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Photoredox synthesis of 6- and 7-membered ring scaffolds *via N*-centered radicals†

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***N*-Containing heterocycles are important scaffolds due to their ubiquitous presence in bioactive compounds. Their synthesis has been considered as an important research field. In this work we report the access to 6- and 7-membered rings *via* a photoinduced strategy. To our knowledge, this work represents the first exemple of photo-induced 7-*endo*-trig cyclization with *N*-centered radicals.**

Synthesis of *N*-containing heterocycles remains an important challenge in organic chemistry, given their ubiquitous presence in nature as well as in pharmaceuticals and agrochemicals.[1] Consequently, researchers have been particularly interested in the synthesis of new *N*-heterocycles in order to develop bioactive compounds with unprecedented structures. To this aim, we intended to synthesize 6- and 7-membered ring scaffolds, 1,2-dihydrophthalazines and 2,3-dihydrobenzodiazepines respectively. Indeed, these structures are found in important pharmaceutical compounds such as AMPA receptor antagonists[2] or antimicrobial agent.[3]

Thus, developing access to such derivatives in a sustainable and efficient way is a useful sought-after objective. To this aim, our research is focused on an attractive strategy, the visible light catalysis, which uses light as an exclusive energy source. Using such strategy, radicals can be generated under smooth conditions and engaged in the formation of new chemical bonds.[4] In recent years, C–C bond formation has been intensively studied in a Diversity-Oriented Synthesis (DOS) fashion,[5] but investigating C–N bond formation would empower medicinal chemistry projects aiming at designing new *N*-containing heterocycles. Thus, we envisioned to build unexplored *N*-containing 6- and 7-membered rings derivatives. Importantly, visible light induced 7-membered ring formation remains rare in the literature and totally unknown for the synthesis of 2,3-dihydrobenzodiazepines[6] or for the 6-membered ring systems of 1,2-dihydrophthalazines. We propose their synthesis using alkenyl-substituted phosphonohydrazones through an Oxidative Deprotonation Electron Transfer (ODET) strategy.[7] Thus, we studied the cyclization of a *N*-centered radical (NCR) onto a pendant alkene in order to perform the designed reactions (Scheme 1). Previously, we developed a methodology using *N*-tosylhydrazones as radical precursors,[8] however the cyclization onto alkenes was in our hands inefficient in an intramolecular fashion. We supposed that the sulfonyl group of tosylhydrazones could be the limiting part for this reaction, in consequence, we turned our attention on phosphonohydrazones derivatives.

Phosphonohydrazones were obtained straightforwardly by a Heck-coupling (or other), followed by a condensation with a hydrazine unit, giving a direct access to our starting materials (Scheme 2, see ESI† for more detail).

With these products in hand, we evaluated the possibility to generate a NCR. Following the Baldwin's rules, we expected the formation of the 6-membered ring.[9,10] However, to our great surprise, the 7-membered ring scaffold has been formed during the reaction in a 1:1 ratio towards the 6-membered ring scaffold. We were surprised by this cyclization since with sulfonohydrazones we never observed such behaviour on alkynes. This observation confirmed our suspicions on the sulfonyl group being the limiting unit in our previous investigations.[8] In addition, 7-*endo*-trig reactions are scarcely reported compared to 6-*exo*-trig reactions, and to the best of our knowledge unknown under visible light catalysis. This observation encouraged us to look deeper into this reactivity.

Starting with in-house optimized conditions (Table 1, entry 1),[11] we were glad to obtain 40% of the C–N bond

Scheme 1 Synthesis design.

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Scheme 2 Synthesis of phosphonohydrazones.

formation with a 1 : 1 mixture of 6-*exo*- and 7-*endo*-trig cyclization products. We then proceeded to an extensive optimization of the reaction conditions. First, a modification of the photocatalyst (PC) from PC-1 to PC-2, PC-3 (Table 1, entries 2 and 3) or other PCs (see ESI†) gave lower yields. We then switched the base from *t*BuONa to KOH, pyridine (Table 1, entries 4 and 5), or others (see ESI†), increasing the yield of the desired product to 46% with KOH (3 equiv.). About the same results (49%, Table 1, entry 6) were obtained decreasing equivalents of KOH (1.5 equiv.). Modifying the solvent did not improve the outcome (see ESI† for full details), for instance no reaction was observed with MeCN (Table 1, entry 7), with an exception for a mixture of MeCN/H_2O (9/1) with 1.5 equiv. of KOH that gave a yield of 65% (Table 1, entry 8). Interestingly, in this entry a 4 : 1 ratio in favour of the 7-membered ring product **2a** was observed. Finally,

Table 1 Optimization of the reaction conditions[a]

Entry	Photocatalyst (PC)	Base (equiv.)	Solvents	Yield (%)	Ratio **2a**/**2b**
1	PC-1	*t*BuONa (3)	MeOH	40	1 : 1
2	PC-2	*t*BuONa (3)	MeOH	0	—
3	PC-3	*t*BuONa (3)	MeOH	20	1 : 1
4	PC-1	KOH (3)	MeOH	46	1 : 1
5	PC-1	Pyridine (3)	MeOH	0	—
6	PC-1	KOH (1.5)	MeOH	49	1 : 1
7	PC-1	KOH (1.5)	MeCN	0	0
8	PC-1	KOH (1.5)	MeCN/H_2O (9/1)	65	4 : 1
9[b]	PC-1	KOH (1.5)	MeCN/H_2O (9/1)	0	—
10	—	KOH (1.5)	MeCN/H_2O (9/1)	0	—
11	PC-1	—	MeCN/H_2O (9/1)	0	—

[a] To an oven-dried sealable glass vial were added phosphonohydrazone (1 equiv.), potassium hydroxide (1.5 equiv.), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ as a photocatalyst (2.5 mol%) and a mixture of MeCN and H_2O (9 : 1) (0.5 mL/0.3 mmol), then sealed with 20 mm crimp caps and stirred under 450 nm irradiation at 20 °C. After completion of the reaction, the mixture was purified by silica gel column chromatography. [b] Without light. See the complete table in the ESI.

the reaction didn't occur in the absence of light, catalyst or base, indicating that the reaction is photoinduced (Table 1, entries 9–11). After this optimization, the best ratio and the best yield for the 7-membered ring were obtained with the following conditions: phosphonohydrazone (1 equiv.), KOH (1.5 equiv.), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ as PC (2.5 mol%) and a mixture of MeCN and H_2O (9/1) (0.5 mL/0.3 mmol), under 450 nm irradiation at 20 °C.

With these optimized conditions, we wanted then to investigate the substrate scope of the reaction. Gratifyingly, the reaction proceeded on a variety of substituted compounds to give the desired cyclized products with good yields (compounds **2–28**). At first, several modifications have been made on the alkene chain (R^1, Scheme 3). We were pleased to obtain the unsubstituted styrene product with a total selectivity for the 7-membered ring **3a** with 50% yield. In addition, the 2-alkyl-1,1-diaryethylene starting material underwent efficiently the reaction affording the corresponding diastereoisomers **4a** with 20 and 22% yields. A mixture of 6- and 7-membered rings was obtained starting from styrenes bearing electron-donating groups on different positions with moderate yields (compounds **5–7**, 22–44%). However, except for the fluoro derivative (**8**), a total selectivity towards 6-membered ring products has been observed while using electron-deficient styrenes. Indeed, phenyls bearing ester, nitrile and nitro groups gave the corresponding products with moderate yields (24–44%, compounds **9–11**) while pyridines gave 45–46% yield of the desired 6-membered rings (compounds **12–13**). Moreover, aliphatic alkenes gave 6-membered rings with 30 and 48% yields (compounds **14–15**), while no reaction occurred with a tetrasubstituted akene (**16**). Next, we have studied the variations around the aromatic cycle (R^2). The reaction worked efficiently in the presence of electron-donating, electron-withdrawing groups as well as heterocycles (compounds **17–21**). To our delight, we formed exclusively the corresponding 7-membered rings with moderate to good yields (34–60%). Finally, compounds bearing different substitutions, both on R^1 and R^2 positions, proceeded successfully affording a variety of 6- or/and 7-membered scaffolds (compounds **22–28**, 21–73%) (see ESI†). Following this scope investigation, electron rich or neutral groups on R1 seem to promote the formation of the 7-membered ring, however, electron poor groups promote 6-membered ring products. These divergent results could demonstrate the major influence of electronic effects in the outcome of the reaction. Nonetheless, one example must be further discussed: the selectivity for the product **8** which favoured the formation of the 7-membered ring. We propose that this selectivity is due to the known mismatching electronic effects of fluorine on the electronic density on the alkene double bond due to its −I and +M effects, mesomeric effect being here predominant for the regioselectivity thus leading to the 7-membered ring as for **22a**.[12] In addition, counter ion, here the K^+, is probably involved in stabilizing the attack during the transition state, as already described in the literature.[13] To gain insight of the reaction mechanism, we have launched the reaction in presence of TEMPO, diphenyl disulfide and NCS in order to trap the formed radical. Unfortunately, no radical adducts could be identified, however, the cyclization reaction did not occur confirming that this transformation is certainly radical-induced. Based on our work and the

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Scheme 3 Scope of the reaction of 6- and 7-membered ring formation. All yields were for isolated compounds. [a] The dimer of **5b** has been isolated.

literature,[14] we thus propose that the first step is the deprotonation of the starting material **I** with the base giving the anion **II**.

This latter anion can be easily oxidized by the excited photocatalyst, as seen in cyclic voltammetry, our model substrate possesses an oxidation potential of 0.67 V *vs.* SCE. This radical can then follow two different pathways depending on the substitution of the double bound. Electron rich double bond substitutions preferentially induce 7-membered ring intermediate **IV** and electron poor ones promote the 6-membered ring intermediate **VIII** as seen in the Scheme 4.

Then, the effective reduction of the generated radical by the photocatalyst[15] allows to produce, respectively, anions **V** and **IX**, leading after protonation to the final compounds **VI** and **X**. The dimer **XI** on the compound **5b** has been isolated in a small quantity allowing us to suppose that the dimer **VII** could also be formed.

In conclusion, herein we report for the first time a 7-*endo*-trig cyclization induced under photoredox conditions,[16] upon the generation of an NCR. The outcome of the cyclization process (6-*exo versus* 7-*endo*) seems to be electronically-driven based on the evaluation of the scope of this reaction.

The reactivity of the photo-induced NCR leads to a 6-*exo*- or/and a 7-*endo*-trig cyclization process paving the way for a large variety of exquisite and unknown structures, related to the benzodiazepine or dihydrophthalazine families, of upmost importance for further biological investigations.

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Scheme 4 Proposed mechanism for 6- and 7-membered rings formation.

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Conflicts of interest

There are no conflicts to declare.

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