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One-Pot Synthesis of Diazirines and $^{15}N_2$-Diazirines from Ketones, Aldehydes and Derivatives: Development and Mechanistic Insight

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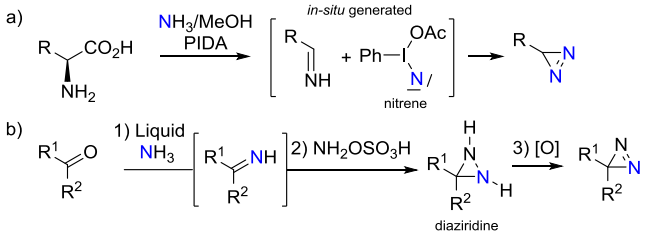
Abstract. Broad scope one-pot diazirine synthesis strategies have been developed using two different oxidants depending on the nature of the starting material. In all cases, an inexpensive commercial solution of ammonia (NH_3) in methanol (MeOH) was employed, avoiding the difficult use of liquid ammonia. With aliphatic ketones, *t*-butyl hypochlorite (*t*-BuOCl) was found to be the best oxidant whereas it is preferable to use phenyliodine diacetate (PIDA) with aromatic ketones, aldehydes and imines. The nature of the imine-protecting group is essential and only *t*-butyl imine allowed the synthesis of $^{15}N_2$-diazirine with complete ^{15}N incorporation, emphasizing a key trans-imination step in the reaction mechanism. These methods are operationally simple, and tolerant to most functional groups, providing diazirines with yields ranging from 20 to 99%.

Keywords: ammonia; *t*-BuOCl; PIDA; diaziridine; diazirine

Introduction

The three-membered heterocyclic ring 3*H*-diazirine (diazirine) is one of the rare chemical scaffolds able to generate a highly reactive species under an external stimulus such as light, heat,[1] or ultrasound.[2] This particular reactivity has been exploited in cross-coupling reactions with aryl halides[3] or boronic acids,[4] and for the generation of sulfur ylides which are useful intermediates in synthetic chemistry.[5] Recently, Lopchuk and co-workers elegantly demonstrated that diazirines could serve as effective electrophilic nitrogen transfer reagents in the decarboxylative amination of redox-active esters.[6] On the other hand, diazirine occupies a privileged position in photoaffinity labeling of biomolecules, which has received a considerable attention in chemical biology for providing new insights into biological mechanisms, as well as in medicinal chemistry for identifying protein-protein interactions and biological targets of small-molecule ligands.[7] Photoaffinity labeling relies on the installation of discrete and biocompatible chemical functions into proteins of interest or pharmacophores, which are then capable of generating highly reactive species upon UV light activation, able to insert into a variety of X-H bonds (X = C, N, O, or S) of biomolecular targets. In this context, diazirine as a carbene precursor, is one of the most popular photoreactive functions mainly due to its small size, remarkable biochemical stability and convenient crosslinking reactivity that is triggered in the range of 350-380 nm.[8] More recently, diazirines have also been used for surface functionalization including carbon nanotubes, fullerenes or graphenes through a [1+2] cycloaddition reaction of carbenes with C=C bonds, in order to tune or improve the material properties.[9] Remarkably, use of diazirines has emerged as a superior cross-linking strategy for the modification of non-functionalized alkane polymers.[10] Recently, a promising application was developed in hyperpolarization using $^{15}N_2$-diazirines, which enhances NMR signals by >10 000-fold for more than an hour.[11]

Despite the importance of the diazirine function, synthetic routes are particularly time-consuming with low efficiency, and based on multi-step tedious protocols, with the isolation, and sometimes purification of instable intermediates which are difficult to obtain in pure forms or poorly compatible with fragile functional groups.[12]



Scheme 1. Routes to diazirine systems.

Although the one-pot synthesis of terminal diazirines from α-amino acids in the presence of phenyliodine diacetate [PIDA, $PhI(OAc)_2$] was recently reported by our group (Scheme 1a),[13] most of the diazirines are usually prepared from corresponding ketones through the formation of diaziridine intermediates (Scheme 1b), requiring a two-step protocol, and multiple temperature modifications:[14] ketones are treated with liquid ammonia at very low temperature (–78 °C) to form imine intermediates, which then undergo the nucleophilic addition of hydroxylamine-O-sulfonic acid (HOSA, NH_2OSO_3H) to enable intramolecular cyclization and furnish corresponding diaziridines.

They can subsequently be oxidized into diazirines with a range of reagents including transition metals such as freshly prepared silver (I) oxide,[15] dichromate,[16] or low-cost oxidants such as sodium or *t*-butyl hypochlorite (*t*-BuOCl),[17] iodine in the presence of trimethylamine, or Hunig's base.[18]

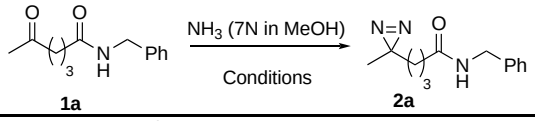
Very recently, a one-pot strategy was reported, based on the successive use of HOSA in liquid ammonia, and potassium *t*-butoxide (*t*-BuOK) under air in order to complete the two oxidation steps.[19] This procedure can however be difficult to implement, in particular due to the use of a large amount of liquid ammonia.

Herein, we describe two, straightforward, one-pot and liquid ammonia-free, access to the diazirine function. *t*-BuOCl was found to be the best oxidant with aliphatic ketones whereas, PIDA was found to be more effective with aromatic ketones, aldehydes and imines. In both conditions, these oxidants enable successive N-N and N=N bond formation.

Results and Discussion

A commercially available and easily storable solution of 7N NH_3 in MeOH was selected as the ammonia source in all these studies in order to circumvent the use of condensed ammonia at low temperature.

Table 1. Optimization of the reaction conditions.



Entry	Conditions[a]	Isolated yield
1	PIDA	11
2	Ag_2O	0
3	MnO_2	0
4	*t*-BuOK, under air	0
5	*t*-BuOCl	32
6	*t*-BuOCl, 35 °C	46
7	a) *t*-BuOCl (3 equiv), 4 h b) *t*-BuOCl (1.5 equiv), 0.5 h	41
8	a) *t*-BuOCl (3 equiv), 4 h b) N_2 degas., then *t*-BuOCl (1.5 equiv), 0.5 h	72 (68)[b]

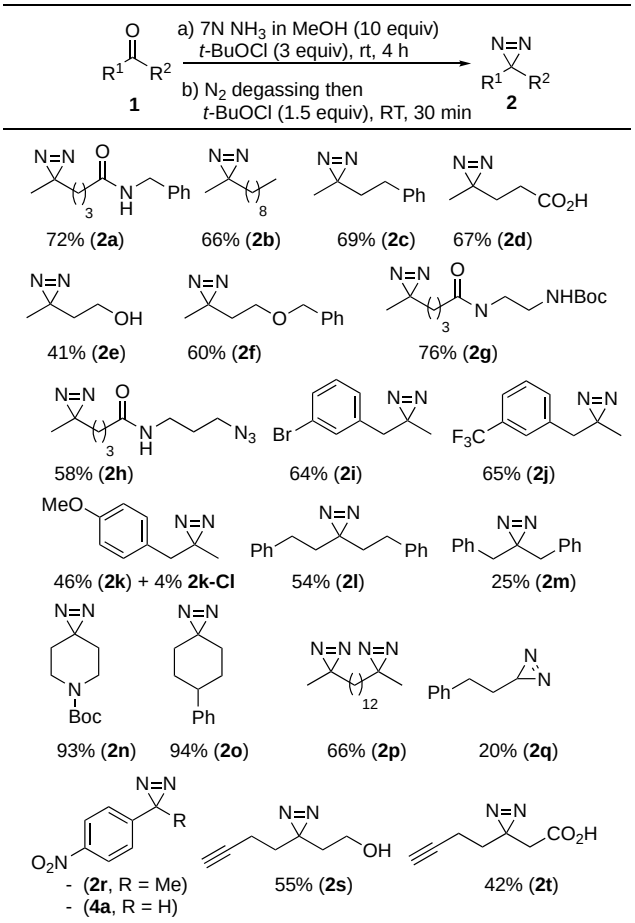
[a] Unless specified, all reactions were carried out in a 7 N NH_3 solution in MeOH (~10 equiv) with corresponding oxidant (4.5 equiv) at room temperature for 4 h. [b] 5-fold scale-up reaction (3.4 mmol), 5 min degassing.

We first focused on the diazirine synthesis from aliphatic ketones and the ketoamide **1a** was selected as a functionalized model substrate. Different oxidants were explored and results are summarized in Table 1.

We first started with PIDA (4.5 equiv) which was successfully used by our group for the synthesis of diazirines from α-amino acids;[13] however, it led to the formation of the expected diazirine **2a** in only 11% isolated yield (Table 1, Entry 1). With metal oxidants such as silver(I) oxide (Ag_2O), or manganese(IV) oxide (MnO_2)[20] that were already reported to oxidize diaziridines into diazirines, ketoamide **1a** did not react and was recovered unchanged (entries 2 and 3). A similar observation was made with the use of *t*-BuOK under air, which has recently been reported as an effective strategy for the dehydrogenation of the NH-NH bond in particular for diazirine synthesis (Entry 4).[19a] Under similar conditions, *t*-BuOCl enabled the formation of **2a** in a promising 32% isolated yield, along with 41% of the intermediate diaziridine (entry 5). This important result reveals that *t*-BuOCl is able to perform both oxidation steps, forming N-N then N=N bond, in one-pot. Following this preliminary screening, the use of *t*-BuOCl as the only oxidant was further investigated. Warming the reaction mixture to 35 °C improved the efficiency of the diazirine formation, which was isolated in 46% yield. Likewise, a sequential addition of *t*-BuOCl, afforded **2a** in 41% yield (Entry 7). As the presence of residual ammonia in the medium may consume *t*-BuOCl and thus compete with the diaziridine oxidation, the excess of ammonia was

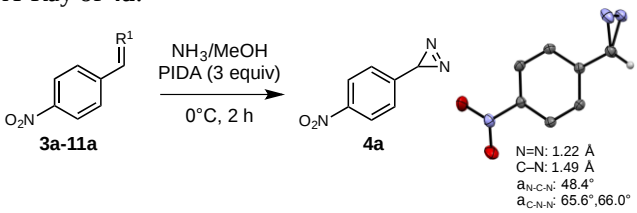
removed by nitrogen bubbling for 20 min before adding the second batch of *t*-BuOCl (1.5 equiv), which then significantly improved the yield to 72% (Entry 8). A 5-fold scale up reaction (3.4 mmol) was carried out leading to the formation of **2a** in 68% yield. The degassing time reduced to 5 min proved sufficient to remove residual ammonia as no diaziridine was observed in the crude reaction mixture.

Table 2. Scope of the one-pot liquid ammonia-free synthesis of alkyl diazirines **2**.



With the optimized reaction conditions in hand, the scope of the reaction was next examined with different ketones. Results obtained are reported in Table 2. A series of aliphatic methyl ketones were transformed into their corresponding diazirines in good yields. Experimental conditions were tolerant to a variety of functional groups including amide (72%, **2a**), carboxylic acid (67%, **2d**), hydroxyl (45%, **2e**), carbamate (76%, **2g**), and azide (58%, **2h**). The presence of electron-deficient (CF_3) and electron-rich group (OMe) on the phenyl ring system were well tolerated, as only 4% of separable 3-chlorinated phenyl diazirine 2k-Cl was observed with the benzyl ketone **1k** (see Supporting Information). Whilst the 1,3-disubstituted ketone **1l** afforded the corresponding diazirine in reasonable 54% yield, the dibenzyl ketone **1m** furnished the diazirine in a low 25% yield, presumably due to the predominance of the enol form stabilized by the phenyl ring systems. In contrast, cyclic 1,3-disubstituted ketones **1n** and **1o** provided the corresponding diazirines **2n** and **2o** in high 93% and 94% yields, respectively. In addition, the diketone **1p** provided the bis-diazirine **2p** in good 66% yield, with the use of twice the amount of oxidant and solvent. Besides, the 3-phenylpropionaldehyde **1q** formed the mono substituted diazirine **2q** in a low 20% yield, partly due to its low boiling point. However, aromatic ketones and aldehydes constitute a limitation of this methodology, as the oxidation of **1r** and **3a** did not form any detectable diazirines. Bifunctional diazirine **2s** and **2t**, bearing an alkyne group, were obtained in satisfying 55% and 42% yield, respectively, which could be used as photoactivable platforms for biological applications.[21]

Table 3. Choice of conditions and imine protecting group. X-Ray of **4a**.



Entry	**R**[1]	**4a** isolated yield [%]
1	O (**3a**)	47[a]
2	N-*t*-Bu (**5a**)	80
3	N-Bn (**6a**)	62
4	N-Ph (**7a**)	traces
5	N-*Cy* (**8a**)	94
6	N-Ts (**9a**)	99
7	N-TMS (**10a**)	55
8	N-OH (**11a**)	50

[a] The corresponding nitrile was also isolated.

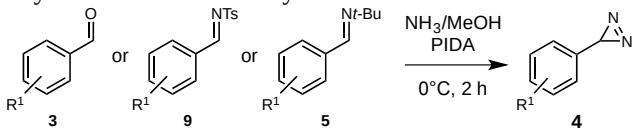
Next, we focused on the synthesis of aromatic diazirines from aldehydes which have been significantly less studied,[22] as well as their reactivity.[23] While this class of diazirines cannot be prepared from α-amino acids (with a combination of PIDA and ammonia) as we previously reported, we were inspired by its mechanism of formation that also involves an imine as an intermediate. In addition, the low yield obtained for aliphatic ketone **2a** in the presence of PIDA (Table 1, entry 1) prompted us to optimize the conditions for aromatic starting materials.

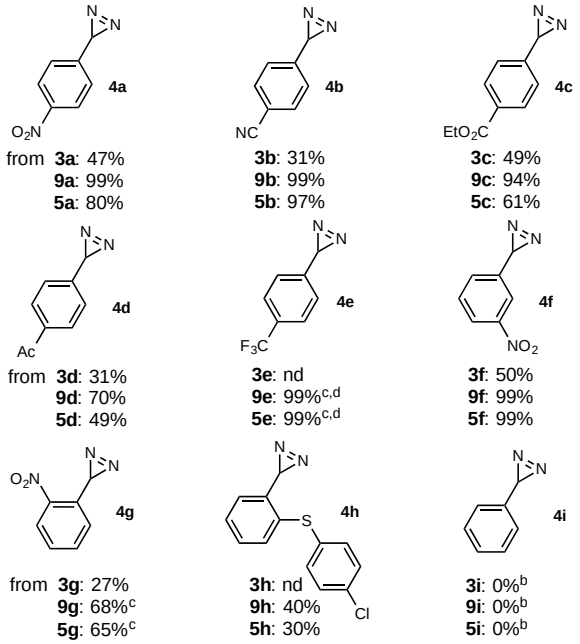
We then tested the one-pot reaction with *p*-nitrobenzaldehyde **3a** as model substrate (Table 3), which under the previous *t*-BuOCl conditions, did not provide the expected diazirine **4a** (Table 2).[24] Once

again, we used commercially available 7N NH_3 in MeOH as the source of ammonia.

After optimization (see supporting information),[25] the best result was obtained using conditions that are similar to the diaziridination reaction of α-amino acids, namely, PIDA (3 equiv) and NH_3 (17.5 equiv) in MeOH at 0 °C for 2 h. Indeed, we were delighted to observe the formation of the expected diazirine **4a** in a moderate isolated yield of 47% (entry 1) along with the corresponding nitrile and unidentified byproducts.[26] This result is quite remarkable as aldehydes are known to lead to the corresponding nitriles in almost quantitative yield under similar oxidative conditions.[27] X-ray cristallography of single crystal of **4a** (obtained by slow evaporation of CH_2Cl_2 solution) confirmed the formation of the terminal diazirine.

Table 4. Scope of diazirine synthesis from aldehydes **3**, N-tosyl imines **9** and N-*t*-butyl imines **5**.[a]





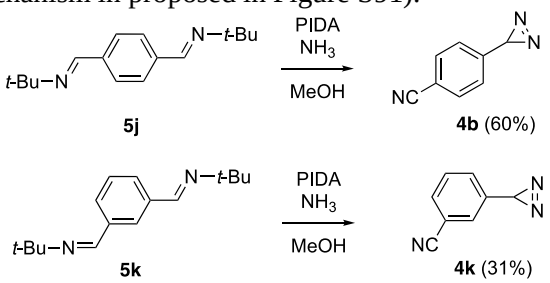
from **3a**: 47% **9a**: 99% **5a**: 80%	**3b**: 31% **9b**: 99% **5b**: 97%	**3c**: 49% **9c**: 94% **5c**: 61%
from **3d**: 31% **9d**: 70% **5d**: 49%	**3e**: nd **9e**: 99%[c,d] **5e**: 99%[c,d]	**3f**: 50% **9f**: 99% **5f**: 99%
from **3g**: 27% **9g**: 68%[c] **5g**: 65%[c]	**3h**: nd **9h**: 40% **5h**: 30%	**3i**: 0%[b] **9i**: 0%[b] **5i**: 0%[b]

[a] Isolated yields. [b] The corresponding nitrile was obtained. [c] Volatile compound. [d] Not isolated, conversion based on ^{19}F NMR analysis of the crude material.

Since the reaction of diazirination from α-amino acids has previously been shown to involve a key trans-imination step, we also decided to use other easily accesible starting material, such as aldimines bearing various protecting groups (Table 3, entries 2-8): alkyl (**5a**, **6a**, **8a**), phenyl (**7a**), tosyl (**9a**), silyl (**10a**) or hydroxyl (**11a**). The unprotected imine (R^1= NH) cannot be employed due to its instability. Among them, the N-*t*-butyl (**5a)** and N-tosyl aldimines **(9a**) afforded the diazirine **4a** in higher yields (80% and 99%, respectively) than others. With these conditions in hand, the scope of this reaction was evaluated using N-tosyl and N-*t*-butyl aldimines (**9** and **5**) obtained from various aromatic aldehydes (Table 4). In addition, these results were also compared with the direct conversion of benzaldehydes **3** to the diazirine (Table 4).

First, with benzaldehydes (**3a-g**) or *t*Bu-imines (**5a-g**) bearing electron withdrawing groups (NO_2, CN, CO_2Et), the corresponding diazirines were isolated in excellent yields, especially from N-tosyl imines. According to ^1H NMR of the crude product, the formation of diazirine **4e** with a CF_3 group was complete (the corresponding nitrile was not observed) but unfortunately, this compound is highly volatile as already observed with some diazirines generated from ketones or α-amino acids.

Diazirine **4h**, bearing a sulfide substituent, was obtained in moderate yield due to concurrent formation of corresponding sulfoximine (12%).[28]. Eventhough sulfur atom is considered as an electron-donating group, the nitrile was not observed in this case, probably because the sulfur atom can participate to the diazirine formation by assistance (a putative mechanism in proposed in Figure S91).

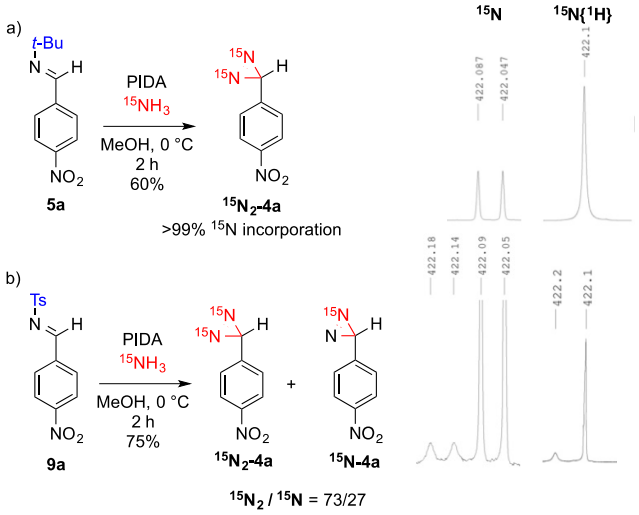


Scheme 2. Synthesis of diazirines **4b** and **4k** from **5j** and **5k**.

Interestingly para-cyano diazirine **4b** and meta-cyano diazirine **4k** were also prepared from di-N-*t*-butyl imine **5j** and **5k** (Scheme 2) in 60 and 31% yield, respectively. This reaction proceeds sequentially but the second diazirination reaction does not take place considering that first formed diazirine ring is not an electron withdrawing group; conversion of the second imine to nitrile is then observed. With benzaldehydes or imines bearing electron-donating groups (ether, halogen), the corresponding diazirines were not obtained, and only the corresponding nitriles were isolated. Unfortunately, imines of heterocycles (indole, pyridine) were found to be not suitable substrates for the diazirination reaction and corresponding nitriles were isolated in quantitative yields.

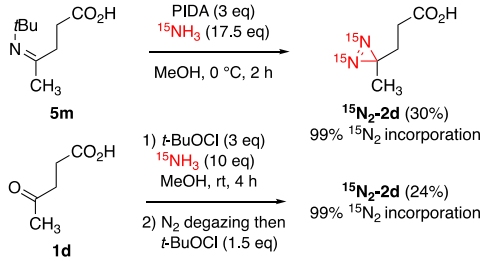
Next, we performed the diazirination reaction using $^{15}NH_3$ generated from $^{15}NH_4Cl$ upon treatment with CH_3ONa, in order to access a series of compounds suitable for hyperpolarization studies, as well as to

provide insight into the reaction mechanism. Thus, diazirine **$^{15}N_2$-4a** was synthesized from N-*t*-butyl imine **5a** in 60% yield (Scheme 3a). In ^{1}H and ^{13}C NMR, the signals of the diazirine were characteristic due to a supplementary $^{2}J_{N\text{-}H}$ (2.5 Hz) and $^{1}J_{C\text{-}N}$ (9.0 Hz) couplings, compared to the unlabeled diazirine. Surprisingly, complete ^{15}N incorporation was observed by ^{15}N NMR with the presence of a single doublet (Scheme 3a). On the other hand, when the diazirination reaction was performed using N-tosyl imine **9a**, although a better yield was obtained (75%), a lower ^{15}N incorporation (73%) [29] was observed according to ^{15}N NMR spectra. Indeed, a second deshielded doublet appeared with the same $J_{N\text{-}H}$ coupling constant (Scheme 3b) corresponding to mono-labeled diazirine **^{15}N-4a** (27%).



Scheme 3. Synthesis of diazirine **$^{15}N_2$-4a** and **^{15}N-4a** from imines **5a** and **9a** and corresponding ^{15}N NMR spectra.

In addition, the same trend was observed when N-*t*-butyl imine of levulinic acid **5m** reacted with $^{15}NH_3$: a complete ^{15}N incorporation was obtained for **$^{15}N_2$-2d**, confirming the presence of a trans-imination step (Scheme 4).[30] $^{15}N_2$-diazirine **2d** also was synthetized in a single step from levulinic acid **1d**, in 24% yield, with almost quantitative incorporation of both ^{15}N atoms.

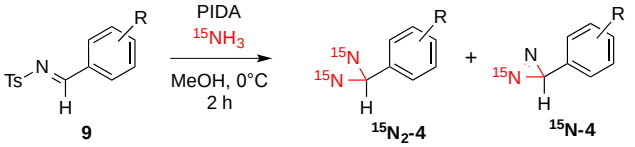


Scheme 4. Synthesis of diazirine **$^{15}N_2$-2d** of levulinic acid.

As $^{15}N_2$-diazirine can be hyperpolarized by a parahydrogen-based method (SABRE-SHEATH) and consequently used as hyperpolarized molecular tag,[11] the scope of reaction was studied, from N-tosyl imine derivatives as they were found to be a good compromise in terms of chemical yield and ^{15}N incorporation (Scheme 3). Under these optimized conditions, moderate but useful chemical yields of $^{15}N_2$-diazirines **$^{15}N_2$-4a-d** and **$^{15}N_2$-4f-g** were obtained (10-75% yield), along with ^{15}N incorporation ranging from 49% to 92% as determined by ^{15}N NMR (Table 5).

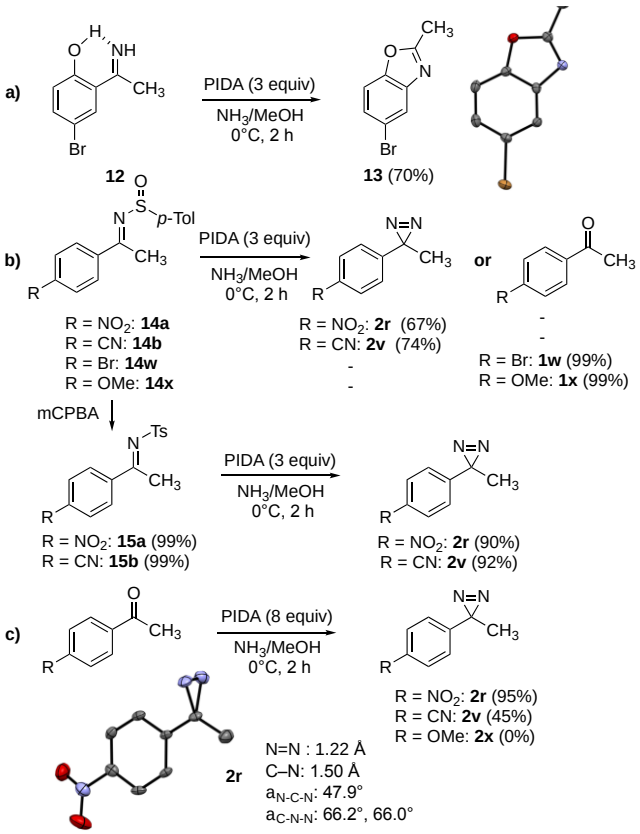
Finally, the reactivity of aromatic ketones was investigated since these are a limitation of the previous methodology using *t*-BuOCl. The NH-ketimine **12**,[31] stabilized by hydrogen bonding with a hydroxy group, was first tested. However, in the presence of PIDA/NH_3/MeOH, the expected diazirine was not observed, but the benzoxazole **13** was isolated in 70% yield,[32] due to a rapid Beckmann rearrangement (Scheme 5a).[33]

Table 5. Scope of $^{15}N_2$-diazirine synthesis from N-tosyl imines **9**.[a]



diazirine **4**	isolated yield (%) $^{15}N_2$ + ^{15}N	incorporation ratio $^{15}N_2$ / ^{15}N
4a (R=*p*-NO_2)	75	73/27
4b (R=*p*-CN)	28	92/8
4c (R=*p*-COOEt)	23	77/23
4d (R=*p*-Ac)	15	49/51
4f (R=*m*-NO_2)	52	53/47
4g (R=*o*-NO_2)	10	79/21

Consequently, N-tosyl ketimines **15** were chosen as substrates based on the aldimine series, which were easily prepared from N-sulfinyl imine **14** (Scheme 5b) by oxidation with mCPBA.[34]



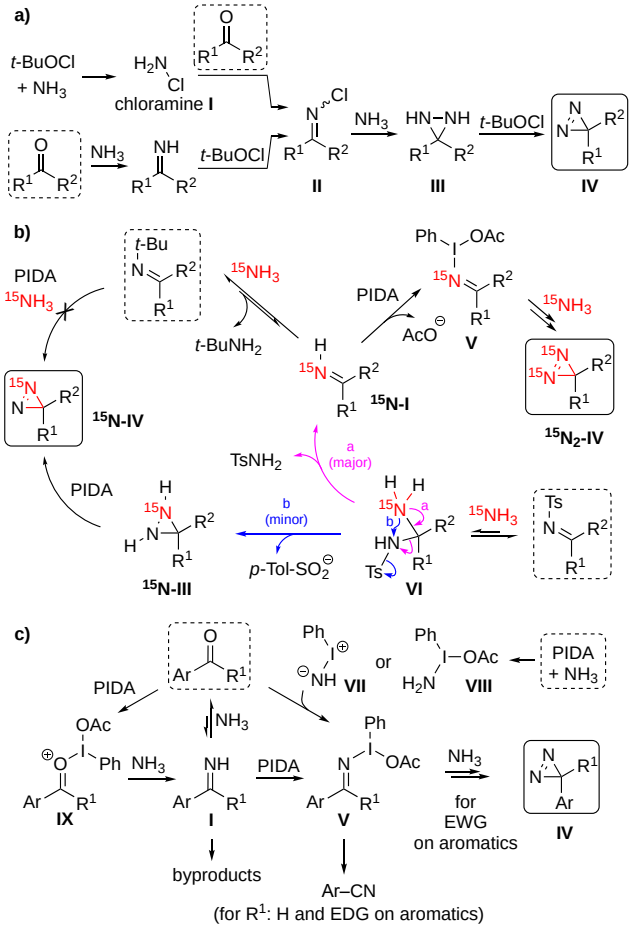
Scheme 5. Synthesis of diazirine **2r**/**2v** and X-ray of **2r**/**13**

Surprisingly, using the same diazirination conditions, N-sulfinyl imine **14w** (R= Br) and **14x** (R= OMe) did not afford the corresponding diazirine but led to the corresponding ketones in quantitative yields, while N-sulfinyl imine **14a** (R= NO_2) and **14b** (R= CN) led to expected diazirines **2r** and **2v** in 67% and 74%, respectively (Scheme 5b). Although the synthesis of N-tosyl imines **15a** and **15b** requires an additional oxidation step, diazirines **2r** and **2v** were obtained in better yields of 90% and 92%, respectively. Additionally, direct transformation of acetophenone into diazirine was also attempted. Satisfyingly, diazirine **2r** and **2v** were isolated in 95 and 45% yield, respectively (Scheme 5c), but the reaction required however a larger amount of PIDA (8 equiv). The X-ray analysis of **2r** was also obtained and revealed similar angles than structure of diazirine **4a** but with a longer C–N bond.

A mechanistic proposal explaining all these results is depicted in Scheme 6. In the presence of *t*-BuOCl and ammonia, chloroamine **I** is formed *in-situ* and allows the formation of chloroketimine **II**. Alternatively, chloroketimine **II** can be formed by *t*-BuOCl oxidation of NH-imine, obtained by addition of ammonia on the carbonyl compound. Chloroketimine **II** can then react with ammonia to led to diaziridine **III** after cyclisation. After evaporation of ammonia, its oxidation with *t*-BuOCl, forms the diazirine **IV** (schema 5a).

As demonstrated by the previous experiment with $^{15}NH_3$, (Scheme 3 and Scheme 4), a trans-imination occurs with N-*t*-butyl imine and would explain the formation of ^{15}N-imine **^{15}N-I** (Scheme 6b). This latter would be trapped by PIDA to lead to the imine **V**. This step and subsequent steps must be highly favored since only $^{15}N_2$-diazirine **$^{15}N_2$-IV** was obtained and not the mono-labeled **^{15}N-IV** one. A similar explanation could be used for N-tosyl imine since aminal **VI** could form the same ^{15}N-labeled imine **^{15}N-I** (path a) with concomitant tosylamine release. [35] On the other hand, the cyclisation of the aminal **VI** (path b) could explain the formation of mono-labeled diaziridine **^{15}N-III**, which is further oxidized with PIDA into corresponding monolabeled diazirine **^{15}N-IV**.

Finally, a plausible mechanism for the formation of diazirines from aromatic carbonyl derivatives in the presence of ammonia and PIDA is proposed in Scheme 6c. The nucleophilic attack of the carbonyl derivative on PIDA would lead to the intermediate **IX** which, after reaction of ammonia, would furnish the corresponding primary imine **I**.[36] But, after ligand exchange between PIDA and ammonia,[37] intermediate **VIII** or iminoiodinane **VII**,[38] can also be formed which reacted with aromatic aldehydes and ketones to form iodinated imine **V**. A large excess of PIDA (8 equiv) is thereby necessary due to formation of iodonitrene from **VII**[38] which dimerized into N_2.[28]



Scheme 6. Proposed diazirination mechanisms from carbonylated or imines derivatives.

Conclusion

In conclusion, this report describes a direct access to aliphatic and aromatic diazirines in the presence of inexpensive oxidizing agents *t*-BuOCl and PIDA, respectively. Reaction conditions are distinguished by their operational simplicity (one-pot protocol, mostly room temperature), and the absence of freshly condensed ammonia. The wide scope of these approaches (although limited to electron-poor aromatics) was demonstrated by the synthesis of more than 30 diversely functionalized diazirines, including amide, carboxylic acid, alcohol, thioether, and azide groups, to cite a few. On one hand, the access to aliphatic diazirines was illustrated by the design of a minimalist bioconjugatable platform **2t** achieved in only 4 steps, which will find applications in proteomics. On the other hand, this strategy also affords a straightforward entry to $^{15}N_2$-diazirines with complete ^{15}N incorporation, with potent applications in hyperpolarized magnetic resonance imaging. Importantly, these labeling experiments contributed to unveil the mechanisms of diazirines formation, in particular from imine precursors in the presence of PIDA.

Experimental Section

CCDC-2074588 (**4a**), CCDC 2074589 (**2r**) and CCDC 2074590 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure A for the synthesis of diazirine (2) from aliphatic ketones

To a solution of the corresponding ketone (0.675 mmol) in a 7N solution of NH_3 (7 mmol, 10.4 equiv.) in MeOH (1 mL) in a dried microwave tube equipped with a rubber septum, was carefully added a solution of t-butyl hypochlorite (229 µL, 2 mmol, 3 equiv.) in t-butanol (1 mL). The mixture was stirred for 4 h at room temperature. Then, the excess of NH_3 was removed by N_2 degassing for 20 minutes before adding the second portion of t-butyl hypochlorite (114 µL, 1 mmol, 1.5 equiv.) in t-butanol (0.5 mL). The consumption of the diaziridine intermediate was followed by ninhydrin testing. The mixture was stirred for 30 minutes at room temperature, then concentrated under reduced pressure. The crude was diluted with a solution of saturated aq. $Na_2S_2O_3$ (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under vacuum. Finally, the crude material was purified by flash chromatography over silica gel.

General Procedure for the synthesis of 3H-diazirines (4) from imines (5) or (9)

(Diacetoxyiodo)benzene (1.5 mmol, 3 equiv.) was added in one portion to a stirred solution of imine **5** or **9** (0.5 mmol, 1 equiv.) in NH_3 in MeOH 7M (1.25 mL, 17.5 equiv.) at 0°C under Argon. After 30 minutes at 0°C, the batch was allowed to reach room temperature and was left stirred for 1h30. After completion (monitored by TLC and ^1H NMR), the batch was concentrated under reduced pressure and the crude was purified by flash chromatography on silica gel to afford diazirine **4**.

General Procedure for the synthesis of 3H-diazirines (4) from aldehydes

(Diacetoxyiodo)benzene (1.5 mmol, 3 equiv.) was added in one portion to a stirred solution of aldehyde **3** (0.5 mmol, 1 equiv.) in NH_3 in MeOH 7M (1.25 mL, 17.5 equiv.) at 0°C under Argon. The batch was left stirred at 0°C for 2h00. After completion (monitored by TLC and ^1H NMR), the batch was concentrated under reduced pressure and the crude was purified by flash chromatography on silica gel to afford diazirine **4**.

General Procedure for the synthesis of $^{15}N_2$-diazirine (^{15}N-2 or ^{15}N-4)

(Diacetoxyiodo)benzene (3 equiv.) was added in one portion to a stirred solution of imine **5** or **9** (1 equiv.) in $^{15}NH_3$ in MeOH 7M (17.5 equiv.) at 0°C under argon. After 30 minutes at 0°C, the batch was allowed to reach room temperature and was left stirred for 1h30. After completion (monitored by TLC and ^1H NMR), the batch was concentrated under reduced pressure and the crude was purified by flash chromatography on silica gel.

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Authors contributions

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One-Pot Synthesis of Diazirines and $^{15}N_2$-Diazirines from Ketones, Aldehydes and Derivatives: Development and Mechanistic Insight

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