Modular Approach to Substituted Pyridoazepinones

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Supporting Information Placeholder

ABSTRACT: Pyridoazepinones are a potentially interesting structures, yet still underexploited in the medicinal chemistry field and hard to obtain synthetically. We present a general and flexible synthetic route to substituted pyridoazepinones, enabled by the xanthate addition-transfer process, and furnishing the target molecules from readily available starting materials in generally good yields. The method shows good functional group tolerance and allows the preparation of pyridoazepinone scaffolds on gram scale.

The pyridine ring is one of the most common subunits in pharmaceuticals and agrochemicals. It also appears in a variety of fused scaffolds possessing a myriad of medicinal properties. Thus, the search for efficient and reliable strategies toward pyridine-containing structures represents an important challenge in organic chemistry.

Figure 1. Some biologically active pyridoazepinones

Pyridoazepinones constitute such scaffolds. They are present in nature as fragments of biologically active substances, for example in adina alkaloids, isolated from *Adina rubescens* (Figure 1).¹ Synthetic derivatives of this class include Nevirapine, a non-nucleoside inhibitor of HIV reverse transcriptase.² Nevirapine was approved in 1996 by the FDA and is currently in the WHO List of Essential Medicines. Another medicinally active pyridoazepinone is 1-azakenpauellone, which inhibits glycogen synthase kinase 3, a therapeutic target in the development of antidiabetic drugs.³

Finally, pyridoazepinones are classical isosteres of benzazepinones, which are an important family of biologically active compounds (they act, for example, as sodium channel blockers).⁴ Thus, it would be desirable to make nitrogen-containing analogues of various biologically active benzazepinones. This sort of modification may result in better binding with protein active sites and in improved pharmacokinetic properties.

This being said, however, it was surprising to find that no general method for the synthesis of these structures has been established,

even though the first record of obtaining such compounds dates from 1969.⁵ The most common method to access pyridoazepinones is based on ring expansion reactions, such as the Beckmann and Schmidt rearrangements (Scheme 1, A).⁶

However, in most cases, this strategy requires the preparation of highly functionalized substrates and includes *de novo* pyridine ring formation. Furthermore, the variety of structures that can be attained by this route is limited due to low functional group tolerance. The same problems arise when the seven-membered ring is constructed via a Dieckmann condensation (Scheme 1, A).^{3,7} Even though these methods have furnished target materials for biological evaluations, they lack flexibility and do not allow the preparation of the large libraries of compounds needed for drug discovery. A completely different method, based on palladium-catalyzed C-H arylation, was described by Cramer and co-workers.⁸ Being tailored mostly for the preparation of benzazepinones containing quaternary stereocenters in the seven-membered ring, this method also allowed the synthesis of pyridoazepinone. However only one example was reported and the reaction required harsh conditions and a high catalyst loading. Summing up the above, a new, practical, and convergent approach to pyridoazepinones would be highly valuable.

Following a longstanding interest in the synthesis of heterocyclic scaffolds in our group,⁹ we developed a few pathways to benzazepinones¹⁰ and *N*-alkyl-substituted pyridoazepinones¹¹ (Scheme 1, B). In this paper, we present a general and modular synthesis of *N*-unsubstituted pyridoazepinones. Our method features the construction of the seven-membered ring by C-C bond formation via xanthate addition-transfer process, radical cyclization, and re-aromatization of the pyridine ring enabled by homolytic cleavage of the sulfonamide bond (Scheme 1, C).

The synthesis of pyridoazepinones from simple precursors must address several challenges. First, the formation of seven-membered

rings is a rather unfavorable process, due to low reaction rates¹² that may result in lower yields and the formation of side products. Additionally, the pyridine moiety is more electron-deficient but is less aromatic than benzene ring, making the final oxidative aromatization step more difficult. Finally, the most interesting examples of this family possess a secondary amide group, which can partake in constructive hydrogen bonding within the receptor or be used as an additional functionalization site. However, an *N*-monosubstituted amide can also be a drawback because it adopts an *E* conformation that prevents the cyclization, as shown by our previous reports;¹⁰ thus, a protecting group is required that can be easily removed, preferably during the last step of synthesis.

Scheme 1. Methods for the Synthesis of Pyridoazepinones

A. Existing methods of synthesis of pyridoazepinones

B. Previous results of our group

N-substituted pyridoazepinones:

Benzazepinones:

C. This work

According to our method, substituted aminopyridines **A** can be converted into xanthates **B** by a simple sequence that includes sulfonylation, introduction of α -chloroacetyl group, and xanthate formation (Scheme 2). Due to the high commercial availability of substituted aminopyridines and the ease of preparation of xanthates, a vast array of starting materials can be synthesized in principle. The next step is the peroxide-promoted intermolecular radical addition of xanthate **C** to an unactivated olefin, which can bear various functional groups. The xanthate addition-transfer process leads to another, more complex xanthate **C**, which in turn gives a radical **D** when treated with peroxide at high temperature. The following intramolecular addition results in the formation of delocalized dihydropyridinyl radical **E**, in which the fragmentation of the N-S bond occurs to give intermediate **F** with extrusion of a methanesulfonyl radical. This latter species can extrude sulfur dioxide to furnish a methyl radical that can participate in the chain propagation. As for intermediate **F**, it rapidly undergoes a tautomerization to yield the desired pyridoazepinone **G**. This last fragmen-

tation thus serves to rearomatize the pyridine ring and furnish at the same time the *N*-unsubstituted seven-membered ring lactam.

For the starting point for our studies, we chose 2-chloro-5-aminopyridine because our previous experience showed the utility of a substituent on position 2 in curtailing the nucleophilicity of the pyridine nitrogen and preventing an ionic destruction of the xanthate group.¹⁰ Following this consideration, we converted 2-chloro-5-aminopyridine into the corresponding xanthate **3a** via a simple three-step sequence, with each step proceeding in good to excellent yield (Scheme 3). It is also worth noting that the reactions were carried on multigram scale. All the materials are crystalline and can be easily purified by recrystallization, which makes this procedure highly suitable for further scaling up.

Scheme 2. Proposed Strategy toward Pyridoazepinones

Scheme 3. First Example of Pyridoazepinone Synthesis

The resulting xanthate **3a** was then introduced into a test reaction with allyl acetate, under thermal conditions with substoichiometric amounts of di-lauroyl peroxide (DLP) as the initiator (10 mol%; DLP is also sold under lauroyl peroxide, Laurox® or Luperox®). This reaction proceeded with very good yield (85%), and the isolated adduct **4aa** was purified by column chromatography. We next examined the ability of this xanthate to undergo the desired key cyclization reaction. Based on our previous experience, a higher temperature is usually required to induce the cleavage of the sulfonamide moiety, and DLP was therefore replaced with the more thermally robust di-*tert*-butyl peroxide (DTBP). After screening three high-boiling solvents (chlorobenzene, *tert*-butylbenzene and octane), we found that the best results were obtained with chlorobenzene. To our delight, the target pyridoazepinone **5aa** was produced good yield (64%).

We next expanded the study to other olefins (Scheme 4). Model xanthate **3a**, derived from 2-chloro-5-aminopyridine, reacted readily with various alkenes, and the cyclization provided pyridoazepinones bearing different substituents, including esters, protected amines, boronate esters, silanes, and more complex structures like purines. 1,1-Disubstituted alkenes can also be used leading to the creation of a quaternary center, as indicated by example **5an**. The fact that the intermolecular addition step to electronically unbiased alkenes proceeds in higher yield than the cyclisation step underscores the general difficulty of producing a seven-membered ring by direct radical ring closure, and even more so when the cyclisation is onto an aromatic or heteroaromatic nucleus. It is also worth noting that, in the absence of alkene, treatment of xanthates such as **B** (Scheme 2) leads to azaxindoles,¹¹ but even this ring-closure mode appears to be slower than the intermolecular addition to the alkene and does not therefore cause any significant complications in the present context.

Scheme 4. Olefin Scope

We also explored the scope of the pyridines that can be involved in this sequence (Scheme 5). Thus, we prepared four xanthates, bearing bromo- (**3b**), methyl- (**3c**) and trifluoromethyl substituents (**3d**) in the 2-position of the pyridine ring, and, finally, a methyl group in the α -position to the carbonyl group (**3e**) (see Supporting Information for details). In the case of xanthates **3b**, **3d** and **3e** we were glad to find that both the radical addition and cyclization steps proceeded with moderate to good yields; for xanthate **3c**, however, we quite surprisingly isolated only the sulfonylated prod-

uct **6ca**. In this case, the oxidation of the intermediate radical (radical **E** in Scheme 2) seems to be more favorable than the extrusion of methanesulfonyl radical, for as yet unknown reasons.

The regioisomeric products **5fa**, **5fc**, **5ga** and **5gc**, derived from 4-amino-2-chloropyridine and 6-amino-2-chloropyridine, were also prepared in the same manner. Even though xanthates **4fa** and **4fc** readily cyclized to the 3-position of the pyridine ring, the reaction proved to be more problematic in case of the products **5ga** and **5gc**, giving a mixture of unidentifiable side products. In order to improve the yield, we tried to perform the cyclization of xanthate **4gc** under microwave heating. However, no increase of the yield was found. We also conducted the reaction in the presence of camphor-sulfonic acid (CSA), bearing in mind the assumption that the protonated pyridine nucleus should react faster ("Minisci-type" reaction conditions). Unfortunately, no improvement in the yield was observed either, and the reaction merely resulted in hydrolysis of the amide bond of most of the starting xanthate **4gc**. The reasons for the delinquent behavior of the 2-chloro-6-amino- series are not clear at the moment and further work is needed to probe this question.

Scheme 5. Scope of Pyridines

To highlight further the practicality of our approach, we performed the sequence leading to benzazepinone **5aa** in a one-pot process, which furnished the desired product in a somewhat better overall yield (Scheme 6). We also prepared pyridoazepinone **5aa** from xanthate **3a** on gram scale, affording 1.26 g of the target product (Scheme 6). In this case, the purification of the product consisted in a single precipitation from the concentrated reaction mixture instead of column chromatography.

Scheme 6. One-pot and Gram-scale Synthesis

Finally, to demonstrate the utility of pyridoazepinone scaffold for medicinal chemistry, we tried to prepare several derivatives of compound **5aa**, exploiting the presence of the secondary amide function (Scheme 7). Tetrazoles belong to an interesting class of pharmacophore groups and are present in various medicaments.¹³ Thus, we prepared tetrazole **7** using the method reported recently by Matsugi and co-workers.¹⁴ Another possible modification of pyridoazepinones relies on the functionalization of the α -position of the amide via the corresponding Vilsmeier salt. Thus, treatment with phosphorus pentachloride furnished dichlorolactam **8** in good yield. Interestingly, under milder conditions, the mono-chlorinated product **9** is produced in fortuitously the same yield.

Scheme 7. Derivatization of Pyridoazepinones

In conclusion, we have developed a modular and scalable synthesis of pyridoazepinones, exploiting cheap and readily available starting materials and reagents. Most of the structures described in the preceding schemes would be quite difficult to obtain by more traditional routes. Indeed, it is the relative inaccessibility of pyridoazepinones that has hitherto hampered their more extensive exploitation by medicinal chemists. It is hoped that the present work will contribute to eliminating this barrier and encourage the incorporation of such structures in the design of biologically active substances.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, full spectroscopic data, and copies of ¹H and ¹³C NMR for all new compounds (PDF)

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