One-Pot Synthesis of Diazirines and 15N2-Diazirines from Ketones, Aldehydes and Derivatives: Development and Mechanistic Insight
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One-Pot Synthesis of Diazirines and $^{15}$N$_2$-Diazirines from Ketones, Aldehydes and Derivatives: Development and Mechanistic Insight

Quentin Ibert, Madeleine Cauwel, Thomas Glachet, Tony Tite, Patricia Le Nahenec-Martel, Jean-François Lohier, Pierre-Yves Renard, Xavier Franck, Vincent Reboul and Cyrille Sabot

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 transamination 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 3H-diazirine (diazirine) is one of the rare chemical scaffolds able to generate a highly reactive species under an external stimulus such as light, heat, or ultrasound. This particular reactivity has been exploited in cross-coupling reactions with aryl halides or boronic acids, and for the generation of sulfur ylides which are useful intermediates in synthetic chemistry. Recently, Lopchuk and coworkers elegantly demonstrated that diazirines could serve as effective electrophilic nitrogen transfer reagents in the decarboxylative amination of redox-active esters. 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. 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. 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. Remarkably, use of diazirines has emerged as a superior cross-linking strategy for the modification of non-functionalized alkane polymers. 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.
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 unstable intermediates which are difficult to obtain in pure forms or poorly compatible with fragile functional groups.\[12\]

A commercially available and easily storable solution of 7N NH₃ 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.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PIDA</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Ag₂O</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>MnO₂</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOK, under air</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOCl, 35 °C</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOCl, 35 °C</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>a) t-BuOCl (3 equiv), 4 h</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>a) t-BuOCl (3 equiv), 4 h</td>
<td>72 (68)[b]</td>
</tr>
</tbody>
</table>

[a] Unless specified, all reactions were carried out in a 7 N NH₃ 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 (Ag₂O), or manganese(IV) oxide (MnO₂)\[20\] 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).\[19\a] 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

**Results and Discussion**

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, NH₂OSO₃H) 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-buty hypochlorite (t-BuOK),\[17\] 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.
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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>4a isolated yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O  (3a)</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>N-t-Bu (5a)</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>N-Bn (6a)</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>N-Ph (7a)</td>
<td>traces</td>
</tr>
<tr>
<td>5</td>
<td>N-Cy (8a)</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>N-Ts (9a)</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>N-TMS (10a)</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>N-OH (11a)</td>
<td>50</td>
</tr>
</tbody>
</table>

[a] The corresponding nitrile was also isolated.

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 (CF₃) 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]

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 NH₃ in MeOH as the source of ammonia. After optimization (see supporting information), the best result was obtained using conditions that are similar to the diaziridination reaction of α-amino acids, namely, PIDA (3 equiv) and NH₃ (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. This result is quite remarkable as aldehydes are known to lead to the corresponding nitriles in almost quantitative yield under similar oxidative conditions. X-ray crystallography of single crystal of 4a (obtained by slow evaporation of CH₂Cl₂ solution) confirmed the formation of the terminal diazirine.

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

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Conversion</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>4a</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
<tr>
<td>9a</td>
<td>4a</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
<tr>
<td>5a</td>
<td>4a</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
<tr>
<td>3d</td>
<td>4d</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
<tr>
<td>9d</td>
<td>4d</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
<tr>
<td>5d</td>
<td>4d</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
<tr>
<td>3g</td>
<td>4g</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
<tr>
<td>9g</td>
<td>4g</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
<tr>
<td>5g</td>
<td>4g</td>
<td>NH₂/MeOH, PIDA</td>
<td>0°C, 2 h</td>
</tr>
</tbody>
</table>

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

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 ¹⁵NH₃ generated from ¹⁵NH₃Cl upon treatment with CH₂ONa, in order to access a series of compounds suitable for hyperpolarization studies, as well as to...
provide insight into the reaction mechanism. Thus, diazirine \( ^{15}\text{N}_2\text{-}4\text{a} \) was synthesized from N-t-butyl imine \( 5\text{a} \) in 60% yield (Scheme 3a). In \(^1\text{H} \) and \(^{13}\text{C} \) NMR, the signals of the diazirine were characteristic due to a supplementary \( ^2J_{\text{NH}} \) (2.5 Hz) and \( ^1J_{\text{CN}} \) (9.0 Hz) couplings, compared to the unlabeled diazirine. Surprisingly, complete \( ^{15}\text{N} \) incorporation was observed by \(^{15}\text{N} \) NMR with the presence of a single doublet (Scheme 3a). On the other hand, when the diazirination reaction was performed using N-tosyl imine \( 9\text{a} \), although a better yield was obtained (75%), a lower \( ^{15}\text{N} \) incorporation (73%) \(^{29} \) was observed according to \(^{15}\text{N} \) NMR spectra. Indeed, a second deshielded doublet appeared with the same \( J_{\text{SN}} \) coupling constant (Scheme 3b) corresponding to mono-labeled diazirine \( ^{15}\text{N}-4\text{a} \) (27%).

![Diagram](image1)

**Scheme 3.** Synthesis of diazirine \( ^{15}\text{N}_2\text{-}4\text{a} \) and \( ^{15}\text{N}-4\text{a} \) from imines \( 5\text{a} \) and \( 9\text{a} \) and corresponding \( ^{15}\text{N} \) NMR spectra.

In addition, the same trend was observed when N-t-butyl imine of levulinic acid \( 5\text{m} \) reacted with \( ^{15}\text{NH}_3 \); a complete \( ^{15}\text{N} \) incorporation was obtained for \( ^{15}\text{N}_2\text{-}2\text{d} \), confirming the presence of a trans-imination step (Scheme 4).\(^{30} \) \( ^{15}\text{N}_2 \)-diazirine \( 2\text{d} \) also was synthetized in a single step from levulinic acid \( 1\text{d} \), in 24% yield, with almost quantitative incorporation of both \( ^{15}\text{N} \) atoms.

![Diagram](image2)

**Scheme 4.** Synthesis of diazirine \( ^{15}\text{N}_2\text{-}2\text{d} \) of levulinic acid.

As \( ^{15}\text{N}_2 \)-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 \( ^{15}\text{N} \) incorporation (Scheme 3). Under these optimized conditions, moderate but useful chemical yields of \( ^{15}\text{N}_2 \)-diazirines \( ^{15}\text{N}_2\text{-}4\text{a-d} \) and \( ^{15}\text{N}_2\text{-}4\text{f-g} \) were obtained (10-75% yield), along with \( ^{15}\text{N} \) incorporation ranging from 49% to 92% as determined by \(^{15}\text{N} \) NMR (Table 5).

Finally, the reactivity of aromatic ketones was investigated since these are a limitation of the previous methodology using \( t\text{-BuOCl} \). The \( \text{NH}- \)ketimine \( 12 \)\(^{31} \) stabilized by hydrogen bonding with a hydroxy group, was first tested. However, in the presence of PIDA/\( \text{NH}_3/\text{MeOH} \), 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 \( ^{15}\text{N}_2 \)-diazirine synthesis from N-tosyl imines \( 9\text{a} \).

<table>
<thead>
<tr>
<th>Diazirine</th>
<th>Isolated yield (％)</th>
<th>( ^{15}\text{N}_2 / ^{15}\text{N} ) incorporation</th>
<th>( ^{15}\text{N}_2 + ^{15}\text{N} ) incorporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a (R=p-NO(_2))</td>
<td>75</td>
<td>73/27</td>
<td></td>
</tr>
<tr>
<td>4b (R=p-CN)</td>
<td>28</td>
<td>92/8</td>
<td></td>
</tr>
<tr>
<td>4c (R=p-COOEt)</td>
<td>23</td>
<td>77/23</td>
<td></td>
</tr>
<tr>
<td>4d (R=p-\text{Ac})</td>
<td>15</td>
<td>49/51</td>
<td></td>
</tr>
<tr>
<td>4f (R=m-NO(_2))</td>
<td>52</td>
<td>53/47</td>
<td></td>
</tr>
<tr>
<td>4g (R=o-NO(_2))</td>
<td>10</td>
<td>79/21</td>
<td></td>
</tr>
</tbody>
</table>

Consequently, N-tosyl ketimines \( 15 \) were chosen as substrates based on the aldime 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 = NO₂) 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, chloramine 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 lead to diaziridine III after cyclisation. After evaporation of ammonia, its oxidation with t-BuOCl, forms the diazirine IV (Scheme 5a).

As demonstrated by the previous experiment with ¹⁵NH₃, (Scheme 3 and Scheme 4), a trans-amination occurs with N-t-butyl imine and would explain the formation of ¹⁵N-imine ²¹⁵N-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 ¹⁵N₂-diazirine ²¹⁵N-II was obtained and not the mono-labeled ¹⁵N-IV one. A similar explanation could be used for N-tosyl imine since aminal VI could form the same ¹⁵N-labeled imine ¹⁵N-I (path a) with concomitant tosylamine release. On the other hand, the cyclisation of the aminal VI (path b) could explain the formation of mono-labeled diaziridine ¹⁵N-III, which is further oxidized with PIDA into corresponding monolabeled diazirine ¹⁵N-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. But, after ligand exchange between PIDA and ammonia, intermediate VIII or iminoiodinane VII, 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 which dimerized into N₂. ¹³⁵NH₃

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 2 that achieved in only 4 steps, which will find applications in proteomics. On the other hand, this strategy also affords a straightforward entry to 15N2-diazirines with complete 15N incorporation, with potential 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 NH3 (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.) at 0°C in t-butanol (0.5 mL). The mixture was stirred for 4 h at room temperature. Then, the excess of NH3 was removed by N2 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. Na2S2O3 (5 mL) and extracted with Et2O (3 x 10 mL). The combined organic layers were dried over MgSO4 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 NH3 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 NH3 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 15N2-diazirine (15N-2 or 15N-4)

(Diacetoxyiodo)benzene (3 equiv.) was added in one portion to a stirred solution of imine 5 or 9 (1 equiv.) in 15NH3 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

[1] Quentin Ibert and Madeleine Cauwel contributed equally to this article.

References


[25] The reaction conditions were optimized using different hypervalent iodine sources (PIDA or PIFA), solvents (MeOH or TFE), ammonia sources (ammonia or ammonium carbamate) and temperatures (−40°C to rt).


[29] The 15N incorporation was estimated by integration of 15N NMR signals.

[30] When the reaction was performed with NH3, a surprisingly 99% yield was obtained.


[32] X-Ray of benzoazole 13 was obtained (see experimental part).


[35] This tosylamime is indeed observed in the crude mixture (table 4, B series).


One-Pot Synthesis of Diazirines and $^{15}$N$_2$-Diazirines from Ketones, Aldehydes and Derivatives: Development and Mechanistic Insight


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