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Aza-Piancatelli Cyclization as a Platform for the Preparation of Scaffolds of Natural and Bioactive Compounds: Application to the Total Synthesis of Bruceolline D

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Abstract: The aza-Piancatelli cyclization is an appealing transformation for the synthesis of 4-aminocyclopentenone building blocks that could be then converted into bioactive aminocyclitol; however, while this approach appears promising, total syntheses of natural products featuring the aza-Piancatelli cyclization as a key step are still unprecedented. Here, we disclose our in-depth investigations regarding this reaction in order to access highly complex structures representing the core of some bioactive molecules. The applicability of the cyclization was highlighted by the 3-step total synthesis of bruceolline D. Thus, we anticipate that this work will lay the ground for further applications in the synthesis.

In the last decade, the aza-Piancatelli cyclization has garnered a growing interest because it enables a rapid and efficient pathway to 4-aminocyclopentenone derivatives from biomass-derived furan feedstocks.^[1] In general, this reaction represents a direct entry to aminocyclitol scaffolds that can be found in numerous bioactive and natural products (Scheme 1).^[2] They include pactamycin (antibiotic, antiprotozoal and antiproliferative properties),^[3] jogyamycin (antiprotozoal),^[4] peramivir (antiviral),^[5] and trehazolin (glycosidase inhibitor).^[6] Furthermore, this reaction may also provide a straightforward access to more complex polycyclic targets such as cephalotaxine,^[7] bruceolline D^[8] and yuehchukene,^[9] which embed a cyclopenta[b]indole unit, or gracilamine.^[10] Since the pioneering work of Denisov et al.^[11] and Read de Alaniz group,^[12] we and others have directed efforts towards the preparation of even more densely functionalized targets using the aza-Piancatelli cyclization as a cornerstone.^[13] For instance, we implemented new strategies for the synthesis of polycyclic structures such as cyclopenta[b]pyrroles,^[14] cyclopenta[b]piperazinones^[15] and tetrahydrobenzo[b]azepines^[16] by pairing the aza-Piancatelli cyclization with a second key transformation, such as hydroamination, annulation or Michael addition. In turn, the studies related to the influence of the substitution pattern of the furan ring on the reactivity has been underexplored.^[17] This issue is particularly critical when considering the compounds mentioned above, which bear a multitude of additional functional groups, including heteroatoms on the cyclopentane ring. As a result, the question remains whether the aza-Piancatelli cyclization could be

truly useful for the synthesis of such natural and bioactive molecules. In this context, we disclose herein our recent findings to increase the synthetic utility of this reaction by developing (1) a general synthetic approach to install several key functionalities of pactamycin, jogyamycin and peramivir, (2) a simple method to build the cyclopenta[b]indole moiety, which was highlighted by the total synthesis of bruceolline D, and finally (3) an aza-Piancatelli/Diels-Alder/fragmentation reaction sequence to access frameworks of interest. Besides, we provide an overview on the scope and limitations of this reaction, demonstrating that the presence of heteroatoms on the furan ring does not impede the reactivity.

Scheme 1. Aza-Piancatelli cyclization as a platform for natural and bioactive compounds.

In our initial investigations, we focused on a general route to access the core of pactamycin, jogyamycin and peramivir (Scheme 2). We noticed that all their structures have in common the presence of an oxygen functionality (hydroxymethyl or carboxylic acid) at the same position. In order to perform the aza-

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Piancatelli cyclization, our first task was to prepare the 2-furylcarbinol precursors, which involved the installation of the desired functional groups at the position C3 of the furan ring. We hypothesized that the simplest way to achieve this goal would be to start from the inexpensive 3-furoic acid **1** (~2 €/g). This strategy brings two advantages: (1) the key functional group or its direct precursor would be already present, and (2) it is well-documented that the carboxylic acid can serve as a directing group for the regioselective alkylation of furans with aldehydes to rapidly introduce the carbinol moiety.^[18] Following this approach, we obtained the 2-furylcarbinol intermediates **3**, which were engaged in the next step without further purification. Then, we conducted the selective methylation of the carboxylic acid upon treatment with trimethylsilyldiazomethane to afford the corresponding esters **4** in good to excellent yields over two steps (up to 97%). Finally, the reduction of the ester with LiAlH_4 and the subsequent protection of the primary alcohol formed **5** with *tert*-butyldimethylsilyl chloride (TBSCl) furnished the targeted precursors **6**. The protection of this alcohol was required to preclude any direct dehydrative nucleophilic substitution during the reaction.

Scheme 2. Preparation of 2-furylcarbinol precursors.

With these precursors in hand, we evaluated their reactivity in the aza-Piancatelli cyclization (Scheme 3). During our previous studies, we developed an efficient promoter system, combining three key components: $\text{Ca}(\text{NTf}_2)_2$ as a catalyst with $n\text{Bu}_4\text{NPF}_6$ as an additive in hexafluoroisopropanol (HFIP) as a solvent.^[19] This catalytic system allows to work under milder reaction conditions than classic ones, and enables to trigger the reaction with less reactive substrates, including anilines bearing strong electron-donating groups, due to the remarkable ability of HFIP to stabilize carbocation species, to strongly donate hydrogen bonds, in addition to its low nucleophilicity.^[20] First, we examined the reaction between **6a** and a series of amines (**7a-7c**). In each case, the 4-aminocyclopentenone was obtained in high yield (up to 95%), with most of the functionalities of jogyamycin being installed. In the same vein, we explored the reactivity of the precursors of peramivir. At the outset, we tested **3b** and **3c** with *p*-anisidine **7a** under our standard reaction conditions. However, the presence of an electron-drawing group at the C3-position of the furan shutdown the reaction and deactivated completely the alcohol, which remained intact. On the other hand, in the case of the reaction for **6b**, the target product **8ba** was formed and isolated in 97% yield. With a sight on peramivir, we also conducted the hydrogenation of the cyclopentenone to deliver **9** in 94% yield. Although the identification of the structure of **9** could not be confirmed by NMR studies due to the overlap of the signals, NOESY NMR experiments pointed toward the correct arrangement of the substituents (see the Supporting Information

for details). Lastly, precursor **6c** was subjected to the same reaction conditions with aniline **7d**. However, under these conditions, the reaction led only to the decomposition of the substrate. It might be caused by the presence of the benzyl ether that could be deprotected under the reaction conditions.^[21] Gratifyingly, switching solvent from HFIP to nitromethane produced compound **8cd** in 78% yield, thereby offering an entry point to pactamycin and potential analogues.^[22]

Scheme 3. Aza-Piancatelli cyclization of 2-furylcarbinols **6a-6c** with amines **7a-7d**. Structure of **9** tentatively assigned. [a] **6b** (1.2 equiv) and **7a** (1 equiv).

Another issue that we addressed was the possibility to directly introduce heteroatoms such as oxygen for the synthesis of trehazolin and cephalotaxine or nitrogen for the synthesis of pactamycin and jogyamycin on the furan ring (Scheme 4). To assess such reactivity, we prepared model substrates bearing methoxy or azide functionalities that were easily introduced by direct nucleophilic substitution on 3-bromofuraldehyde, forming the products **6d-e** in high yields. Importantly, in contrast with the case mentioned above with a strong electron-withdrawing group, the presence of a strong electron-donating renders the 2-furylcarbinol highly reactive and, therefore, not compatible with the standard conditions (with HFIP). In turn, the reaction with nitromethane in place of HFIP provided **8db** in 70% yield. Besides, the excellent result obtained for the reaction of azide offers also a plausible alternative to the synthesis of pactamycin.

Scheme 4. Influence of the presence of heteroatoms on the aza-Piancatelli cyclization.

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Our second objective was to determine whether the aza-Piancatelli could be used to generate cyclopenta[*b*]indole scaffolds. As a proof of concept, we explored the total synthesis of bruceolline D (Scheme 5). This molecule was isolated in 1994 by the group of Ohmoto from the root wood *Brucea mollis* Wall. var. *tonkinensis* Lecomte and is mostly employed in China for the treatment of malaria.^[8a] To date, only three total syntheses were described for this molecule.^[8c-d] Here, we envisioned an intramolecular aza-Piancatelli cyclization from precursor **11** to deliver bruceolline D. This substrate was rapidly synthesized from commercially available methyl 4-bromofuran-2-carboxylate by addition of methyl Grignard reagent (90% yield) to the ester group and subsequent a Suzuki-Miyaura cross-coupling reaction with 2-aminophenylboronic acid **7e** (42% yield). However, independent of the solvent employed, the cyclization step did not occur. We only observed the decomposition of **11**, which might suggest that the structure is too strained to allow the cyclization. Thus, we changed our approach by performing the aza-Piancatelli cyclization first, which was followed by a Suzuki-Miyaura cross-coupling. First, we studied the cyclization with a model substrate **6f** and aniline **7b** as a nucleophile. We noticed that the solvent was critical for this transformation because the dehydration of the alcohol occurred easily in HFIP or nitromethane, presumably due to the presence of both methyl groups. On the other hand, conducting the reaction in a solvent less prone to H-bonding such as toluene provided the targeted 4-aminocyclopentenone **8fb** in 66% yield.^[23] Next, we examined the reactivity of 2-furylcarbinol **10** with both 2-aminophenylboronic acid **7e** and 2-aminophenylboronic acid pinacol ester **7f** in toluene. The reaction with the latter formed the cyclization product in higher yield (67% vs 40%). Finally, a Suzuki-Miyaura cross-coupling reaction^[24] led to bruceolline D in 48% yield (3 steps, overall yield 29%), demonstrating the synthetic utility of the aza-Piancatelli cyclization.

Scheme 5. Total synthesis of bruceolline D.

Similarly, we sought to exploit the same strategy to access the framework of yuehchukene (Equation 1). While the cyclization reaction worked smoothly, without even requiring the utilization of $\text{Ca}(\text{NTf}_2)_2$ due to the intrinsic acidity of HFIP, all our attempts to

achieve the Suzuki-Miyaura cross-coupling reaction failed. At this stage, we do not have specific explanation for this result. Although further optimization studies would be necessary to accomplish this sequence, the approach enabled the construction of the cyclopentane ring of yuehchukene.

Finally, we evaluated the possibility of taking advantage of the alkene moiety of the 4-aminocyclopentenone to implement a Diels-Alder reaction and, thus, build the 5-6-5 aza-tricyclic core of gracilamine in a single step. To fulfil this goal, we prepared an aniline derivative incorporating a furan moiety (**7g**), which is a well-established diene system for Diels-Alder processes. To our surprise, in contrast with precedent reports,^[13f-g] we did not obtain the classic Diels-Alder adduct, forming instead tetrahydro-1*H*-indene **13** in 90% yield in HFIP (Scheme 6). This reactivity was also extended to 1,3-dienes to furnish the corresponding skeleton **14** in a good yield (65%) under identical reaction conditions.^[25] To account for the formation of such products, we hypothesized that, following the aza-Piancatelli cyclization and the Diels-Alder reaction, the amine might be protonated under the highly acidic reaction conditions and a subsequent Ei elimination would take place.

Scheme 6. Aza-Piancatelli/Diels-Alder/fragmentation reaction sequence.

In conclusion, we have demonstrated that the aza-Piancatelli cyclization could be used successfully to access densely decorated molecules that closely resemble natural and bioactive molecules. It was notably showcased by the concise total synthesis of bruceolline D, which was achieved in 3 steps with 29% overall yield. More importantly, we gained a better insight into the group functional tolerance of this transformation and the influence of solvent on it, which should pave the way for its increasing utilization in total synthesis.

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Keywords: aza-Piancatelli • bruceolline D • electrocyclization • Lewis acid • natural products

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