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Acylation of 2-benzylpyridine *N*-oxides and subsequent *in situ* [3,3]-sigamatropic rearrangement reaction

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ABSTRACT

An effective method for the acylation of 2-benzylpyridine *N*-oxides and their fast *in situ* [3,3]-sigmatropic rearrangement was reported. This transformation has a wide substrate scope under mild conditions, giving moderate to excellent yields. The application for the synthesis of chiral phenyl-2-pyridylmethanol products was briefly explored. Furthermore, an interesting example of tandem substitution and *in situ* [3,3]-sigamatropic rearrangement of 2-benzylpyridine *N*-oxide with benzenecarboximidoyl chloride was reported.

Introduction

Pyridine derivatives are important moieties in many bioactive compounds as well as in organic materials and ligands [1]. Among of them, 2-benzylpyridine and their analogues are the most potential derivatives, which have recently attracted strong attention in the field of medicinal chemistry because of their unique pharmacological and biological properties [2] (e.g., Carbinoxamine maleate [3], Bepotastine [4], PGI2 agonist [5], 2-APB analogue [6] etc. Fig. 1). Therefore, it is of particular significance to develop or improve the synthetic methods for the 2-benzylpyridine derivatives.

Pyridine *N*-oxide, first made by Meisenheimer in 1926, provides a new process for the synthesis of various pyridine derivatives due to their unique chemical properties and reactivity [7]. In 1947, Katada reported the first rearrangement reaction of pyridine *N*-oxide with acetic anhydride, after hydrolysis, to 2-pyridone [8]. Later, Ochiai and his collaborators further applied this rearrangement to the *N*-oxides of quinine, dihydroquinine and benzoquinoline to give the corresponding α-pyridones [9]. In 1954, as an excellent research work, Boekelheide demonstrated the rearrangement reaction of 2-alkyl substituted pyridine *N*-oxides with acetic anhydride. Surprisingly, the corresponding pyridyl carbinol derivatives were obtained, which is now known as the Boekelheide rearrangement (entry 1, Scheme 1) [10]. After that, many researchers focused on the derivation and application of this rearrangement reaction [11]. As a result, the Boekeheide-like rearrangement reaction of aromatic heterocycles *N*-oxides with alkyl substituents have been extensively explored, which is very important for synthesizing various complex compounds. However, the research on aromatic heterocycles *N*-oxides with benzyl substituents is still limited.

In 2009, Oshima's group developed the Boekeheide-like rearrangement reaction of 2-benzylpyridine *N*-oxides refluxing with acetic anhydride, while the reaction showed narrow substrate

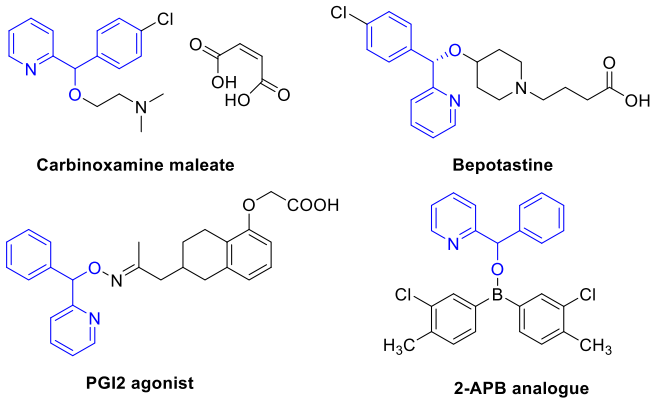

Fig. 1. Examples of the 2-benzylpyridine moiety in drugs and bioactive compounds.

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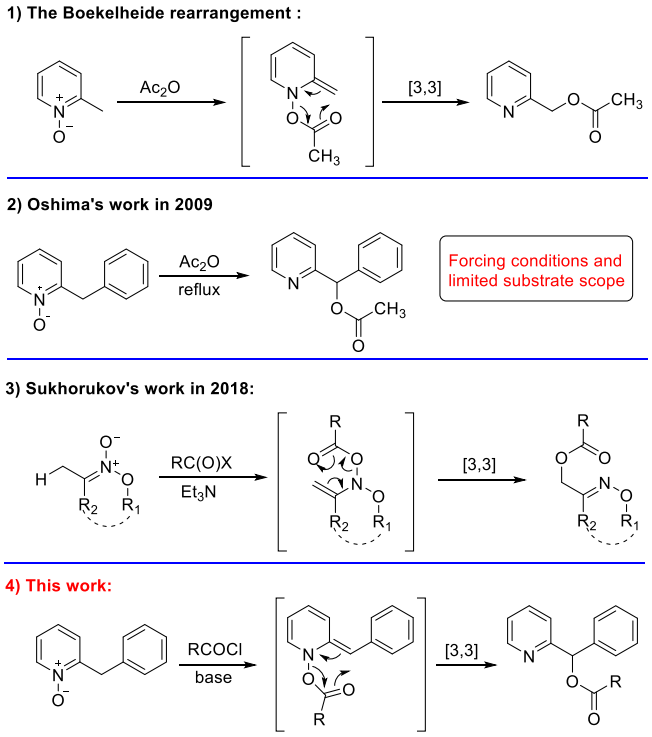


Scheme 1. The Boekelheide-like rearrangement for the preparation of 2-benzylacyloxy pyridine derivatives.

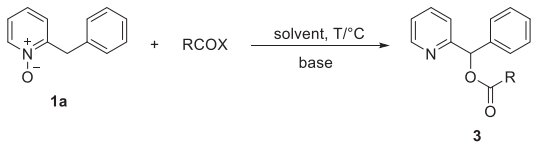
scope (entry 2, Scheme 1) [11c]. Recently, Sukhorukov and his coworkers reported the acylation of nitronates and their fast *in situ* [3,3]-sigmatropic rearrangement in the presence of triethylamine, which undergoes a similar process as the Boekelheide-like rearrangement (entry 3, Scheme 1) [12]. Inspired by this work, we assumed that the 2-benzylpyridine *N*-oxide with acyl chloride could also proceed with the similar process in the presence of a base (entry 4, Scheme 1). Herein, we report an effective and practical method for the tandem acylation and *in situ* [3,3]-sigmatropic rearrangement reaction of 2-benzylpyridine *N*-oxides with acyl chloride.

We started the reaction by identified different acylation reagents (entries 1–4, Table 1). Treatment of 2-benzylpyridine *N*-oxide (**1a**) and different acylation reagents (**2a**) at 110 °C give product **3a** in 70% and 81% yield respectively (entries 2, 4, Table 1). We then investigated different bases (entries 5–9, Table 1) and found that pyridine performed most efficiently giving 80% isolated yield even at room temperature. After that, a variety of solvents (entries 9–13, Table 1) were investigated, and DCM was the best, which could improve the yield to 92% (entry 10, Table 1).

With the optimized conditions in hand (entry 10, Table 1), we studied the substrates scope of this reaction (Scheme 2). A series of substituted 2-benzylpyridine *N*-oxides reacted with acetyl chloride **2a** giving acylation products (**3b**–**3n**) in 55% to 94% yield. Introducing electron-donating groups, such as methyl and methoxy at *ortho*-, *meta*-, and *para*-position of benzene ring afforded the desired products in excellent yield (**3b–3d, 3g–3h**). The slightly lower yield was obtained by introducing weak electron-withdrawing group (such as –COOMe and -F) on substrates (**3e**, **3f**, **3i**, **3j**). Substrates with strong electron-withdrawing group as trifluoromethyl and cyano group gave moderate yields in 55% to 68%. These results indicated that electron-withdrawing groups on the benzene ring diminished the reactivity of this reaction. We speculated that substrates with electron-donating substituents could form more stable conjugated transition intermediates.

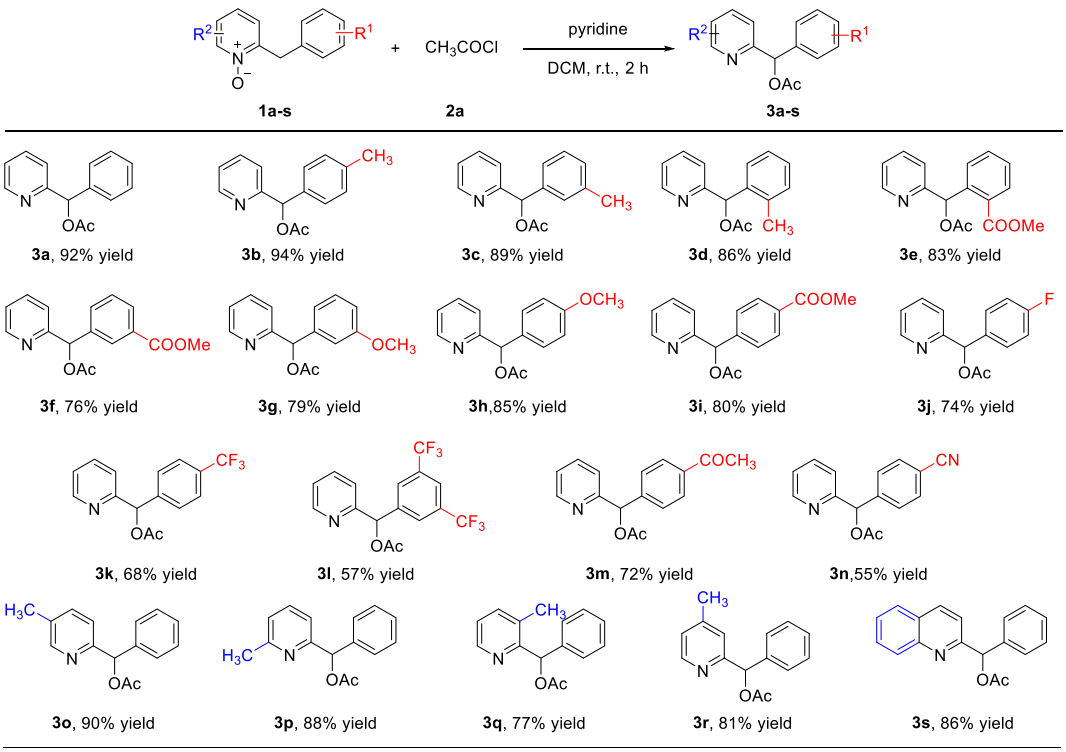
Subsequently, substrates with different substituents on the pyridine ring were also investigated. Methyl substitution at the 3-, 4-, 5-, 6-positions of the pyridine ring (**3o-s**) also worked very well, and giving desired products in excellent yields. Substrate **3q** gave a slightly diminished yield, possibly due to its steric effect. Gratifyingly, when we tried to change the pyridine ring to a quinoline ring, the desired product **3s** was obtained in a high yield of 86%. Furthermore, we also investigated different acyl chlorides as acylation reagents (Scheme 3). Under the standard condition, several acyl chlorides (propionyl chloride, butyryl chloride, pivaloyl chloride and benzoyl chloride) reacted with **1a** to afford the desired products **3t–w** in excellent yields of 92–96%. It is worth mentioning that the benzoyl chloride gave the best result, the product **3w** was obtained in an excellent yield of 96%.

Table 1
Optimization of the reaction conditions.[a]

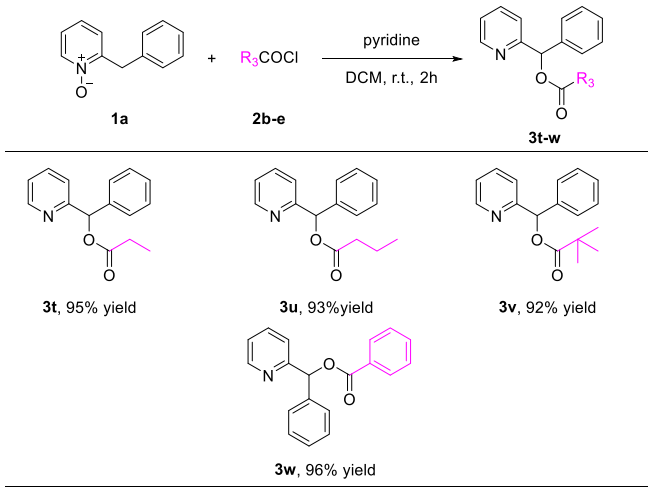


Entry	RCOX	Temp/℃	Time/h	Base	solvent	Yield /%[b]
1	Ac_2O	rt	48	–	toluene	20
2	Ac_2O	110	12	–	toluene	70
3	AcCl	rt	48	–	toluene	28
4	AcCl	110	12	–	toluene	81
5	AcCl	rt	2	DBU	toluene	62
6	AcCl	rt	2	DMAP	toluene	68
7	AcCl	rt	2	Et_3N	toluene	35
8	AcCl	rt	2	DIPEA	toluene	40
9	AcCl	rt	2	Py	toluene	80
10	**AcCl**	**rt**	**2**	**Py**	**DCM**	**92**
11	AcCl	rt	2	Py	THF	64
12	AcCl	rt	2	Py	Et_2O	53
13	AcCl	rt	2	Py	CH_3CN	30

[a] Reaction conditions: **1a** (0.16 mmol), RCOX (0.24 mmol, 1.5 equiv), base (0.32 mmol, 2.0 equiv), solvent (1.0 mL). [b]Isolated yield.



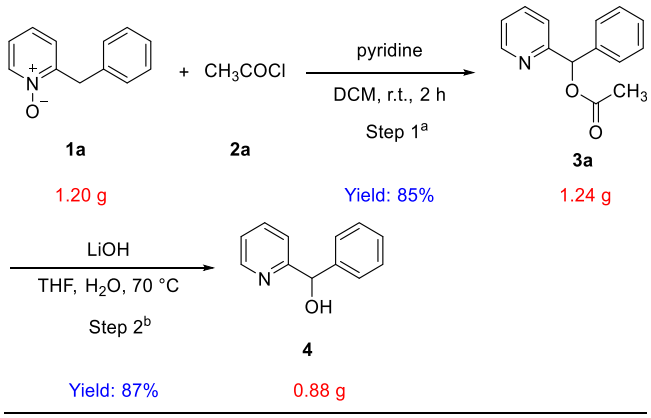
Scheme 2. Substrate scope of 2-benzylpyridine *N*-oxides **1a–s**.[a,b] [a]Reaction conditions: **1a–s** (0.16 mmol), **2a** (0.24 mmol, 1.5 equiv), pyridine (0.32 mmol, 2.0 equiv), DCM (1.0 mL). [b]Isolated yields of compounds **3a–s**.



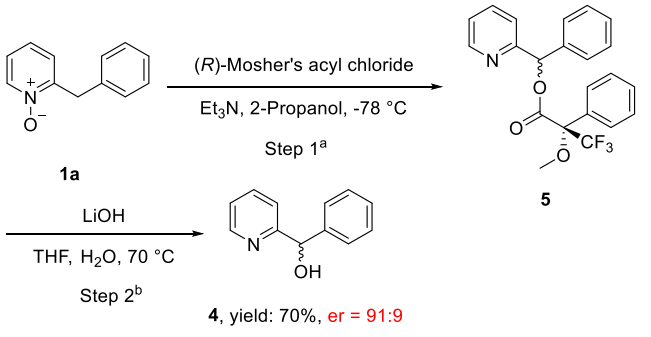
Scheme 3. Substrate scope of acyl chloride **2b–e**.[a,b]. [a]Reaction conditions: **1o-s** (0.16 mmol), **2a** (0.24 mmol, 1.5 equiv), pyridine (0.32 mmol, 2.0 equiv), DCM (1.0 mL). [b]Isolated yields of compounds **3o-s.**

Results and discussion

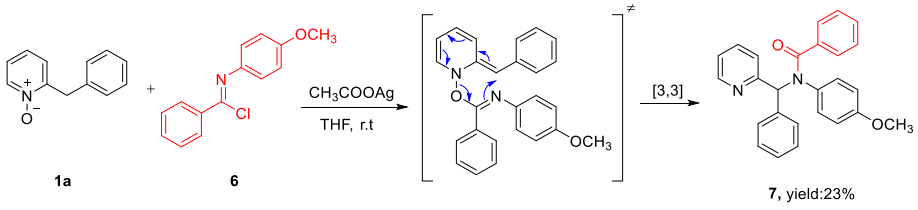
We then conducted this reaction in gram scale. Treatment of 1.20 g of 2-benzylpyridine *N*-oxide **1a** with acyl chloride under optimized conditions gave 1.24 g acylated product **3a** in yield of 85% (step 1, Scheme 4). And the application of this reaction was further demonstrated through hydrolysis of **3a** giving phenyl-2-pyridylmethanol **4** (step 2, Scheme 4) [13], which can be used as various biological compounds and analogues [14]. Envisioned by Andreotti's work on the stereoselective Boekelheide-like rearrangement using chiral Mosher's acyl chloride as an activator in 2010 [11d], we also tried to achieve enantioselectivity of this



Scheme 4. Gram-scale reaction and application. [a]Reaction conditions: **1a** (6.4 mmol), **2a** (9.6 mmol), pyridine (12.8 mmol), DCM (20 mL). [b]Reaction conditions: **3a**, LiOH in THF and H_2O, 70 ℃, 8 h.



Scheme 5. Reaction of 2-benzylpyridine *N*-oxide with (*R*)-Mosher's acid chloride and hydrolysis reaction. [a]Reaction conditions: **1a** (0.48 mmol), (*R*)-Mosher's acyl chloride (0.96 mmol), Et_3N (1.44 mmol), 2-Propanol (5 mL), −78 ℃, 18 h. [b]Reaction conditions: **5** (138 mg, 0.34 mmol), LiOH in THF (5 mL) and H_2O (3 mL), 70 ℃, 8 h.



Scheme 6. The new derivative reaction of 2-benzylpyridine *N*-oxide with benzenecarboximidoyl chloride.[a] [a]Reaction conditions: **1a** (30 mg, 0.16 mmol), **6** (48 mg, 0.19 mmol, 1.2 equiv), CH_3COOAg (26.7 mg, 0.16 mmol, 1.0 equiv), DCM (20 mL), r.t., 8 h.

reaction by using 2-benzylpyridine *N*-oxide and (*R*)-mosher's acyl chloride obtained the phenyl-2-pyridylmethanol in 70% yield with an enantiomeric ratio of 91:9 (Scheme 5), and efforts on further improving enantioselectivity is underway in our lab. Finally, based on the research of aminoarylation of 2- and 4-picoline l-oxides [15], we also successfully developed a novel reaction of 2-benzylpyridine *N*-oxide with benzenecarboximidoyl chloride giving amide derivatives in yield of 23%, through a tandem process of substitution and *in situ* [3,3]-sigamatropic rearrangement (Scheme 6).

Conclusion

In summary, we successfully developed an effective Boekelheide rearrangement of 2-benzylpyridine *N*-oxide derivatives, which proceeds *via* tandem acylation and *in situ* [3,3]-sigmatropic rearrangement under mild conditions. This reaction could proceed in good to excellent yield with wide substrates scope and high functional group tolerance, even in gram-scale. We also achieved good enantioselectivity of this reaction by using chiral induction policy. In addition, we also developed a novel rearrangement reaction of 2-benzylpyridine *N*-oxide with benzenecarboximidoyl chloride to introduce amide group at benzyl position. We hope this method could become a new powerful method to synthesize bioactive 2-benzylpyridine derivatives.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152401.

References

[1] (a) J.A. Bull, J.J. Mousseau, G. Pelletier, A.B. Charette, Chem. Rev. 112 (2012) 2642;
(b) T.J. Ritchie, S.J.F. Macdonald, S. Peace, S.D. Pickett, C.N. Luscombe, Med. Chem. Commun. 3 (2012) 1062;
(c) M. Itoh, K. Hirano, T. Satoh, M. Miura, Org. Lett. 16 (2014) 2050.
[2] N. Sperber, D. Papa, E. Schwenk, M. Sherlock, J. Am. Chem. Soc. 73 (8) (1951) 3856.
[3] G. Hite, V. Barouh, H. Dall, D. Patel, J. Med. Chem. 14 (9) (1971) 834.
[4] J.R. Proudfoot, Bioorg. Med. Chem. Lett. 12 (2002) 1647.
[5] N. Hamanaka, K. Takahashi, Y. Nagao, K. Torisu, S. Shigeoka, S. Hamada, H. Kato, H. Tokumoto, K. Kondo, Bioorg. Med. Chem. Lett. 5 (10) (1995) 1087.
[6] H. Zhou, H. Iwasaki, T. Nakamura, K. Nakamura, T. Maruyama, S. Hamano, S. Ozaki, A. Mizutani, K. Mikoshiba, Biochem. Biophys. Res. Commun. 352 (2007) 277.
[7] F.E. Cislak, Ind. Eng. Chem. 47 (1955) 800.
[8] M. Katada, J. Pharm. Soc. Jpn. 67 (1947) 51.
[9] E. Ochiai, T.J. Okamoto, Pharm. Soc. Jpn. 68 (1948) 88.
[10] V. Boekelheide, W.J. Linn, J. Am. Chem. Soc. 76 (1954) 1286.
[11] (a) A. McKillop, M.K. Bhagrath, Heterocycles 23 (1985) 1697;
(b) C. Fontenas, E. Bejan, H.A. Haddou, G.G.A. Balavoine, Synth. Commun. 25 (1995) 629;
(c) T. Suehiro, T. Niwa, H. Yorimistu, K. Oshima, Chem. Asian J. 4 (2009) 1217;
(d) D. Andreotti, E. Miserazzi, A. Nalin, A. Pozzan, R. Profeta, S. Spada, Tetrahedron Lett. 51 (2010) 6526;
(e) A. Massaro, A. Mordini, A. Mingardi, J. Klein, D. Andreotti, Eur. J. Org. Chem. (2011) 271;
(f) X.D. Xun, M. Zhao, J.Z. Xue, T. Hu, M. Zhang, G.F. Li, L. Hong, Org. Lett. 21 (2019) 8266.
[12] A.O. Kokuev, Y.A. Antonova, V.S. Dorokhov, I.S. Golovanov, Y.V. Nelyubina, A.A. Tabolin, A.Y. Sukhorukov, S.L. Ioffe, J. Org. Chem. 83 (2018) 11057.
[13] S.J. deSolms, T.M. Ciccarone, S.C. MacTough, A.W. Shaw, C.A. Buser, M. Ellis-Hutchings, C. Fernandes, K.A. Hamilton, H.E. Huber, N.E. Kohl, R.B. Lobell, R.G. Robinson, N.N. Tsou, E.S. Walsh, S.L. Graham, L.S. Beese, J.S. Taylor, J. Med. Chem. 46 (2003) 2973.
[14] (a) J. Gearien, E. Frank, M. Megahy, C. Polorny, J. Med. Chem. 14 (1971) 551;
(b) J.Y. Yang, G.B. Dudley, J. Org. Chem. 74 (2009) 7998;
(c) F. Schmidt, R.T. Stemmler, J. Rudolph, C. Bolm, Chem. Soc. Rev. 35 (2006) 454.
[15] R.A. Abramovitch, D.A. Abramovitch, J. Chem. Soc., Chem. Commun. 561 (1981).