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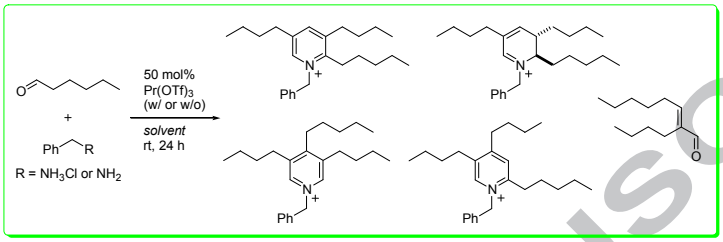

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Chichibabin pyridinium synthesis

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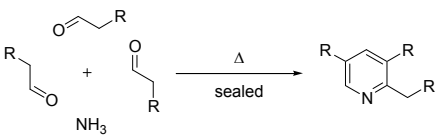
ABSTRACT

Chichibabin pyridine synthesis involves the reaction of three aldehydes and ammonia to form 2,3,5-trisubstituted pyridines. This study examined the synthesis of tetrasubstituted pyridinium from aldehydes and an amine hydrochloride in the presence/absence of $Pr(OTf)_3$. Important insights into the reaction mechanisms of Chichibabin pyridinium synthesis were proposed through the investigation of reaction intermediates along with quantitative GC-MS analysis.

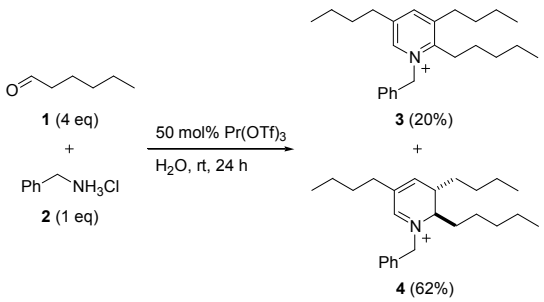
Indroduction

In 1905, the Russian chemist Aleksei Yevgen'evich Chichibabin reported the synthesis of 2,3,5-trisubstituted pyridine from three equivalents of aldehyde and ammonia (Scheme 1)[1] using high pressure and high temperature. Almost a century later, Wang and co-workers screened several simple aldehydes, amine hydrochlorides, and lanthanide triflates as catalytic Lewis acids for their utility in this reaction.[2] In 1997, they reported the condensation of aldehydes and amine hydrochlorides at room temperature in aqueous media in the presence of lanthanide trifluoromethanesulfonates ($Ln(OTf)_3$) to give 1,2,3,5-tetrasubstituted pyridiniums and their dihydro-forms.[2] A representative of this synthesis was the reaction of four equivalents of hexanal (**1**) and one equivalent of benzylamine hydrochloride (**2**) in the presence of 50 mol% $Pr(OTf)_3$ in H_2O at room temperature for 24 hours to afford 1,2,3,5-tetrasubstituted pyridinium (**3**) in 20% yield and its 2,3-dihydropyridinium (**4**) in 62% yield, respectively (Scheme 2).



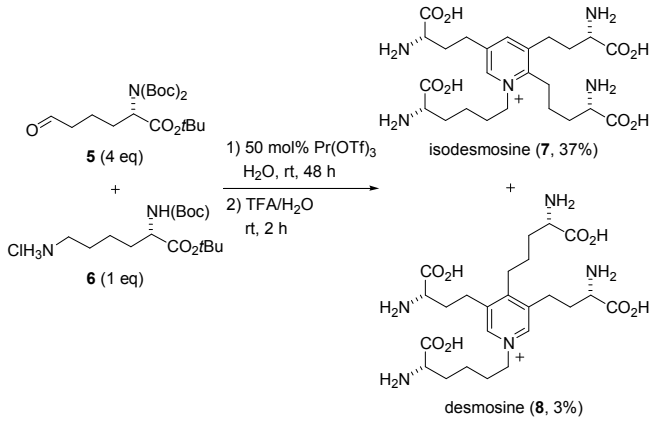
R = Me, Et, *n*Pr

Scheme 1. Original Chichibabin pyridine synthesis.[1]



Scheme 2. $Pr(OTf)_3$-promoted Chichibabin pyridinium synthesis.[2]

In 2014, we described the $Pr(OTf)_3$-promoted Chichibabin pyridinium synthesis of isodesmosine (**7**) and desmosine (**8**) starting from protected allysine (**5**) and protected lysine hydrochloride (**6**).[3] Compounds **7** and **8** are elastin crosslinking amino acids and chronic obstractive pulmonary disease (COPD) biomarkers and their yields in this synthesis were 37% and 3%, respectively, after quantitative removal of the protecting groups (Scheme 3).[4] 1,2,3,5-Tetrasubstituted pyridinium is the typical product of Chichibabin pyridinium synthesis and 1,3,4,5-tetrasubstituted pyridinium can be regarded as an isomer. Several biosynthetic studies on crosslinkers **7** and **8** have been reported over the past several decades[5,6] but the detailed mechanisms underlying these synthetic strategies remain unclear. In this study we therefore examined Chichibabin pyridinium synthesis using hexanal **1** and benzylamine hydrochloride **2** as model compounds.

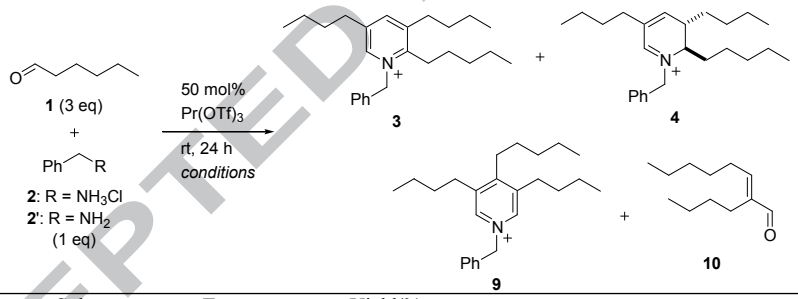


Scheme 3. $Pr(OTf)_3$-promoted Chichibabin pyridinium synthesis of isodesmosine (**7**) and desmosine (**8**).[4]

Results and discussion

Chichibabin pyridinium synthesis was examined by altering the reaction conditions, as shown in Table 1. We first repeated Wang's reaction conditions[2] and obtained **3** and **4** in 29% and 42% yield, respectively (entry 1), as well as desmosine **8**-type 1,3,4,5-substituted pyridinium (**9**) in 2% yield and aldol condensate **10** (the self-condensed product of **1**) in 32% yield based on the amount of **2** as the main byproduct. We reduced the number of equivalents of **1** from four to three to prevent side reactions, although **10** was obtained in 32% yield along with **3**, **4** and **9** in 19%, 25%, and 1% yield, respectively (entry 2). Increasing the reaction temperature to 37 °C did not improve to yields of **3**, **4**, **9** and **10** (18%, 22%, 1%, and 40% yield, respectively) (entry 3). Reaction in the absence of **2** provided no product, suggesting that **2** is involved in the formation of **10** (entry 4). Reactions were then conducted in organic solvent using amine **2**' instead of **2** because of solubility issues. The non-polar aprotic solvent CH_2Cl_2 and the polar aprotic solvents DMSO, DMF and MeCN were screened (entries 5-8). Conducting the reaction in CH_2Cl_2, interestingly, provided the **8**-type pyridinium **9** in 20% yield and **3**, **4**, and **10** in 11%, 4%, and 39% yield, respectively (entry 5). The use of DMSO resulted in a decreased total yield of pyridiniums (entry 6) whereas the use of DMF and MeCN afforded pyridiniums only as aromatized products (entries 7, 8). The results shown in Table 1 suggest that the preference for certain pyridinium types changes depending on the solvent system and that the yield of **10** is higher in organic solvent compared to in H_2O.

Table 1. Investigation of Chichibabin pyridinium synthesis.



Entry	Nitrogen source	Solvent	Temperature	Yield/%[a]				
				3	**4**	**9**	**3**+**4**+**9**	**10**
1[b,c]	**2**	H_2O	rt	29[e]	42	2[e]	73	32
2	**2**	H_2O	rt	19[e]	25	1[e]	45	32
3	**2**	H_2O	rt	18[e]	22	1[e]	41	40
4[d]	-	H_2O	rt	0	0	0	0	0
5	**2'**	CH_2Cl_2	rt	11[e]	4[e]	20[e]	35	39
6	**2'**	DMSO	rt	6[e]	5[e]	3[e]	14	42
7	**2'**	DMF	rt	5[e]	0	15[e]	20	48
8	**2'**	MeCN	rt	11[e]	0	12[e]	23	40

[a]Isolated yield based on **2** or **2'** except mixture of **3**, **4**, and **9**.

[b]See ref. 2.

[c]Four equivalents of **1** were used.

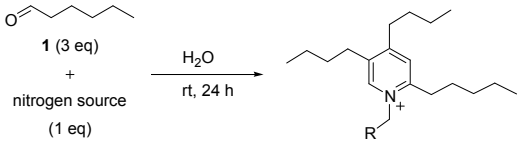
[d]Reaction conducted without **2**.

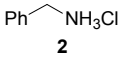
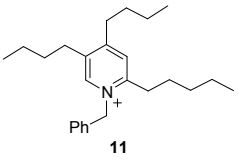
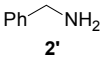
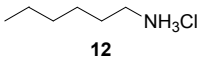
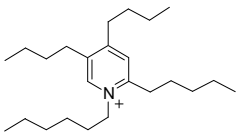
[e]Ratio was determined by ^{1}H NMR.

Conducting the reaction under the same conditions as entry 2 (Table 1) but without $Pr(OTf)_3$ (Table 1) interestingly provided 1,2,4,5-tetrasubstituted pyridinium **11** in 17% yield (entry 1, Table 2). Unidentified oligomerization and polymerization of aldol condensate were observed as other products. Compound **11** was not obtained when benzyl amine **2'** was used instead of **2** (entry 2), suggesting that acidic conditions are required for the formation of 1,2,4,5-tetrasubstituted pyridiniums. Indeed, Brønsted acid-promoted pyridinium synthesis was previously reported starting from cyclic imine and aldehydes in AcOH.[7] The

use of hexylamine hydrochloride **12** in place of **2** provided the corresponding 1,2,4,5-substituted pyridinium **13** in 10% yield (entry 3).

Table 2. Investigation of Chichibabin pyridinium synthesis in the absence of $Pr(OTf)_3$.

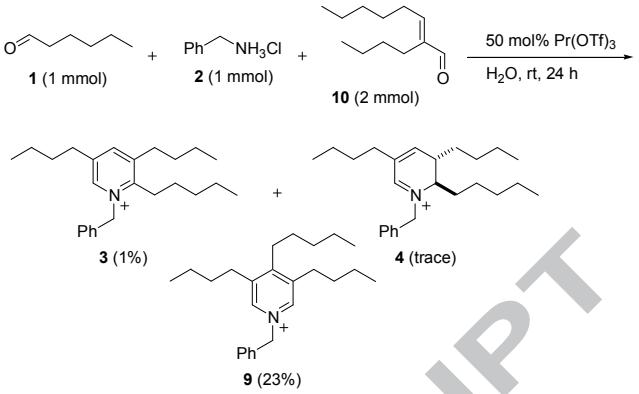


Entry	nitrogen source	product	yield/%[a]
1			17
2			0
3			10

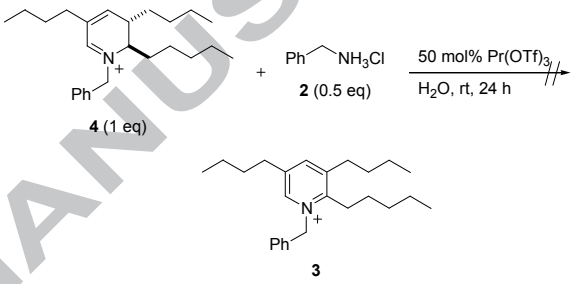
[a]Based on the corresponding nitrogen source.

We quantified **10** by GC-MS analysis every two hours during the reaction of three equivalents of **1** and one equivalent of **2** in H_2O in the presence of 50 mol% $Pr(OTf)_3$ at room temperature (Figure S3, conditions for entry 2, Table 1). The amount of **10** initially increased rapidly, then remained constant after 6 hours. It was suggested two possibilities; generated **10** was used to form **3** and **4**; aldol condensation was completed without being used for the formation of **3** and **4**. Conducting Chichibabin pyridinium synthesis from **1**, **2**, and **10** in H_2O interestingly afforded **8**-type pyridinium **9** in 23% yield and only trace amounts of **3** and **4** (Scheme 4), probably suggesting that **10** is the intermediate of **9** and not of either **3** or **4**. In this reaction, ca. 2 mmol of **10** was also obtained. In other word, **10** was not used for the formation of **3** and **4**.

Isolated dihydropyridinium **4** was stirred with 0.5 equivalents of **2** in H_2O in the presence of 50 mol% $Pr(OTf)_3$ at room temperature (Scheme 5). It was previously reported that the synthesis of **3** from **4** was achieved by stirring under basic or reflux conditions.[2] However, in our case, aromatized pyridinium **3** was not obtained and starting material **4** was recovered quantitatively, indicating that **3** is not formed from **4** in this reaction system.

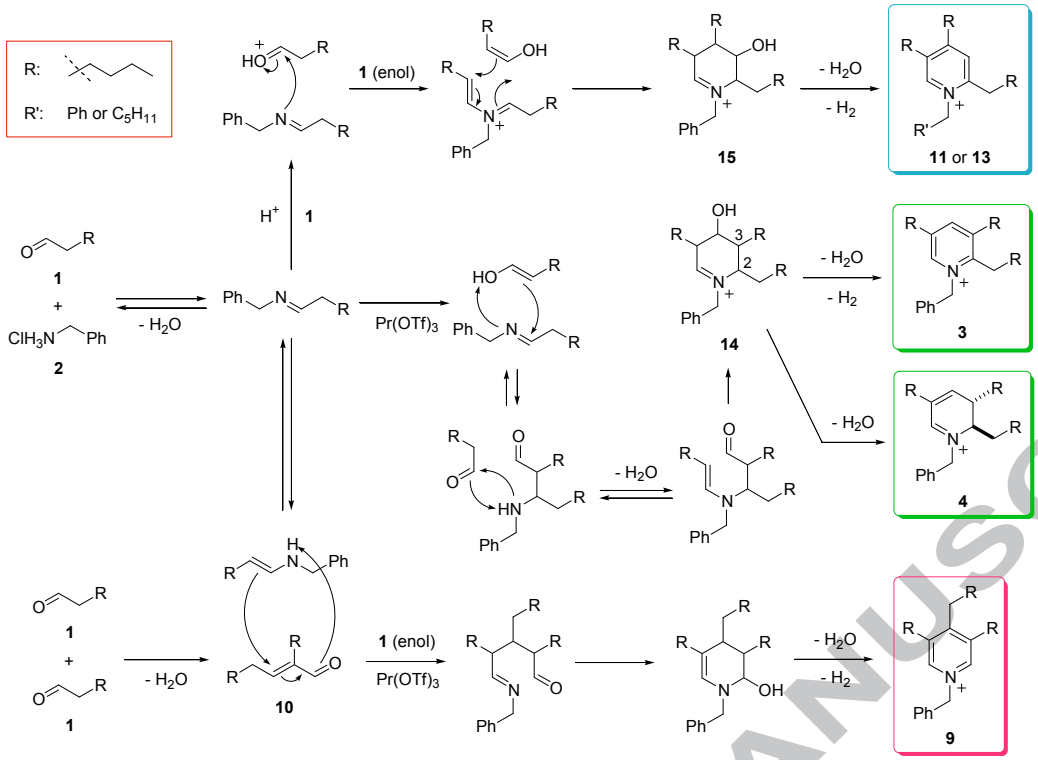


Scheme 4. Chichibabin pyridinium synthesis with **10**.



Scheme 5. Attempt to form **3** from **4**.

Based on the above results, we propose the reaction mechanisms shown in Scheme 6. In the synthesis of **7**-type compounds **3** and **4**, imine formation occurs first, followed by Mannich reaction with enol **1** promoted by $Pr(OTf)_3$.[8] Subsequent addition of **1** results in the formation of cyclized product **14**. Based on Scheme 5, compounds **3** and **4** are individually formed from **14**. For the formation of **8**-type pyridinium **9**, aldol condensation likely occurs as the first step. Subsequent condensation between **10** and enamine, which is promoted by $Pr(OTf)_3$,[8] then cyclization is promoted. Aromatization might proceed more easily with the precursor of **9** than with **14** due to the resonance structure after dehydration of precursor of **9**. The solvent altered the type of pyridinium obtained because **10** is soluble in organic solvents and not in H_2O, and thus the substrates (including intermediate **10**) were mixed in the organic layer, and thereby **9** was obtained as a one of the main product. In contrast, imine is relatively dissolved in H_2O and exposure to neat aldehydes resulted in the formation of **14** and the generation of **3** and **4**. The formation of **11** and **13** in the absence of $Pr(OTf)_3$ resulted first in the generation of imine, followed by proton assisted-nucleophilic attack by the imine on the aldehyde. This promoted nucleophilic attack by enol on the iminium cation, or a perycyclic-type reaction, to give **11** or **13** via cyclized product **15**. Finally, dehydration and dehydrogenation occurred, similar to the synthesis of other pyridiniums.



Scheme 6. Proposed mechanisms of Chichibabin pyridinium synthesis.

Conclusion

In conclusion, Chichibabin pyridinium syntheses under various conditions were screened to obtain three types of pyridinium isomers: isodesmosine-type **3**, desmosine-type **9**, and the new types **11** and **13**. Quantitative GC-MS analysis indicated that the aldol condensate **10** is an intermediate of **9**. Reaction mechanisms for the synthesis of these pyridiniums were proposed. Computational studies would be helpful to confirm these proposed routes.

Acknowledgments

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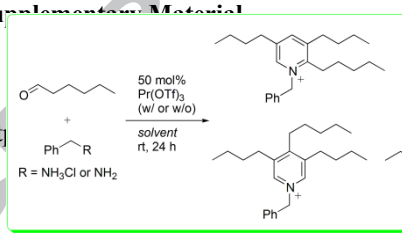

- Mechanistic studies of Chichibabin pyridinium synthesis were examined.
- Interesting pyridinium skeleton was formed under several conditions.
- GC-MS analysis of intermediate aldol condensate was carried out.