above-mentioned nucleophilic addition and C−H insertion reactions, the putative 1*H*-diazirine intermediates exhibit nitrenoid reactivity. In the literature, 1*H*-diazirines are often postulated to isomerize to imidoylnitrenes,[3b,8,9,10a,19] but no such ring opening has been observed experimentally[20] or described computationally. In fact, calculations supported by observation in a cryogenic matrix show that the CN_2 ring of 3-methyl-1*H*-diazirine (**23**) is distorted, with a N−C−N angle of ca. 78° resembling the ground-state singlet acetimidoylnitrene in which the nitrene center is stabilized by nonbonding electrons of the imidoyl nitrogen (Figure 5).[21] No other structures with a smaller or larger N−C−N angle were found computationally on the singlet potential energy surface. The same effect has been generally accepted for the ground-state singlet acetylnitrene/3-methyloxazirene (**24a**) and benzoylnitrene/3-phenyloxazirene (**24b**) hybrids[22] with the larger O−C−N angle of ca. 86°, most likely due to the less efficient stabilization of the nitrene center by the more electronegative

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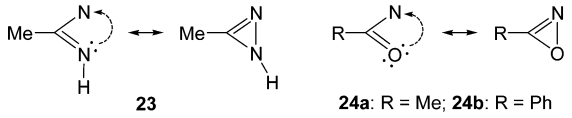

Figure 5. Imidoylnitrene/1*H*-diazirine and acylnitrene/oxazirene duality.

oxygen atom. The lack of recognition of the 1*H*-diazirine/imidoylnitrene duality has led to a conclusion that, based on computational results, singlet imidoylnitrenes are not intermediates in amidine-forming double nucleophilic additions of phosphines to bromodiazirine **1a**.[10b] The properties of 1*H*-diazirine nitrenoids should therefore be studied in detail to determine the effect of intramolecular stabilization on their reactivity.

The following conclusions can be drawn from this work: (i) 3-Halo-3-phenyl-3*H*-diazirines may be considered as mechanistic probes for distinguishing between SET and the direct nucleophilic reactivity of organolithiums under various conditions, affording benzonitrile in the former and *N,N′*-disubstituted amidines in the latter case. (ii) The bis-electrophilic nature of the N═N bond in halodiazirines may be more extensively exploited in the synthesis of *N,N′*-disubstituted amidines. (iii) The 1*H*-diazirine/imidoyl-nitrene duality should be considered in future work, with special regard to the reactivity with nucleophiles under various conditions—both reactions at positions N2 and C3 are possible.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01753.

Experimental procedures and spectroscopic data for compounds **4**, **5**, **12**−**16**, and **18**; summary of DFT calculations and detailed description of EPR experiment (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: martinut@vscht.cz.

Notes

The authors declare no competing financial interest.

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