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# Diazirines as Potent Electrophilic Nitrogen Sources: Application to the Synthesis of Pyrazoles

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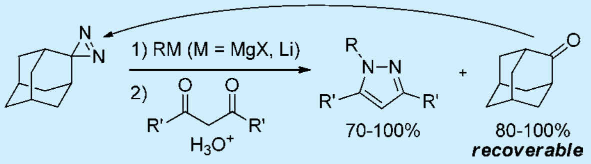
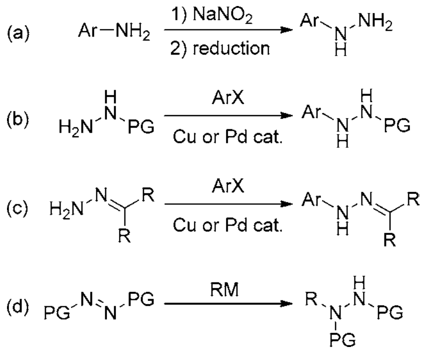
Ⓢ *Supporting Information*

**ABSTRACT:** Even after more than 50 years since its discovery, the electrophilic potential of diazirines was never truly exploited. This longstanding limitation has been resolved. *N*-Monosubstituted diaziridines and hydrazones are obtained by nucleophilic additions. They release, under hydrolysis conditions, the corresponding monosubstituted hydrazines. The latter were converted to pyrazoles in high yields. The adamantanone can be recovered in 80−100% yields. This work demonstrates the potential of diazirines as electrophilic nitrogen sources with recoverable protecting groups.



The hydrazine functional group and its derivatives are a very important family of compounds and have found numerous applications in chemistry. They are for example used as precursors for a variety of heterocycles. Monosubstituted hydrazines are particularly useful for the synthesis of indoles[1] and pyrazoles.[2] Their synthesis can be a challenge due to the similar reactivity of the two nitrogen atoms. In some cases, it is possible to monofunctionalize hydrazine ($N_2H_4$) through nucleophilic substitution or reductive amination,[3] but this often leads to the oversubstitution of the hydrazine. The reduction of diazonium salts with sodium sulfite[4] or tin(II) chloride[5] is a common strategy, although limited to the preparation of *N*-aryl substituted hydrazines (Scheme 1a).

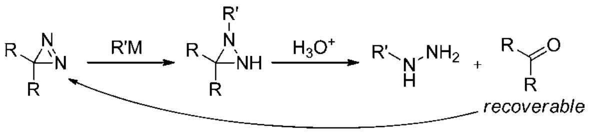
**Scheme 1. Strategies To Access Monosubstituted Hydrazines**



Transition-metal-catalyzed C−N coupling reactions of monoprotected hydrazines (Scheme 1b) and hydrazones (Scheme 1c) using palladium[6] or copper[7] as catalysts were developed. Very recently Stradiotto et al. reported the selective monocoupling of aryl chlorides and tosylates with free hydrazine.[8] Alternatively, monosubstituted hydrazines can be obtained by the reaction of a nucleophilic reagent with an electrophilic nitrogen moiety, in particular a N═N system with a low lying LUMO (Scheme 1d).[9] This approach has the advantage of a wider *N*-substituent scope, as numerous nucleophiles (RM) are accessible. The nitrogen atoms will usually require electron-withdrawing protecting groups to lower the N═N LUMO and replace acidic protons on the nitrogen atoms. An elegant example of this approach was recently reported by Moody et al. using di-*tert*-butylazodicarboxylates for the synthesis of indoles and other heterocycles.[10] The substituted hydrazine is released by removal of both *N*-protecting groups. Amination of anilines is also a possible avenue.[11]

The electrophilic character of diazirines has also been recognized,[12] in particular for the synthesis of *N*-substituted diaziridines.[13] However, their potential as general electrophilic nitrogen sources, in which the resulting diaziridine moiety is hydrolyzed to release the hydrazine group, has never been truly exploited.[14] This could be explained by side reactions during the diaziridine hydrolysis process. They would be particularly useful, as the protecting group (i.e., carbonyl compound) could be easily recovered (Scheme 2). With this in mind, we considered that a simple solution to this longstanding limitation would be to use a nonenolizable carbonyl precursor, stable under hydrolysis conditions. Herein we report the proof of concept and application of this strategy to use the potential of diazirines as general electrophilic nitrogen sources.

**Scheme 2. Concept of Hydrazine Formation from Diazirine Compounds**



The diazirines illustrated in Figure 1, made from non-enolizable carbonyl compounds, were considered. The

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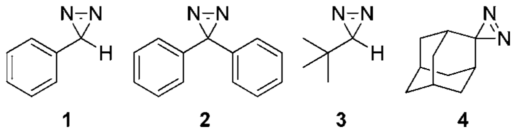


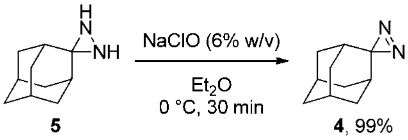
**Figure 1.** Potential diazirine candidates from nonenolizable aldehyde and ketone compounds.

diazirines from aromatic aldehydes and ketones (**1** and **2**) could suffer from light-induced isomerization to the corresponding diazo compounds,[12] resulting in a diminished reagent shelf life. The synthesis of diazirine **3**, derived from pivalaldehyde, proved to be low yielding. We turned to **4**, derived from adamantanone. Conformational restriction prevents its enolization. This compound has been widely used as a carbene precursor.[15]

Compound **4** is rapidly obtained in two steps from adamantanone. Diaziridine **5** is made using a literature procedure.[16] Diaziridine oxidation usually involves transition metals (e.g., $Ag_2O$, $CrO_3$).[12b] Sodium hypochlorite was evaluated as a low cost oxidant.

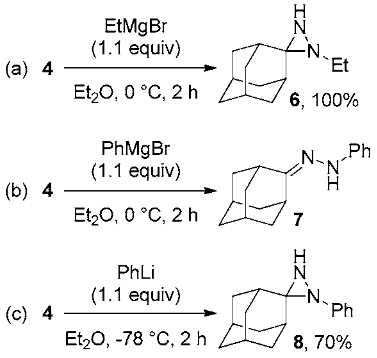
Gratifyingly, a biphasic reaction using bleach afforded the desired diazirine **4** in 99% yield within 30 min, with no need for further purification (Scheme 3). Diazirine **4** is a white hydrophobic solid, facilitating its storage and use. It can be isolated or kept in solution, to prevent its manipulation on a large scale. To ensure a suitable anhydrous solution, the latter can be rigorously dried under reflux over $CaH_2$ for 24 h. The resulting solution shows absolutely no loss or degradation of the diazirine, demonstrating stability under these conditions. With **4** in hand, initial addition reactions were made to ensure acceptable reactivity despite the increased steric hindrance around the diazirine moiety from the adamantyl group. The results are illustrated in Scheme 4.

**Scheme 3. Bleach-Mediated Oxidation of 5 to 4**



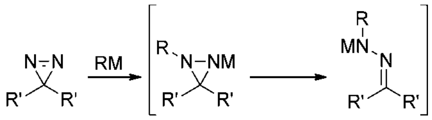
Alkyl and aryl Grignard reagents add cleanly and rapidly within 2 h at 0 °C (Scheme 4a and b). The *N*-ethyl diaziridine **6** is obtained in quantitative yield following purification by flash chromatography. In contrast, addition of PhMgBr did not lead to the *N*-phenyl diaziridine, but hydrazone **7**. Although the crude product is clean, it could not be purified due to the low stability of **7** on silica gel. Addition of phenyl lithium at −78 °C did result in the expected diaziridine **8** cleanly. The lower isolated yield is due to isomerization to the corresponding hydrazone and degradation during flash chromatography.

**Scheme 4. Initial Additions Attempts on Diazirine 4**



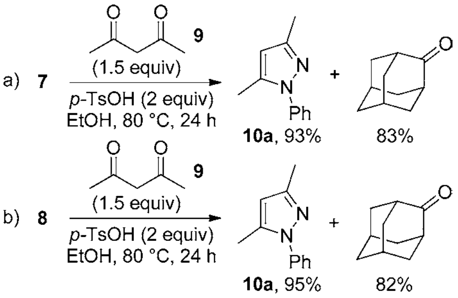
While the acid-catalyzed diaziridine−hydrazone isomerization is known,[12a,17] it is not reported for *N*-metalated diaziridines (Scheme 5). To determine if the in situ rearrangement was related to temperature, control experiments were carried out. Reaction with PhLi at 0 °C for 2 h did not result in the isomerization. Reaction of PhMgBr at −40 °C for 2 h did result in addition to the diazirine (86% conversion), and a mixture of **7** and **8** (14:86) was isolated. The isomerization process is thus slowed at lower temperature but mainly affected by the metal counterion. This metal-dependent isomerization will prove particularly interesting in further studies to selectively functionalize the metalated intermediates.

**Scheme 5. Diaziridine−hydrazone Rearrangement of *N*-Metalated Species**



Since pure monosubstituted hydrazines can be difficult to isolate and manipulate, we devised to evaluate direct deprotection condensation procedures. We elected to test the concept with 1,3-diketones to isolate pyrazoles. They are an important class of molecules in the pharmaceutical industry. Indeed, they are found in numerous drug compounds with multiple biological activities (e.g., antiviral, antitumor, antidepressant).[18] The transfer reactions were tested with pure **7**[19] and **8**, using acetylacetone (**9**). Gratifyingly, the desired pyrazole **10a** was obtained with excellent yields in both cases (Scheme 6), and the adamantanone was recovered in >80% yield.

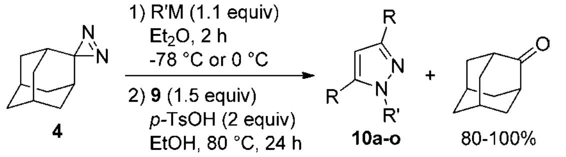
**Scheme 6. Initial Hydrazine Transfer Attempts**



While the optimized conditions involve the use of *p*-TsOH as the acid to promote the hydrazine transfer, it can be replaced by other strong acids to lessen the reaction waste products.[19]

The addition process is very clean, and to simplify the methodology and prevent degradation of the diaziridine or hydrazone intermediate, we elected to directly use the crude addition product for the transfer reaction. The conditions of addition/transfer were optimized, and the results are summarized in Table 1. As described in Scheme 4c, the isolated yield of the *N*-phenyl diaziridine **8** was due to purification issues. In fact, when crude **8** is used for the transfer

## Table 1. Preparation of Pyrazoles 10 by Addition/Transfer Procedure from Diazirine 4[a]



| entry | R′ | M | product | yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph | Li | **10a** | 95 |
| 2 | Ph | MgBr | **10a** | 67 |
| 3 | 4-Me-$C_6H_4$ | Li | **10b** | 83 |
| 4 | 4-F-$C_6H_4$ | Li | **10c** | 82 |
| 5 | 4-Br-$C_6H_4$ | Li | **10d** | 86[c] |
| 6 | 3,5-$(CF_3)$-$C_6H_3$ | Li | **10e** | 88 |
| 7 | 2-Me-$C_6H_4$ | Li | **10f** | 89 |
| 8 | 2-Et-$C_6H_4$ | Li | **10g** | 74 |
| 9 | 2-OMe-$C_6H_4$ | Li | **10h** | 67 |
| 10 | 2-$(SO_2NEt_2)$-5-Me-$C_6H_3$ | Li | **10i** | 84 |
| 11 | 2-$(SO_2NEt_2)$-5-Me-$C_6H_3$ | Li | **10j** | 73[d] |
| 12 | *n*-Bu | Li | **10k** | 82 |
| 13 | *n*-Bu | MgCl | **10k** | 79 |
| 14 | Et | MgBr | **10l** | 41 (74)[c] |
| 15 | *i*-Pr | MgCl | **10m** | 49 (70)[c] |
| 16 | Allyl | MgBr | **10n** | 72 |
| 17 | Bn | MgCl | **10o** | 100 |

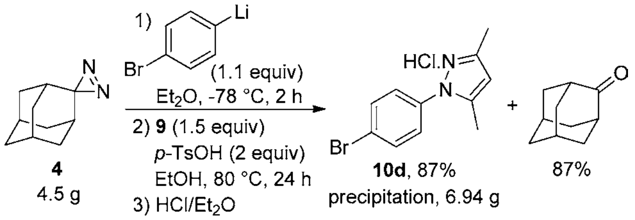
[a] All reactions with lithium reagents were performed at −78 and at 0 °C for Grignard reagents. In all cases, the adamantanone was recovered in 80−100% yield. See Supporting Information for details on the generation of the lithium reagents. [b] Isolated yields. [c] Product was isolated as the hydrochloride salt. [d] 1,3-Diphenyl-1,3-propanedione was used instead of **9** for the transfer reaction, affording **10j** (R = Ph).

reaction, the pyrazole is obtained in excellent yield (Table 1, entry 1), identical to the yield from pure **8** (Scheme 5b). This confirms the quantitative addition of PhLi on **4**. In contrast, a lower yield of **10a** is obtained after addition of the phenyl Grignard to **4** (Table 1, entry 2). Aryl lithium reagents were thus used to explore the scope of the reaction. They were either generated by halogen−metal exchange or directed ortho-metalation.[19]

The method proved to be quite general: 2-substituted, 4-substituted, and polysubstituted aryl moieties with varying electron density afforded good yields of the pyrazole (Table 1, entries 3 to 11). Acetylacetone can be replaced by another 1,3-diketone (Table 1, entry 11). As stated earlier, the use of an electrophilic nitrogen source has the advantage of a larger substituent scope. The addition of aliphatic, allylic, and benzylic nucleophiles is also possible on diazirine **4** (Table 1, entries 12 to 17). Both organolithium and Grignard reagents lead to very good yields (Table 1, entries 12 and 13). Lower isolated yields were observed for pyrazoles bearing small alkyl chains, due to their volatility (Table 1, entries 14 and 15). In such cases, precipitation of the pure hydrochloride salt of the pyrazole did increase substantially the isolated yield. This proved to be efficient when flash chromatography proved difficult (Table 1, entry 5). Finally, the procedure is easily scalable, as described by the example illustrated in Scheme 7. On a larger scale, the precipitation is facilitated, leading to a very good yield of the final pyrazole hydrochloride salt and recovered adamantanone.

In conclusion, we have demonstrated the synthetic potential of diazirines as general electrophilic hydrazine precursors. Diazirine **4** is stable over time, making it a desirable storable reagent in the laboratory. This compound has the added advantage that the diazirine precursor (i.e., ketone) can easily be recovered in the reaction process, reducing its overall environmental impact. Additionally, the variety of accessible nucleophiles makes it a great complement to transition-metal-catalyzed C−N coupling methods. The examples described herein have focused on the synthesis of numerous pyrazoles compounds. The potential of diazirines in methodologies to access polysubstituted hydrazines, as well as yield simple amination products, is currently investigated and will be reported in due course.

## Scheme 7. Multigram Scale Example



## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Characterization and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(19) See the Supporting Information for more details.