N-H Insertion of Anilines on N-Tosylhydrazones Induced by Visible Light Irradiation

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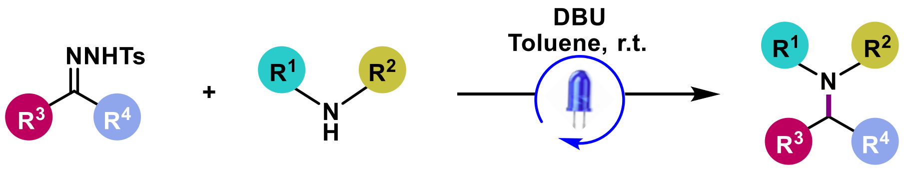


- Mild reaction conditions
- *In-situ* carbene generation
- 29 products up to 78% yield

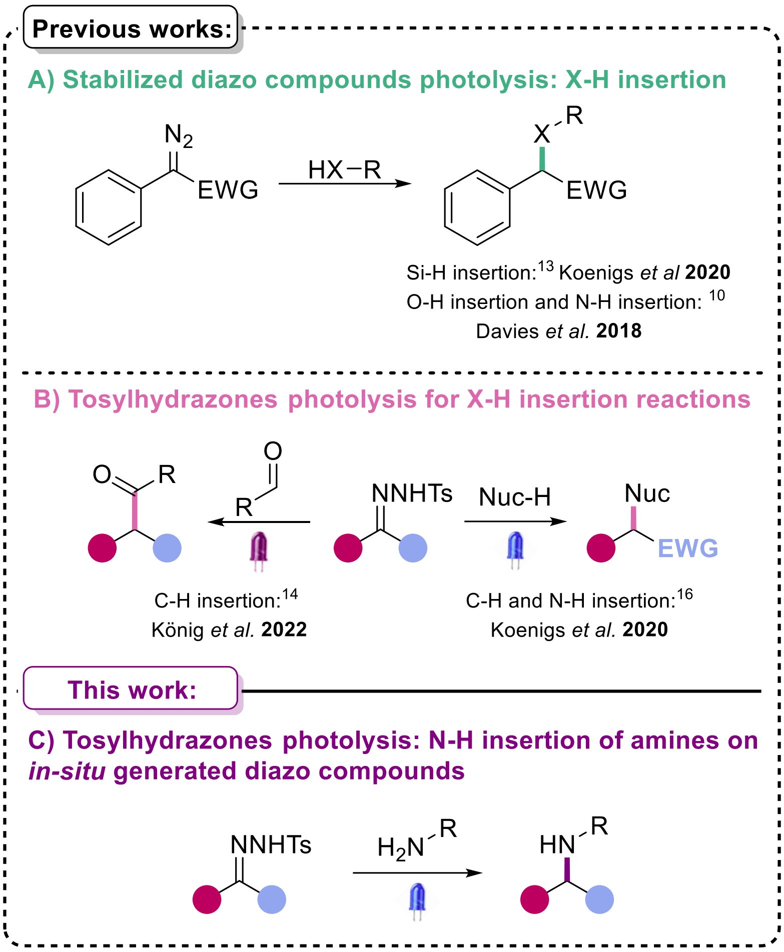
ABSTRACT: Diazo compounds as well as their precursors represent an interesting category for organic synthesis. Particularly N-tosylhydrazones, have attracted attention for their easy accessibility and diverse reactivity, including carbene transfer reactions. We described a visible light induced N-H insertion reaction of anilines on in-situ generated diazo compounds. Optimal conditions using DBU in toluene yielded desired products efficiently. Mechanistic studies enabled us to trap a car-bene intermediate that has a key role in this transformation.

Diazo compounds constitute an intriguing class for organic synthesis. They have proven to be versatile for a multitude of transformations such as cyclopropanations,[1] olefinations[2] and X-H insertion reactions.[3] However, most of these studies are limited to the use of diazo compounds stabilized or semi-stabilized by the presence of an electron-withdrawing group, aryl or vinyl groups, in ▯ position. In consequence, several methods have been developed using precursors which enable the *in-situ* generation of diazo compounds, regardless of their stabilization. Among these compounds, we can distinguish the family of *N*-sulfonylhydrazones that have garnered growing interest over the past decades in view of their easy accessibility and stability and intriguing reactivity. Indeed, in a basic medium, their decomposition leads to their use as carbene precursors under thermal[4] and transition-metal-catalyzed conditions.[5] However, the use of harsh thermal conditions may restrict the scope expansion due to the high reactivity of carbene intermediates, which can undergo unselective transformations, yielding diverse decomposition or side products.[6,7] Consequently, photolysis of diazo compounds has emerged in the past decade as an attractive method for carbene transfer under mild and gentle reaction conditions.[8–10] Several groups reported their studies concerning photoinduced carbene transfer in cycloadditions,[11] rearrangements[12] and X-H insertions, such as Si-H insertion of silanes[13], O-H insertion of alcohols and carboxylic acids and N-H insertion of amines (Scheme 1A).[10] Despite recent advancement, the development of new and attractive methodologies for C–N bond formation is of considerable importance especially to advance the field of medicinal chemistry.

Very recently, a few reports have proved that *N*-tosylhydrazones can undergo photolysis and serve as diazo compounds precursors (Scheme 1B).[14–17] Thus, König and coworkers have developed an attractive approach for carbene insertion into C−H bonds of aldehydes under 390 nm irradiation.[14] Furthermore, the same group have developed an efficient method to synthesize spirocyclopropanes from *N*-tosylhydrazones and *α*-substituted

Michael acceptors.[15] Finally, Koenigs *et al.* have demonstrated a metal-free photochemical carbene-transfer for efficient cyclopropanation, C-H and N-H insertion reaction starting from aryl-*N*-tosyl hydrazones acetates.[16]

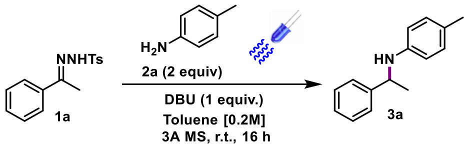
Given this context and our keen interest in photoinduced C-N bond formation[18,19] as well as diazo chemistry,[20,21] we were intrigued by investigating photochemical N-H insertion reactions of amines with *in-situ* generated diazo compounds from *N*-tosylhydrazones. Here we describe a gentle and metal-free method for Csp^3-N bond formation through a carbene transfer reaction (Scheme 1C).



Scheme 1. Diazo compounds photolysis for X-H insertions

For this purpose, our optimization study began using phenyltosylhydrazone **1a** and *p*-toluidine **2a** as model substrates for our hypothesized N-H insertion. Subsequently to our thorough and extensive optimization (See SI), the use of DBU as a base and toluene as a solvent pleasingly afforded the targeted product **3a** with a 63% yield (Table 1, entry 1). Modification of the base to other organic ones such as Et_3N or DBN resulted in a decrease of the yield (entries 2-3). Mineral bases were also investigated but gave diminished yields compared to DBU (see S.I.), for instance, Cs_2CO_3, gave a low 14% yield. Next, we carefully studied the solvent effect on the outcome of the reaction. In this aim, DCM, DMSO or anisole were evaluated but yielded to lowered yields; up to 42% in the case of anisole (entries 5-7). Several solvents have been examined but none of them gave better yield than toluene (see S.I.). Then, the reaction concentration towards compound **1a** was evaluated. Increasing concentration to 0.4 M or decreasing to 0.06 M only resulted in reduced yields, 46% and 40% respectively (entries 9-10). Control experiments were conducted either without DBU or in darkness, leading to the absence of the desired product **3a** (table 1, entries 11-12). Ultimately, the reaction was conducted under thermal conditions at 100 °C, the desired product was not formed thereby confirming the photoinduced nature of this transformation. Consequently, we identified the optimal reaction conditions as follows: *N*-tosylhydrazone (1 equiv.), aniline (2 equiv.), DBU (1 equiv.), in toluene [0.2 M].

Table 1. Optimization of the reaction conditions[a]

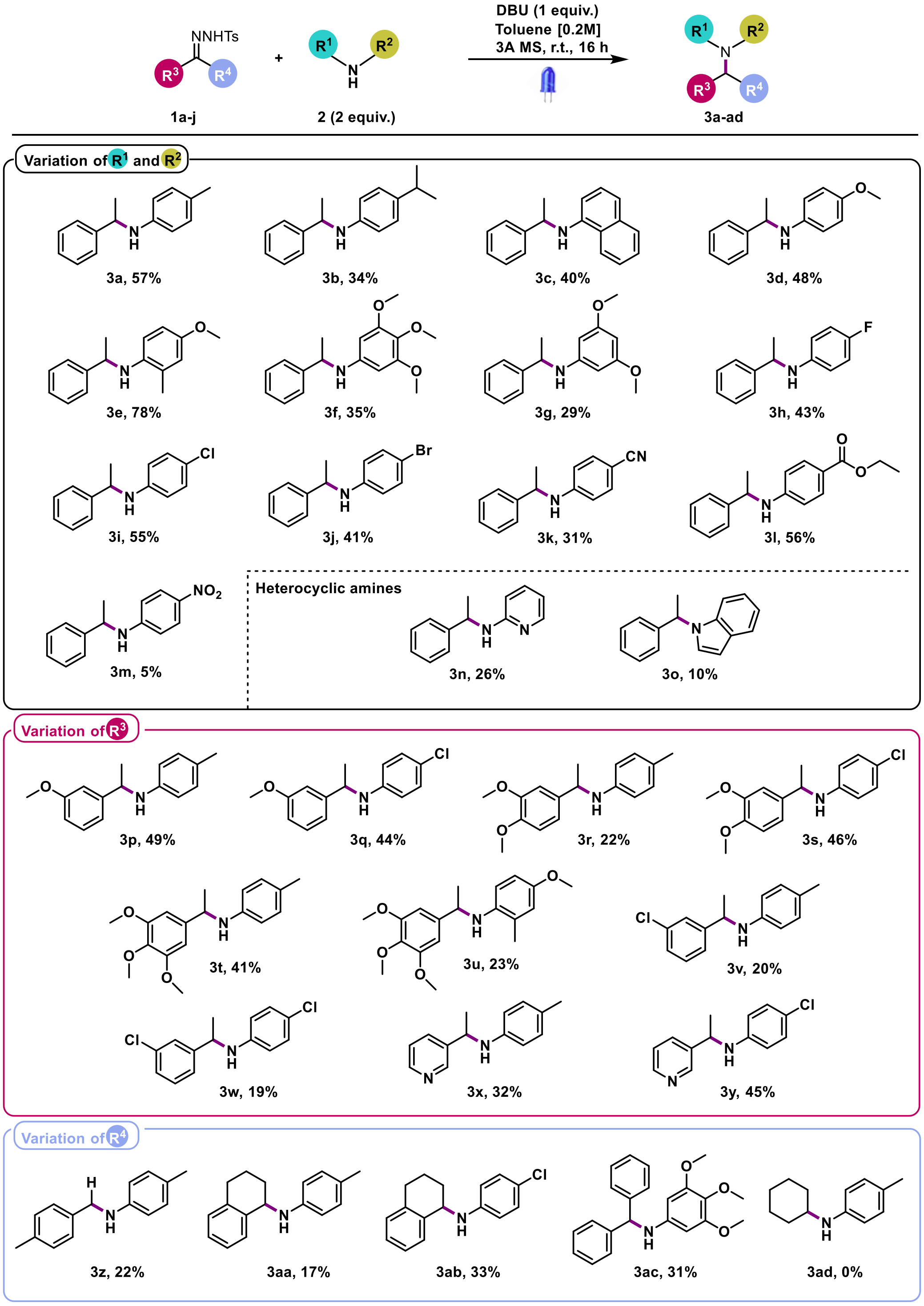


Entry	Variation from standard conditions[a]	Yield (%)[b]
1	**-**	**63 (57%)[c]**
2	Et_3N instead of DBU	n.d.
3	DBN instead of DBU	27
4	Cs_2CO_3 instead of DBU	14
5	DCM instead of Toluene	34
6	DMSO instead of Toluene	7
7	Anisole instead of Toluene	42
9	0.4M instead of 0.2M	46
10	0.06M instead of 0.2M	40
11	Without DBU	n.d.
12	In dark or heating at 100 °C	n.d.

[a] To an oven-dried sealable glass vial were added N-4-methyl-N'-(1-phenylethylidene)benzenesulfonohydrazide **1a** (1 equiv.), p-toluidine **2a** (2 equiv.), DBU (1 equiv.) in Toluene (0.2 mmol.mL^{-1}) under air atmosphere. The vials were sealed with 20mm crimp caps and put under 450 nm irradiation at 20°C. After completion of the reaction, the mixture was purified by silica gel column chromatography. [b] NMR yields using *m*-dinitrobenzene as internal standard reference.

With these optimized conditions in hand, we have investigated the scope of this transformation by varying the aniline moiety. First, we studied neutral anilines; the *p*-methyl, *p*-isopropylaniline and 1-napthylamine gave moderate to good yields (compounds **3a-c**). Next, the presence of electron-donating groups such as methoxy substitution was investigated, *p*-methoxyaniline and *ortho* substituted 4-methoxy-2-methylaniline gave the corresponding products **3d-e** with good yields, 43% and 78% respectively. 3,4,5-Trimethoxyaniline and 3,5-dimethoxyaniline conducted the reaction moderately affording 35% and 29% yields. Thereafter, we turned our attention on anilines bearing electron-withdrawing groups. Halogens such as *p*-fluorine, *p*-chloride or *p*-bromide conducted the transformation efficiently giving corresponding products **3h**, **3i** and **3j** in 43%, 55% and 41% yields respectively. Sensitive functions such as *p*-cyano or *p*-ethylester were also compatible in these conditions providing products respectively **3l** and **3m** in 31% and 56%. Strong nitro electron-withdrawing function was not compatible in these conditions giving product in only 5% yield certainly due to side reactivities of such function under light irradiation. Then, we directed our attention on *N*-containing heterocyclic structures, for instance, 2-aminopyridine proved to be compatible substrate to furnish compound **3n** although with a low 26% yield. Indole partner was also subjected to our reaction conditions, we were pleased to observe the C-N bond formation affording the product **3o** despite the low nitrogen nucleophilicity with low 10% yield.

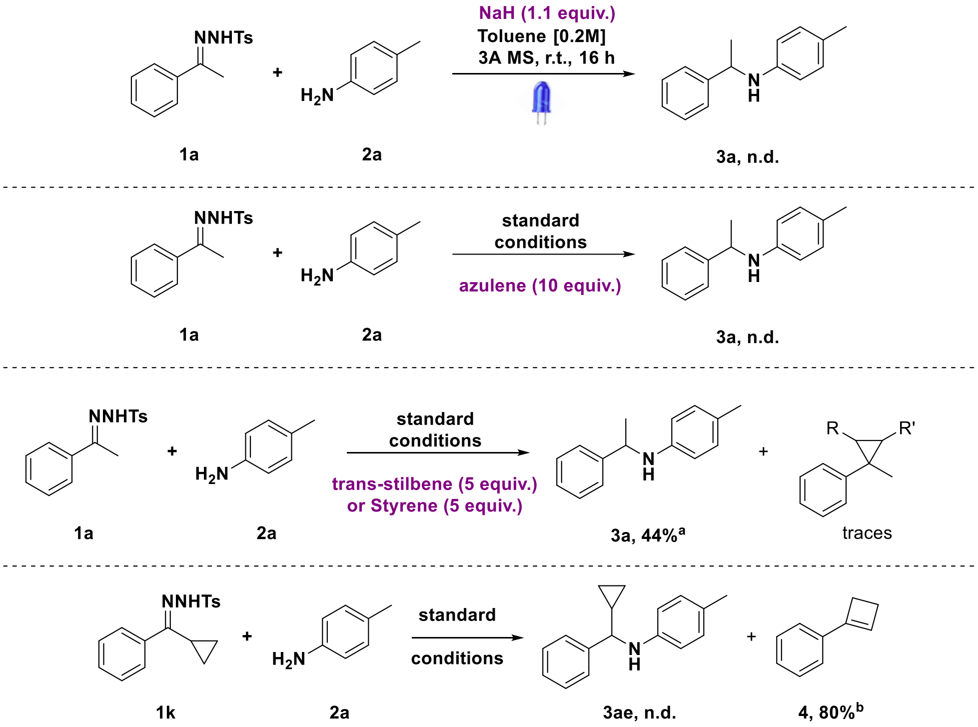
After investigating the aniline compatibility, we further took a closer look on the *N*-tosylhydrazones by investigating several substitutions. Firstly, methoxy substituted derivatives were envisaged as shown in compound **3p** to **3u**, we were pleased to observe that such substitutions were compatible in our conditions giving desired products in good yields up to 49%. *meta*-chloride *N*-tosylhydrazone has also been engaged in these conditions giving products **3v** and **3w** in a 20% and 19% respectively. Finally, pyridine derived *N*-tosylhydrazones conducted the reaction sufficiently to give compounds **3x** and **3y** with 32% and 45% yields.



Scheme 2. Scope of the reaction.

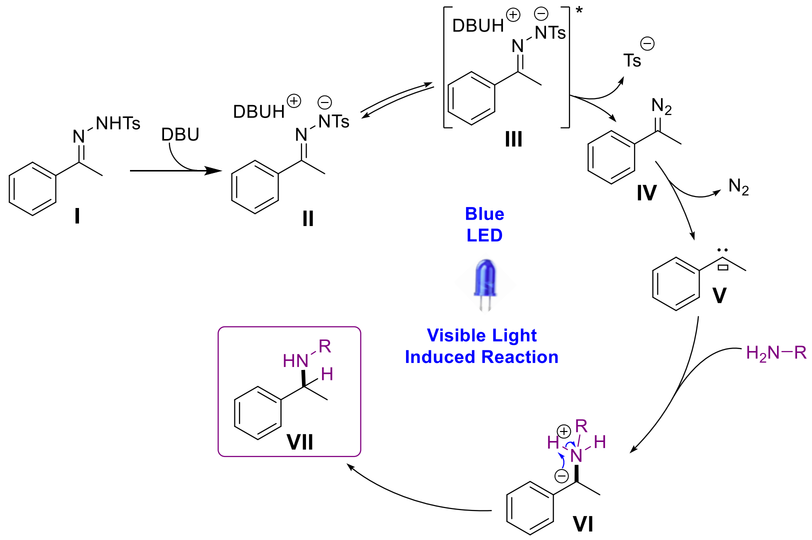
N-tosylhydrazone from aldehyde derivative was also compatible giving product **3z** in 22% yield. In addition, tetralone derived tosylhydrazones were tested and gave desired products **3aa** and **3ab** with 17% and 33% yields. Moreover, *N*-tosylhydrazone derived from benzophenone afforded the desired product **3ac** with 31% yield. Finally, alkyl tosylhydrazone such as cyclohexanone did not conduct the reaction.

In order to elucidate the mechanism, we first conducted several experiments to understand the role of DBU and the photo-induced activation mode of this transformation. Thus, UV-visible studies were launched in presence of DBU as base. Compared to *N*-tosylhydrazone, a red shift is observed indicating that the deprotonated substrate is able to absorb in the visible region (See S.I.). We then conducted our reaction in the presence of NaH instead of DBU, however, these conditions did not afford the desired compound **3a** (See S.I.). Thereby, we can suggest that the ionic complex between deprotonated *N*-tosylhydrazone and $DBUH^+$ could be certainly excited under visible light irradiation and is essential for this transformation. Later, we launched the reaction in the presence of azulene, an energy quencher. The desired product was not observed confirming that the energy of the excited ionic complex has been quenched. Finally, based on our hypothesis that after *N*-tosylhydrazone photolysis a carbene could be generated, we conducted several carbene trapping experiments. First, we ran the reaction in presence of 5 equivalents of *trans*-stilbene or styrene.[14,15] In both cases, the N-H insertion of the aniline occurred and only traces of cyclopropane containing products were detected. Consequently, we decided to undertake an intramolecular carbene trapping experiment by introducing a cyclopropyl moiety on the *N*-tosylhydrazone. Indeed, it has been proved that cyclopropyl carbene could undergo a thermal or metal-catalyzed rearrangement to afford cyclobutenes.[22,23] With this idea in mind, cyclopropyl *N*-tosylhydrazone was synthesized and subjected to our optimized conditions. Pleasingly, cyclobutene **4** was observed with 80% NMR yield (see S.I.) while no N-H insertion occurred. This result confirms that the proposed carbene intermediate is generated and this latter is the reactive species in our reaction.



Scheme 3. Mechanistic investigations. [a]: 32% of **3a** was observed with styrene. [b]: NMR yield.

Thanks to mechanistic studies and based on literature data, we can propose the following mechanism. In the presence of DBU, *N*-tosylhydrazone is able to be deprotonated to furnish the corresponding anion **II**. Based on our UV-Vis experiments, we observed that **II** is prone to absorb light thanks to a red-shift effect compared to starting material **I**. Upon its excitation to state **III**, losing tosylate anion is favorized giving diazo compound **IV**. This latter can then extrude dinitrogen moiety by photolysis to provide carbene **V**. Nucleophilic addition of the aniline followed by 1,2 hydrogen migration provided the desired product **VII**.



Scheme 4. Proposed mechanism.

In summary, we have described a mild synthesis method for *N*-containing derivatives, allowing the mono-substitution of anilines. This approach is user-friendly as it utilizes easily accessible *N*-tosylhydrazones and anilines without the need for toxic or expensive catalysts. Our proposed mechanism suggests the involvement of a carbene intermediate, supported by our observations and consistent with existing literature. We believe that these gentle reaction conditions will have practical applications in the synthesis of biologically relevant derivatives.

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by ANR JCJC granted to E.B. "LightNing" n°21-CE07-0017-01 allowing the PhD financial support of C.F. Authors also acknowledge the MESR for the financial support of S.B. The authors would like to thank also to P.N.A.S. team for the constant support on their work. The authors would like to thanks Cyril Colas from the "Fédération de Recherche ICOA/CBM (FR2708)" for HRMS analysis.

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