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Synthesis of Substituted Pyridines from 1,2-Nucleophilic Addition Products of Functionalized *N*-Acyl-2,3-dihydropyridones

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ABSTRACT

We describe herein a general and efficient synthetic approach toward substituted pyridines from functionalized *N*-Acyl-2,3-dihydropyridones in two steps; 1,2-addition with organocerium reagents and subsequent oxidative aromatization with chloranil. This strategy allows the generation of pyridines with various substitution patterns and introduces a variety of substituents including aryl, alkyl, alkynyl, alkenyl, heteroaryl groups at the desired positions.

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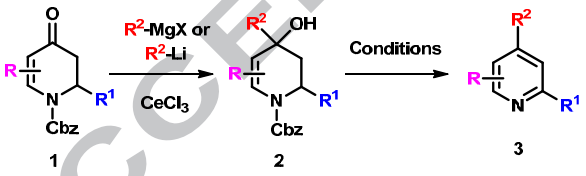
Over the years, many synthetic tools have been developed to access substituted pyridines, which are among the most important and versatile organic substances.[1] Due to the significance as pharmaceuticals, agrochemicals, ligands, and in organocatalysis and materials, the development of new synthetic routes to build them has always been in the focus of organic chemists.[2] Even though current approaches offer many advantages, there is still need to improve efficiency, diversity and flexibility of construction of pyridine derivatives from simple, inexpensive and readily available starting materials under mild reaction conditions. A synthetic protocol that introduces a variety of groups with various substitution patterns such as di, tri, tetra, etc. has been an important and attractive research theme in the area of synthetic organic and medicinal chemistry. We report here an efficient and convenient methodology to reach pyridines having diverse substituents and controllable substitution patterns from readily available substituted *N*-Acyl-2,3-dihydropyridones (**1**) in two steps (Scheme 1).[3] The key step in this strategy is the oxidative aromatization of a highly substituted adduct (**2**), which could be obtained via a 1,2 nucleophilic addition to **1**. It was envisioned that pyridine ring formation from **2** could be realized via elimination of water, nitrogen deprotection and subsequent oxidative aromatization in a single step. No detailed study has been reported in the literature for this type of transformation (e.g. **2** to **3**), except for a limited study done by Munoz's group.[4] They applied similar strategy to *N*-resin-bound dihydropyridones and generated 2,4-disubstituted pyridines upon reaction of 1,2 adducts with TFA in CH_2Cl_2. However, this condition afforded pyridines in low yields (20-30%) and substrate scope was limited.

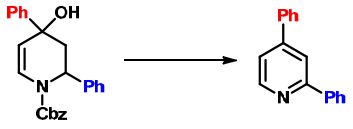
A wide variety of reagents and conditions have been extensively studied to oxidatively aromatize such molecules as α,β-unsaturated cyclic compounds,[5] Hantzsch 1,4 dihydropyridines,[6] pyrazolines,[7] etc., some of which require heat and protic acids. In the case of **2**, it seemed likely that some of these conditions will trigger the formation of an easily oxidizable 1,2-dihydropyridine intermediate formed after dehydration and removal of the *N*-acyl group. Hence, we became interested in examining various reagents such as protic and Lewis acids, oxidizing agents as well as bases to promote the formation of the pyridine ring.

Scheme 1. General approach toward substituted pyridines



As depicted in Table 1, the investigations for the oxidative aromatization were initiated with the compound **5a** as a model substrate to find optimal conditions. We started with protic acids (TFA, HCl, p-TsOH, entries 1-3) and found that these conditions furnished **6a** in low yields, even higher temperatures did not promote the product formation (entry 4). Among the Lewis acids (entries 5-10), $TiCl_4$ was found to generate **6a** in 40% yield at room temperature, and in a higher yield (52%) at colder temperature -78°C. Then, we turned our attention to basic conditions (entry 11-13) and found KOH in water and methanol mixture at 80°C led to the formation of **6a** in the moderate yield of 65%. We also tested a variety of oxidizing agents under acidic conditions including $FeCl_3.H_2O$,[8] $Ce(SO_4).4H_2O$,[9] $NaClO_2$,[10] $Cu(OTf)_2$,[11] $Ni(II)OAc.4H_2O$,[8] I_2,[12] Sulfur,[13] Pd/C[14] (entries 14-20) and obtained low to moderate yields. Gratifyingly, we discovered that chloranil in refluxing acetic acid (entry 21) generated **6a** in a nearly quantitative yield.[15]

Table 1. Studies for oxidative aromatization



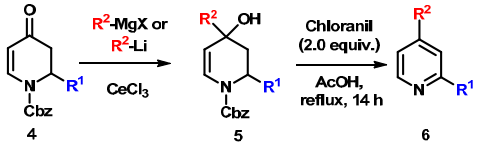
5a 6a

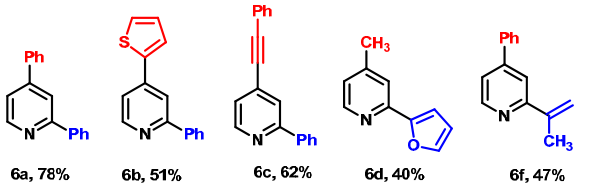
Entry[a]	Reagents (equiv)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	TFA (1.2)	CH_2Cl_2	rt	14	12
2	AcCl (2.5)	EtOH	rt	14	16
3	p-TsOH (1.2)	CH_3CN	rt	14	18
4	p-TsOH (1.2)	CH_3CN	82	14	20
5	$BF_3.OEt_2$ (1.3)	CH_2Cl_2	-78 to rt	14	23
6	TMSOTf (1.3)	CH_2Cl_2	-78 to rt	14	0
7	$EtAlCl_2$ (1.3)	CH_2Cl_2	-78 to rt	14	5
8	$TiCl_4$ (1.3)	CH_2Cl_2	-78 to rt	14	40
9	$TiCl_4$ (2.3)	CH_2Cl_2	-78 to rt	14	52
10	*t*-BuOK	DMSO	rt	24	5
11	NaOMe (2.0)	MeOH	65	14	54
12	KOH (10%)	H_2O:MeOH	80	14	65
13	$FeCl_3.H_2O$ (0.1)	AcOH	rt	24	23
14	$Ce(SO_4).4H_2O$ (0.5)	H_2O/AcOH (5:1)	100	14	58
15	$NaClO_2$ (1.5)	HCl, EtOH/ H_2O (1:1)	rt	14	5
16	$Cu(OTf)_2$	AcOH	118	14	21
17	$Ni(II)OAc.4H_2O$	AcOH	118	14	33
18	Iodine (2.0)	MeOH	65	14	41
19	Sulfur (2.0)	Toluene	110	48	43
20	%5 Pd/C (cat.)	AcOH	118	14	67
21	**Chloranil (2.0)**	**AcOH**	**118**	**14**	**98**

[a] All reactions were run under air, except the ones with the Lewis acids (entry 5-9). [b] Yields were determined after purification by column chromatography.

With the best reaction conditions in hand (Table 1, entry 21), we focused to broaden the scope of the methodology to access 2,4-disubstituted pyridines with diverse groups such as aryl, alkyl, heteroaryl, alkenyl and alkynyl. The incorporation of various R1 group can be realized via the synthesis of **4**, which is obtained from the well-established protocol using the reaction of C-4 methoxysubstituted acylpyridinium salts with Grignard reagents.[3] In the next step, R2 groups can be introduced via a 1,2 addition of Grignard or organolithium reagents in the presence of cerium (III) chloride. Comins' group reported this type of addition to similar substrates, but only with three nucleophiles; methyllithium, butyllithium and dimethylphenylsilyllithium.[16] In order to place more versatile groups on the C-4 positon of a pyridine ring, we used more functionalized organocerium reagents holding such groups as aryl, alkyl, heteroaryl, and alkynyl.[17] In these studies, 1,2 nucleophilic addition products (e.g. **5**, Table 2) were quickly purified via short column chromatography and treated immediately with chloranil in refluxing acetic acid to generate 2,4 disubstituted pyridines in moderate to good yields (51 to 78% over two steps, Table 2). As seen from these results, this methodology allows generation of 2,4-disubstituted pyridines with diverse groups at C2 and C4 positions.

Table 2. Synthesis of 2,4-disubstituted pyridines[a]

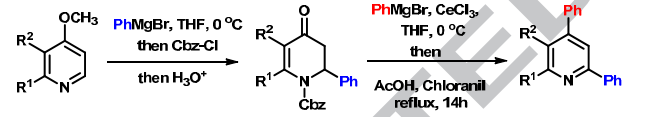




[a] Yields were determined after purification on silica gel chromatography and reported over two steps.

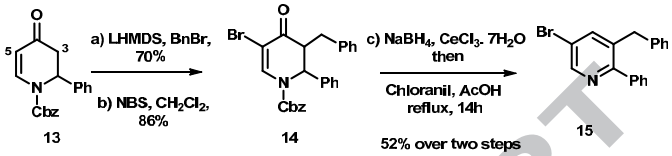
To access more substituted pyridines with this protocol, we focused on introducing more groups on dihydropyridones **4** in Table 2, which can be achieved via both synthesis and functionalization of these intermediates. There are many available methods for the synthesis of these useful building blocks,[18] among which we exploited the addition of Grignard reagents to substituted 4-methoxypyridinium salts to generate substituted dihydropyridones (i.e. **9** and **10**, Scheme 2).[19] Accordingly, 2-methyl-4-methoxypyridine (**7**) and 3-methyl-4-methoxypyridine (**8**) were used to synthesize substituted dihydropyridones at the C-5 and C-6 positions.[20] Thus, dihydropyridones **9** and **10** were easily generated from the addition of Cbz-Cl to a premixed solution of PhMgBr and pyridines **7** and **8** followed by acidic hydrolysis in yields of 76% and 60%, respectively. In the next step, the addition of phenyl Grignard in the presence of cerium chloride to **9** and **10** afforded the corresponding 1,2 addition products, which were quickly chromatographed, and then aromatized under our optimal conditions to access 2,4,5- and 2,4,6-trisubstituted pyridines (**11** and **12**, Scheme 2) in 47% and 52% yields over two steps, respectively.

Scheme 2. Synthesis of 2,4,5-tri- and 2,4,6-trisusbtituted pyridines



Next, our effort was directed toward the functionalization of dihydropyridones (e.g. **13**, Scheme 3), which is well precedented in the literature.[21] They have served as versatile intermediates to reach complex molecules, mainly due to hosting reactive sites at any position around the ring. For instance, such groups as alkyl, ester, acetoxy, arylsulfide and arylselenide can be introduced at the C-3 position via enolate chemistry.[22] In addition, halogens can be easily placed at C-5 due to the presence of an enamine functionality, which could be used for a subsequent transition metal catalyzed cross-coupling reaction to provide various 5-substituted derivatives. We decided to take advantage of these transformations and synthesize substituted pyridines with functionalities at the C-3 and C-5 positions using our synthetic protocol (Scheme 3). Accordingly, benzylation of **13** at C-3 and followed by bromination at C-5 gave rise to **14**. Attempts at 1,2 addition to **14** with various organocerium reagents resulted in the formation of 1,2 adducts in low or no yields, which could be attributable to steric congestion around the carbonyl group in **14**. However, 1,2-hydride addition to **14** generated the corresponding tertiary alcohol in almost quantitative yield, which was subsequently aromatized to **15** under our conditions in 52% yield over two steps.[23] Theoretically, this methodology has the potential to increase diversity in substitution patterns and enable access to highly substituted pyridines (tetra or penta) from pre-functionalized *N*-Acyl-2,3-dihydropyridones.

Scheme 3. Synthesis of 2,3,5-trisubstituted pyridines



In conclusion, we have developed a concise and flexible approach for the assembly of a wide variety of substituted pyridine scaffolds without regioselectivity issues. Another salient feature of this approach is avoiding expensive and toxic transition metals. This route is complementary to known methodologies and should be applicable for the preparation of many interesting compounds hosting a substituted pyridine motif.

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Supplementary Material

Supplementary data associated with (experimental procedures and compound characterization data) this article can be found, in the online version.

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23. General Procedure for oxidative aromatization: A solution of an 1,2 addition product in AcOH (0.02 M) is treated with chloroanil (2.0 equiv.) and refluxed for 12 h. The reaction mixture is quenched with saturated 2M NaOH solution and extracted with EtOAc. The combined extracts are dried over Na_2SO_4 and the solvent is removed under vacuum. The residue is purified with flash chromatography on silica gel using a mixture of hexane and ethyl acetate as an eluent to give a pyridine product.