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Dearomatization of Pyridines: Photochemical Skeletal Enlargement for the Synthesis of 1,2-Diazepines

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Supporting Information Placeholder

ABSTRACT: In this report, we developed a unified and standardized one-pot sequence that converts pyridine derivatives into 1,2diazepines by inserting a nitrogen atom. This skeletal transformation capitalizes on the *in situ* generation of 1-aminopyridinium ylides which rearrange under UV light irradiation. Thorough evaluation of the key parameters (wavelength, reaction conditions, activating agent) allowed us the elaborate a simple, mild and userfriendly protocol. The model reaction was extrapolated to more than 30 examples including relevant substrates affording unique 7membered structures.

Heterocyclic scaffolds are ubiquitous in bioactive molecules and particularly coveted in drug design as they confer selectivity and valuable properties to a potential drug candidate.¹⁻³ Among them, pyridine-containing compounds could be found in a vast part of the FDA-approved bio-relevant molecules (Figure 1A).⁴⁻⁷ Indeed, this aromatic core can be prepared and modified in many efficient ways.⁸⁻⁹ On the other hand, 7-membered-ring azaheterocycles, like 1,2-diazepines, are much less studied.¹⁰ Having only one extra nitrogen-atom, these scaffolds are nevertheless in strike contrast. Reported syntheses of 1,2-diazepines exclusively rely on the combination of well-designed 1,5-dielectrophiles and hydrazine as the N -N bond formation is reputed to be challenging.¹⁰ The latter induces side-reactivities such as oligomerization, polyalkylation or even potential hydrolysis of the substrate. Therefore, it is not surprising to find this motif in a handful of bioactive substrates.¹¹⁻¹⁵ Among them, benzofused derivatives represent the vast majority as the aromatic ring restricts the conformation of the 1,5-dielectrophile, thus facilitating the key annellation step with hydrazine. In contrast, the synthesis of monocyclic 1,2-diazepines suffers from both a tedious protocol and inefficient purification.¹² However, 1,2diazepines could be very compelling if one wants to modulate the geometry and/or the properties of a target compound. According to

the Hückel rule, 1,2-diazepine is non-aromatic and its planarity is disrupted offering the benefits in terms of selectivity of a tridimensional architecture.

Over the past years, many elegant strategies have emerged aiming at editing aromatic skeletons¹⁶⁻¹⁷ by inserting,¹⁸⁻²⁵ deleting,²⁶ or swapping atoms²⁷ in a short amount of time and steps (**Figure 1B**). Thus, one could rapidly evaluate the potential interest of drug analogs by interchanging the nature of one (or more) aromatic ring(s). This paradigm-shift would greatly accelerate drug discovery and prevent time-consuming and in-depth retrosynthetic analysis to access complex analogs through non-traditional disconnections.²⁸ Therefore, we wondered if pyridines could be seen as an abundant feedstock for the synthesis of 1,2-diazepines by developing a methodology to incorporate a nitrogen-atom into the pyridine core.

Early results from the 70s reported the photochemical rearrangement of 1-aminopyridinium ylides into 1,2-diazepines (Figure **1C**).²⁹⁻³⁰ Several research groups slightly extended the scope of accessible 1,2-diazepines.³¹⁻³⁴ However, the tedious synthesis and isolation of the starting materials remained a significant drawback. Despite the indisputable interest of 1-aminopyridinium salts in organic synthesis,³⁵ this reaction remained a scientific curiosity and was never applied to any synthesis. In fact, we do believe this rearrangement is still underestimated due to the lack of experimental details regarding the photochemical setup. In addition, only few mechanistic evidences are reported which testifies a misunderstanding of the reaction. To tackle these hurdles, a unified and standardized protocol is required to ensure reproducibility. Based on this statement, we aim at developing a sequential protocol in which the photo-active 1-aminopyridinium ylide is generated in *situ* from pyridine derivatives; thus, unlocking the dearomative ring enlargement for the synthesis of 1,2-diazepines from readily available building blocks (Figure 1D).³⁶ In order to provide a general and user-friendly strategy, the key parameters of this transformation would be scrutinized.



Figure 1. Context of the study.

Our investigations started by studying the optimal wavelength by UV-vis absorbance to trigger the photochemical rearrangement (**Figure 2A**).³⁷ Ylides bearing various substituents on the exocyclic nitrogen atom were prepared according to the reported procedures.³⁸⁻³⁹ In all the cases, an absorbance band was found between 330 and 370 nm in CH₂Cl₂ whose intensity decreases over time. Therefore, we monitored the conversion of one aminopyridinium ylide by ¹H NMR in deuterated DMSO by directly irradiating the solution at 365 nm with a coaxial optical fiber in the spectrometer. A first order decay of the starting material was clearly identified leading to the clean formation of a dearomatized product which turns out to be the corresponding 1,2-diazepine. In addition, several *para*-substituents were interrogated in a Hammett study (**Figure 2B**). In fact, electron-donating groups reacted faster furnishing the desired products as seen on the negative slope (see SI for kinetics).

We next turned our attention to the photochemical rearrangement of readily available and bench stable 1-aminopyridinium ylides (**Figure 2C**). Several representative substrates were prepared and isolated in order to assess the influence of the substituent on the negatively charge nitrogen atom (see SI for synthetic procedures). After a preliminary optimization phase, we found out that irradiation of ylides under UV light was very effective in both CH₂Cl₂ and DMSO, the latter ensuring a better solubility. First of all, benzoyl derivatives bearing different substituents were engaged. In general, good to excellent yields were obtained after isolation of the desired 1,2-diazepines (1 to 6). Noteworthy, 1 was still isolated in 81% yield when 2 equivalents of TEMPO, a radical scavenger, were added in the reaction vessel. Moreover, the chlorinated analog 5 afforded suitable crystals for X-ray diffraction, thus confirming the structure of the product. Nonetheless, electronwithdrawing groups attached to the para or ortho position of the benzoyl core were detrimental for the outcome (7 to 9); in the case of a nitro group, the reactivity was switched off. This trend was confirmed when sulfonylated analogs were prepared. Although the corresponding diazepine 10 could be isolated in 59% yield and crystalized, one can observe the concomitant formation of both pydirine and tosylamide resulting from the N - N bond cleavage. Indeed, given the withdrawing nature of the tosyl group, this side reactivity follows the trend observed in the benzoyl series. Thus, replacing a methyl for a methoxy group in 11 to counterbalance the electronics seems to improve the yield. Already reported decades ago,²⁹⁻³⁰ we could achieve good yields of the 1,2-diazepine when carbamates derivatives were engaged in our photochemical setup (12 and 13). This feature is particularly interesting if one wants to functionalize the inserted nitrogen atom at will after a deprotection step. As expected, electron-deficient aromatic substituents like a 2,4-dinitrophenyl did not lead to the desired product 14. In fact, the irradiation of the parent ylide gave intractable crude mixtures in which the starting material could be detected in low amounts (ca 25%). Finally, the commercially available 1-aminopyridinium iodide **22** was engaged under the same protocol. Even in the presence of additives, the crude analyses showed no conversion, or, in the presence of triethylamine, a mixture of both the starting material and pyridine.

We next turned our attention to substituted pyridines and their impact on the selectivity during the photochemical rearrangement. As expected, when the C2-position is blocked either with a phenyl or a methyl group, the insertion exclusively occurs between N1 and C6 as showed with compounds **16** and **17**. The ylide prepared from 2,6-lutidine failed to give the desired product **18** thus confirming the sensitivity of the reaction towards steric hindrance when both active sites are inaccessible. When the C3-position is substituted, two regioisomers are obtained, independently of the electronic nature of the corresponding substituent (**19** to **21**). In the case of **20**, the two different 1,2-diazepines were easily separated and the major product was unambiguously confirmed by X-ray diffraction. This result indicates that the selectivity is once again in favor of the less hindered reactive site.



Figure 2. Optimization of the photochemical rearrangement. Isolated yields of pure products are reported. a) 2 equiv. of TEMPO were added. b) Neat compound **3** is unstable and rapidly decomposes. The yield of the pure material in solution was estimated by ¹H NMR spectroscopy. c) same outcome is observed if 1 equiv. of AcOH or NEt₃ is added. d) Obtained as an inseparable mixture.

In order to develop a one-pot sequence to convert pyridines into 1,2-diazepines, we envisaged to generate the 1-aminopyridine ylide *in situ*. Based on our previous observations, the substrate **22** should remain intact under UV light irradiation. Furthermore, as some *N*-benzoyl-1,2-diazepines appear to be poorly stable (**2** and **3** especially; **1** to a lesser extent), we selected ethyl chloroformate and triethylamine as reactants to generate the corresponding ylide. To our delight, we rapidly identified CH₂Cl₂ as a good candidate to

perform both the generation of the ylide and the photochemical rearrangement as **12** was detected in the crude NMR in 78% yield (**Figure 3** top, inset table, entries 1 to 4). While DIPEA lead to a slight erosion of the yield, it remains quite efficient (entry 5). However, the use of inorganic bases like Cs_2CO_3 failed to improve the yield, mainly due to their poor solubility in CH₂Cl₂ (entry 6). Similarly, analogous activating agents such as PhCOCl or Boc₂O performed very well under these conditions giving the corresponding 1,2-diazepines 1 and 13 in excellent isolated yields (entries 7 and 8). Finally, increasing the concentration allowed us to reduce the amount of CH_2Cl_2 while preparing 12 in similar yields (entry 9).

With these optimal conditions in hands, we had to find the most suitable aminating agent in order to elaborate a fully compatible protocol to convert pyridines into 1,2-diazepines in a single-flask operation (Figure 3 bottom, inset table). After questioning the literature (see details in SI), we selected MSH (O-(mesitylsulfonyl)hydroxylamine) for several reasons: a) it can be easily prepared in 2 steps from cheap and commercially available reactants and collected by filtration; b) as an hydrate, usually between 20 and 40% water, it is an air and moisture tolerant solid which could be stored under regular atmosphere for several days without any noticeable alteration (see SI for potential hazard).⁴⁰ Thus, we could generate the 1-aminopyridinium in situ from the parent pyridine 23 within an hour at 40 °C. Noteworthy, 4Å molecular sieves appeared to increase the yield although it is not mandatory to achieve synthetically useful yields. Taking advantage of our previous conditions, we achieve our goal of dearomatizing pyridine 23 via an N-atom insertion and we could isolate the desired product 12 in 84% yield.



Figure 3. One-pot synthesis of 1,2-diazepines. a) Isolated yields of pure products are reported.

The scope and limitations of our protocol were explored (Figure 4). First, we found that several *N*-activators were compatible with our one-pot procedure including PhCOCl (1), Boc₂O (13), CbzCl (24) and even base-sensitive FmocCl (25). Alkylpyridines gave satisfactory results affording the desired diazepines; although the yield drops when the pyridine is substituted with a benzyl group in 4-position (26 to 29). Aromatic groups, including furan and thiophene, on the C2 carbon boded well under our conditions (30 to 32). We then questioned the functional group tolerance of our strategy. Indeed, nitrile (33), methoxy (34), ketones (35, 36 and 43), esters (37 and 41), amides (42, 46 and 47) or halogens (38 to 40 and 46) were all tolerated and smoothly reacted to afford the corresponding 1,2-diazepines in modest to very good yields. Worth mentioning, these examples highlight the undeniable interest of this methodology as it permits to access previously out-of-reach molecules. As stated before, the most straightforward route to make 1,2diazepines capitalizes on the use of hydrazine, which can be incompatible and particularly challenging with electrophilic moieties or polycarbonylated fragments.

Only one 7-membered heterocycle is obtained when a 2- or 4substituted pyridine is engaged. However, for 3-substituted substrates, both regioisomers were often obtained. In all cases, the selectivity is governed by the steric factors yielding preferentially the 4-substituted 1,2-diazepine (40, 41, 42 and 45). Therefore, one reaction enables the synthesis of up to 2 analogs with potentially different properties. Interestingly, compound 43 was isolated as sole isomer from the crude mixture. Pyridine bearing an aldoxime functional group could undergo the rearrangement although in low yield. In addition, the free OH group readily reacted with the ethyl chloroformate in excess. Electron-withdrawing groups in the C4 position inhibited the rearrangement;⁴¹ we could nonetheless isolate the unreacted ylide 48 with a good yield. In the case of 2-vinylpyridine, the double bond was well tolerated as we could not notice any side reactivity on the pending olefin (49). In contrast, the ethynyl derivative lead to the unexpected formation of a 1,2diazepine bonded with a fused pyrazolo [1,5-a] pyridine ring in 80% yield (50).⁴² The structure of the latter was unambiguously unveiled by X-ray diffraction. Then, we engaged 2,2'-bipyridine with twice the amount of MSH, ethyl chloroformate and triethylamine. To our delight, we could easily separate the two main products 51 and 52 which turned out to result from one and two rearrangements respectively. Finally, we could successfully prepare the 1,2-diazepinebased analogs of some relevant complex molecules like loratadine 53 (antihistamine drug), an ester of cholesterol and niacin (vitamin B₃) 54, a tyrosine derivative 55 (neurotransmitters synthesis) and bisacodyl 56 (laxative). Even though 53 was obtained in moderate yield, the unusual structure of this tricyclic scaffold comprising two contiguous 7-membered-rings makes it very challenging to prepare with another route.



Figure 4. Substrate scope. Isolated yields of the pure products are reported. a) Yield determined by ¹H qNMR spectroscopy with mesitylene as internal standard. b) Obtained as an inseparable mixture. c) **MSH** (2.8 equiv.), $CICO_2Et$ (4 equiv.), NEt_3 (6 equiv.).

In conclusion, we have established a unified protocol using commercially available resources and easily prepared reagents to dearomatize pyridine derivatives by inserting nitrogen-atoms within the aromatic core. The ring expansion is triggered by the photochemical activation of 1-aminopyridinium ylides formed *in situ*. The synthesized products, even the simplest ones, were previously out-of-reach due to the lack of efficient methods to selectively prepare 1,2-diazepines. In fact, our protocol can be applied to pharmaceuticals to prepare the 7-membered-ring analogs in a short amount of time and thus accelerate the discovery of potential drug candidates. Further transformations involving the formed 1,2-diazepines are currently under study in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, NMR experiments, crystallographic data (PDF)

Accession Codes

CCDC **2279846**, **2279847**, **2279848**, **2279849** and **2279850** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via <u>www.ccdc.cam.ac.uk/data_request/cif</u>, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interests.

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