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Magnesiate-Utilized/Benzyne-Mediated Approach to Indenopyridones from 2-Pyridones: An Attempt To Synthesize the Indenopyridine Core of Haouamine

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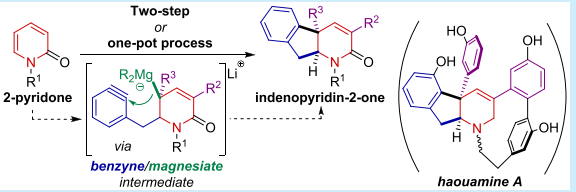
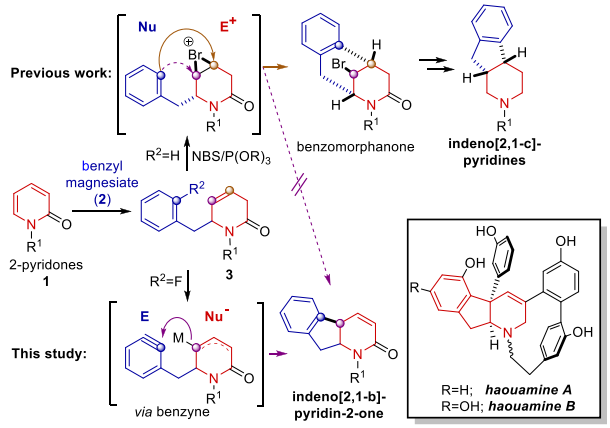
Supporting Information

ABSTRACT: An efficient, short-staged synthesis of *cis*-fused indeno[2,1-*b*]- and indeno[1,2-*c*]pyridin-2-ones, starting from 2-pyridones, using magnesiates of type R_3MgLi as nucleophilic and deprotonation agents, mediated by benzyne generated in situ, under optimized conditions, is described. Following the developed protocol, rare C4a-arylsubstituted indeno[2,1-*b*]pyridones, resembling the core of haouamine, were obtained. The protocol offering the one-pot synthesis directly from 2-pyridone is also described.



The indenopyridine(piperidine) ring-fused system occurs in many bioactive compounds, including synthetic 11β-HSD-1 inhibitor,[1] anticancer agents,[2] compounds exhibited strong antispermatogenic activity,[3] and naturally occurring sisterly alkaloids—haouamines A and B (Scheme 1) isolated from the marine ascidian *Aplidium haouarianum*.[4] The unique structure of the latter, and their strong and selective anticancer activity against the human colon carcinoma cell line HT-29, are the reasons why attempts to synthesize these alkaloids have been continued.[5] Some of the difficulties encountered in the synthesis of their derivatives are linked to obtaining the indenotetrahydropyridine system, which has a quaternary chiral center.[5a−c,h,j−l]

Scheme 1. Benzyl Moiety of 3 Acting (Top) as a Nucleophile Results in Benzomorphanone Formation and (Bottom) as an Electrophile in the Direct Synthesis of the Indenopyridine Ring System



Being aware of the high value of indenopyridines and their derivatives as potential pharmaceuticals, we decided to obtain this fused system by intramolecular cyclization of benzyl group of 6-benzyl-3,6-dihydropyridin-2-one derivatives, which were obtained by us earlier in the nucleophilic addition of benzylmagnesiate to 2-pyridones.[6] In planning the synthesis, we considered the use of substrates with or without a substituent at C5, bearing in mind that C5-aryl-functionalized substrates could lead to C4a-substituted indenopyridones with quaternary chiral center at C4a, which are closely related to the haouamine core. As far as the construction of the indenotetrahydropyridine center of haouamines is concerned, the strategies based on the intramolecular annulation of benzyl moiety connected to a piperidine ring at a position adjacent to the N atom have been successfully applied, using the Friedel–Crafts,[5a,c,j,m] Pd-catalyzed α-C-arylation[5k] and Heck's[5f] ring closure methods. In the hitherto-described attempts, 6-benzyl-3,6-dihydropyridin-2-ones have not yet been used as substrates. Moreover, although 4-methoxypyridine,[5k] 3,5-dimethoxypyridine,[5c] and pyridinium salts[5h] have been used as primary starting compounds, 2-pyridones have not, although 2-pyridones have been recognized as a universal precursor applied in the synthesis of alkaloid-inspired compounds.[7]

In our earlier work, the annulation of 6-benzyl-3,6-dihydropyridin-2-one with the use of the electrophilic aromatic substitution, prompted by $NBS/P(OR)_3$, did not bring the indenopiperidine ring system but benzomorphanone derivatives,[8] which, only after the subsequent thionation and reduction, gave hexahydro-1*H*-indeno[2,1-*c*]pyridines (Scheme 1, top).[9] Since the direct synthesis of indenopyridinones was not possible in this way, in the present study, we decided to reverse the electrons flow between the reacting

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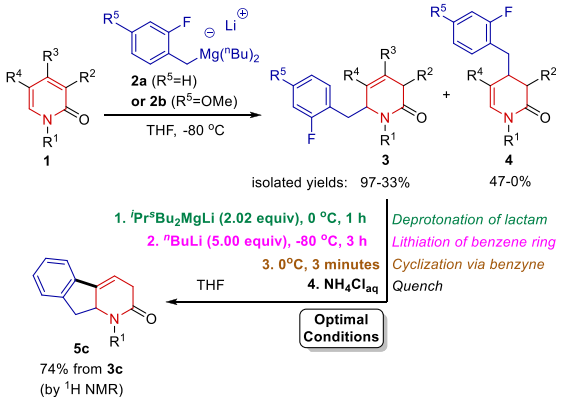
fragments by applying benzyne (as an electrophilic site) formed from the benzyl group and metalated lactam as the nucleophilic center (Scheme 1, bottom).

The last two decades have witnessed great progress in the field of aryne-mediated synthetic organic chemistry. Among many synthetic applications,[10] an approach based on benzyne methodology has played a particularly important role in the synthesis of heterocyclic compounds[11] and natural products,[12] including alkaloids[13] and other polycyclic azaheterocycles.[14] Nevertheless, the aryne chemistry has not been often applied for the functionalization of 2-pyridones and their derivatives.[15]

Exploring the aryne strategy, herein, we report the result of our study, that is a new method for the synthesis of the indenopyridine system mediated by benzyne, generated from benzyl-functionalized moiety of unsaturated δ-lactams, and the results of our efforts on the extension of developed procedure for the synthesis of indenopyridine core of haouamine.

Our investigation started by choosing the functionalization type of benzyl group of **3** capable for benzyne formation. Among many methods allowing the generation of benzyne from a functionalized benzene ring,[10] we have chosen that involving spontaneous elimination of LiF from the appropriate fluorosubstituted benzene derivatives initiated by *ortho*-lithiation using organolithium reagents.[16] For these reasons, *o*-fluorobenzyl group was introduced into 3,6-dihydropyridin-2-one **3** by the addition of nucleophilic magnesiates **2a** and **2b**, to diversely substituted 2-pyridones **1**, according to the method described earlier (Scheme 2).[6] The detailed results are collected in Table S1 in the Supporting Information.

Scheme 2. Synthesis of 6-(*o*-fluorobenzyl)-3,6-dihydropyridin-2-ones 3 and 4-(*o*-fluorobenzyl)-3,4-dihydropyridin-2-ones 4 and Optimized Conditions for 5c Formation



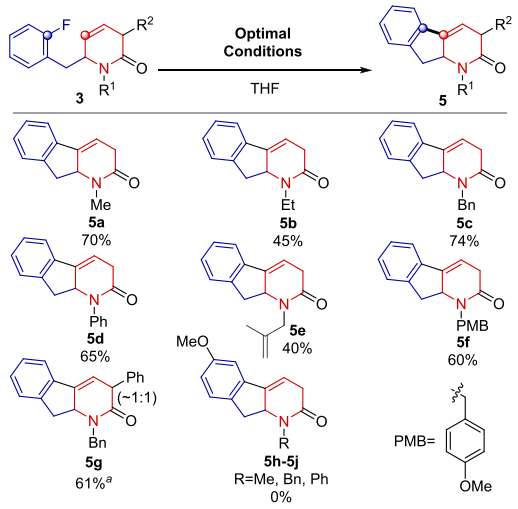
We next searched for the best conditions to obtain indenopyridone **5** from **3** adjusting the time and temperature of the following steps: deprotonation of lactam ring, lithation at benzene moiety, benzyne formation and cyclization (Scheme 2, detailed results are collected in Table S2 in the Supporting Information). In the first two steps, the appropriate metalation agents were searched considering their different quantities, relative to **3**. Because in the primary attempts, organolithium bases (*n*-BuLi, *sec*-BuLi and *t*-BuLi, LiTMP) used in 2-fold to 4-fold excess as sole deprotonation agents definitively gave no positive results, we turned our attention to magnesiates of the type $R^1R^2{}_2MgLi$, obtained prior to use by simple mixing of 1 equiv of a Grignard reagent (R^1 MgCl) and 2 equiv of organolithium (R^2Li). We decided to use lithium magnesiates[17] because these species, applied by us mainly in the addition reactions,[18] were recognized also as powerful metalating agents.[19]

The results of optimization of the model transformation of **3c** into **5c** showed that the best conditions included application of 2 equiv of $^{i}Pr^{s}Bu_2MgLi$ in the first deprotonation step (at 0 °C, 1 h) and 5-fold excess of *n*-BuLi to cause *ortho*-lithiation at the fluorobenzene ring (−80 °C, 3 h) and temperature 0 °C for 3 min in order to achieve benzyne formation and effective cyclization (see Scheme 2).

On the basis of the results presented above, we can conclude that successful synthesis of indenopyridines through benzyne annulation to a lactam moiety is dependent on the proper selection of deprotonating reagents ($^{i}Pr^{s}Bu_2MgLi$ and $^{n}BuLi$), which are able to deprotonate the substrate at different sites at different temperatures. It means that there is no conflict between magnesiate and *n*-BuLi, which permits the reaction control. Furthermore, an important factor observed in the reaction of obtaining indenopyridone is a short cyclization time at 0 °C, which is 3 min. A short reaction time as a factor enabling efficient reaction with benzyne has also been described earlier.[20]

Having optimized the reaction conditions, we next tested the use of the following compounds: 6-(*o*-fluorobenzyl), *N*-substituted (**3a**−**3f**) and *N*-Bn, C3-Ph disubstituted (**3g**), as well as 6-(*o*-fluoro-*p*-methoxybenzyl), *N*-substituted (**3s**−**3u**) derivatives. According to the result depicted in Scheme 3, 6-(*o*-fluorobenzyl)-substituted compounds gave the corresponding indenopyridone products **5a**−**5g** in satisfactory isolated yields, while, surprisingly, 6-(*o*-fluoro-*p*-methoxybenzyl)-substituted **3s**−**3u** did not lead to products **5h**−**5j**, because of their instability during the reaction or decomposition after extraction.

Scheme 3. Synthesis of indeno[2,1-*b*]pyridin-2-ones 5 under Optimized Conditions



The next group of compounds tested were 5-substituted and 3,5-disubstituted derivatives **3** (Scheme 4). Fortunately, in most reactions, the desired indenopyridone products **6** containing quaternary C4a-carbon atoms and α,β-positioned double bonds in lactam moieties were obtained. However, note that the yields were dependent on the structure of the substrate and, in a few reactions, the formation of additional byproducts **7a**, **7b**, and **8a** was observed. Most importantly, products **6e**

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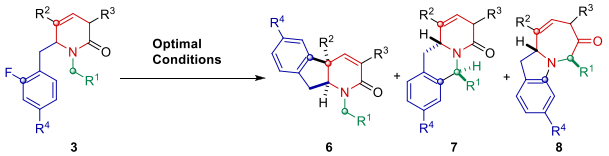
Scheme 4. Yields of Desired Product 6 and Byproducts 7 and 8 Obtained As the Result of Cyclization of 3 under Optimized Conditions



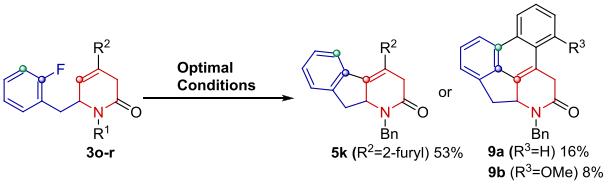
Entry	3	R^1	R^2	R^3	R^4	6	7	8
1	**3h**	Ph	Me	H	H	**6a** 49%	-	-
2	**3i**	H	Ph	H	H	**6b** 24%	-	**8a** 13%
3	**3k**	Ph	Ph	H	H	**6c** 61%	-	-
4	**3l**	4-OMePh	Ph	H	H	**6d** 32%	**7a** 10%	-
5	**3m**	Ph	3-OMePh	H	H	**6e** 61%	-	-
6	**3n-1**	Ph	Ph	Ph	H	**6f**[a] 23%	-	-
7	**3v**	Ph	Me	H	OMe	**6g** 39%	-	-
8	**3w**	H	Ph	H	OMe	-[b]	-[b]	-[b]
9	**3y**	Ph	3-OMePh	H	OMe	**6h** 12%	**7b** 16%	-

[a] - The lack of full conversion. (Isomerisation of **3n-1** to **3n-2** was observed. Table S1);
[b] - The complex mixture.

and **6f**, structurally similar to houamine, were isolated in 61% and 23% yields, respectively. The low yield of the latter is the effect of incomplete conversion and isomerization of the substrate to α,β-unsaturated isomer **3n-2** during the reaction (see Table S1, entry 14, in the Supporting Information).

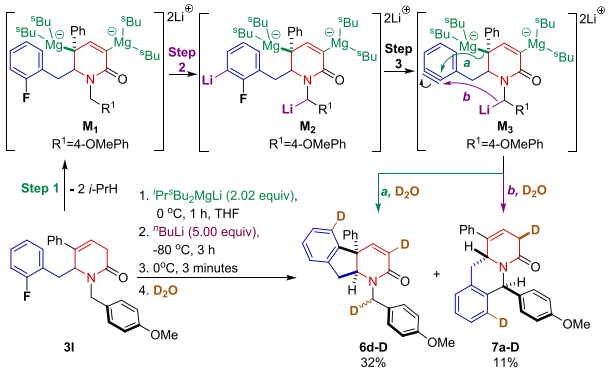
In continued studies, an attempt to cyclize 4-methyl-substituted compounds (**3o**) led to a complex mixture while 4-aryl substituted derivatives **3p**, **3r** yielded polyaromatic compounds **9a** and **9b** in low yields; this indicates a competitive sequential [4 + 2] cycloaddition reaction, followed by an aromatization process (Scheme 5). Only the 4-(furan-2-yl)-substituted derivative **3r** gave an indenopyridone product (**5k**) in 53% yield.

Scheme 5. Magnesiate/Benzyne Cyclization of 3o−3r



To shed more light on indenopyridones **5** and **6** and byproduct formation, a deuteration experiment was performed, which consisted of quenching the reaction of **3l** conducted under optimized conditions by treatment with D_2O (Scheme 6). The analysis of deuterated products **6d-D** and **7a-D** revealed that they were obtained in yields comparable to nondeuterated products **6d** and **7a** and that they contained 3 and 2 deuterium atoms, respectively, hence indicating the metalation sites in the final products before quenching. On the basis of the above results, a formation mechanism of indenopyridones **6** and **7** is proposed, in which two issues should be highlighted. First, since our earlier investigation, we have observed that 3,5-dialkylated products were formed in alkyl-allylation of β,γ-unsaturated δ-lactams, deprotonated by magnesiates;[19] furthermore, 2 equiv of magnesiate are required

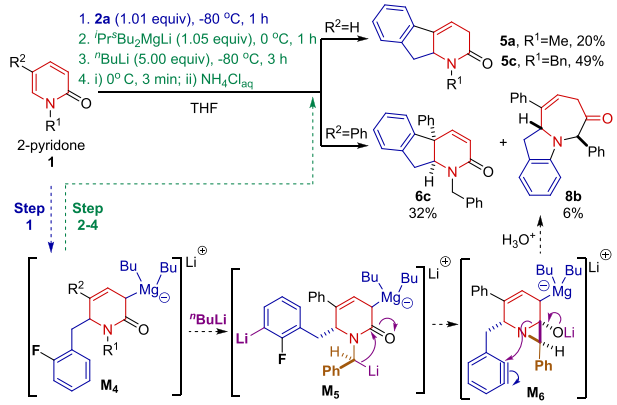
Scheme 6. Possible Mechanism of 6 and 7 Formation



at the first deprotonation step under the optimized conditions. In addition, in the final product **7d-D**, the deuterium atom is present at a vinyl position adjacent to carbonyl, and this position cannot be easily deprotonated; therefore, we conclude that, at the first step, dimagnesiated product **M1** is formed by CH-α deprotonation, double bonds are shifted, and a second deprotonation of benzyl/allyl position C5 of the lactam ring occurs. Second, deuteration of the CH_2 of *N*-PMB group in **7d-D** clearly proved that byproduct **6a-D** is formed through a less-preferred nucleophilic attack of *N*-CHLiPMB toward the benzyne site (see Scheme 6, route b). Finally, note that, in almost all of the reactions, cyclization involving the connection of C5-magnesiate to benzyne sites is preferred (see Scheme 6, route a).

At this stage, the potentially useful sequential one-pot synthesis of indenopyridones obtained directly from 2-pyridones was also tested (Scheme 7). Thus, after addition

Scheme 7. Sequential One-Pot Synthesis of Indenopyridones Obtained Directly from 2-Pyridones



of *o*-fluoro-benzylmagnesiate **2a** to an appropriate 2-pyridone, the optimized conditions were applied for cyclization, except the quantity of ^{i}Pr(^{s}Bu)$_2$MgLi, because only 1 equiv of this reagent was added, because another one was already introduced in the addition reaction. The results, which are not fully satisfactory, because of moderate yields, indicate, however, a high prospect of this reaction, which probably requires additional optimization adjustment. Note the fact that byproduct **8b** formed in this reaction has the same skeleton as product **8a** described above (Scheme 4, entry 2). An in-depth structural analysis showed that, in the formation of **8**, the δ-lactam ring is expanded to azepan-3-one ring. A plausible

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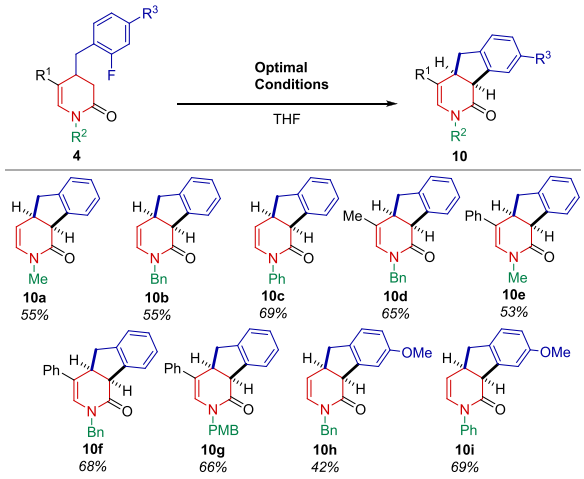
mechanism consisting of the main stages of this reaction, starting from **3k**, is presented in Scheme 7. It includes single magnesiation of the lactam ring, lithiation at *N*-CH_2 and benzene groups (**M5**), subsequent aziridination by intramolecular nucleophilic addition to carbonyl group, its restoration with simultaneous opening of aziridine ring, and addition of nitrogen nucleophile to benzyne, formed independently from *o*-fluorobenzene moiety (**M6**). Since, here, the cyclization of the lactam site with benzyne is not preferred (in contrast to the reaction of indenopyridine formation), we can conclude a lower degree of magnesiation of the lactam ring and infer that, under these circumstances, the reactivity of the *N*-CHLi site comes to the forefront.

Finally, we apply our magnesiate-utilized benzyne-mediated protocol for the construction of *cis*-fused indeno[1,2-*c*]pyridin-1-ones **10** from **4** (see Scheme 8). Generally, the products

Scheme 8. Syntheses of Indeno[1,2-*c*]pyridinones 10



were obtained in good yields and formation of byproducts was not observed. Substrates **4d**, **4h**, **4t**, and **4u**, obtained as second regioisomeric products from the additions of benzyl magnesiates **2a** and **2b** to *N*-functionalized 2-pyridones in sufficient quantity (see Scheme 2, as well as Table S1 in the Supporting Information), were submitted directly for cyclization, while substrates **4a**, **4c**, **4i**, **4k**, and **4l** were synthesized via a different route by applying the regioselective C4 addition of an appropriate magnesiate to *N*-Li 2-pyridone, followed by *N*-alkylation (see Table S3 in the Supporting Information).[6,18a−e]

The structures of all compounds were elucidated with the aid of one-dimensional (1D) and two-dimensional (2D) nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass spectroscopy (GC-MS) and high-resolution mass spectroscopy (HRMS) analyses (for details, see the Supporting Information).

In summary, we have demonstrated a novel approach to indeno[2,1-*b*]- and indeno[1,2-*c*]pyridones, achieved from 2-pyridones as primary substrates. A synthetic, concise methodology relies on the addition of *o*-fluorobenzyl magnesiate to 2-pyridones, providing *o*-fluorobenzylated dihydropirydyn-2-ones, followed by *cis*-stereoselective cyclization of pendant benzyne intermediate that was generated in situ from *o*-fluorobenzyl moiety under optimized conditions. The methodology is based on the application of magnesiates enabled metalation of *δ*-lactam ring and facilitated nucleophilic cyclization at the electrophilic benzyne site. The synthesis of rare C4a-aryl-functionalized indeno[2,1-*b*]pyridones with quaternary C4a-atom, resembling the core of haouamine, is a promising premise to receive this alkaloid or its derivatives. Besides, the deuteration experiment pointed toward a broader range of possible functionalizations of indenopyridine core through treatment with electrophiles other than D_2O. A study to extend indenopyridine functionalization via trapping of various electrophiles by metalated indenopyridones intermediates is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03806.

Experimental procedures, spectroscopic data and ^1H, ^{13}C, ^{19}F NMR spectra for all new compounds (PDF)

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Author Contributions

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

Notes

The authors declare no competing financial interest.

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