ORGANIC LETTERS

2013
Vol. 15, No. 8
1902–1905

Ir(I)-Catalyzed Synthesis of *N*-Substituted Pyridones from 2-Alkoxypyridines via C−O Bond Cleavage

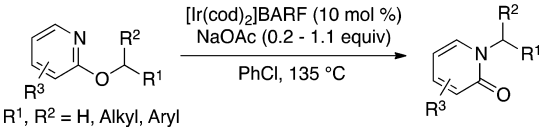
Shiguang Pan,[†] Naoto Ryu,[†] and Takanori Shibata*[,†,‡]

Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, Shinjuku, Tokyo 169-8555, Japan, and JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

tshibata@waseda.jp

Received February 28, 2013

ABSTRACT



A cationic Ir(I) complex-catalyzed *O*-to-*N*-alkyl migration in 2-alkoxypyridines bearing a secondary alkyl group on the oxygen atom by C−O bond cleavage is described. The present transformation gave various *N*-alkylpyridones in moderate to good yields. The addition of sodium acetate played a key role in suppressing β-hydrogen elimination.

N-Alkylpyridone is an important structural unit and is widely found in heterocyclic compounds with biological activities and medicinal applications.[1] Although the direct N−H alkylation of pyridone has been explored under the basic conditions, *O*-alkylation is a competing process because of the aromatic character of 2-oxypyridine.[2] Thus, the synthetic protocols that begin with 2-alkoxypyridines via *O*-to-*N*-alkyl migration have attracted significant attention for the efficient synthesis of *N*-alkylpyridone because 2-alkoxypyridines can be easily synthesized by the nucleophilic aromatic substitution of 2-halopyridines.[3] Various salts have been used in these migration reactions; typically, stoichiometric amounts of metal salts are required.[4] Pt and Pd complexes realized catalytic reactions, but they were Claisen rearrangements and the substrates were limited to 2-allyloxypyridines.[5,6] Therefore, a more general method for *O*-to-*N*-alkyl migration is required. Recently, Dong published a useful protocol using a Ru

[†] Waseda University.
[‡] JST, ACT-C.

(1) (a) Lindenblad, G. E.; Kaihara, M.; Price, J. M. *J. Biol. Chem.* **1956**, *219*, 893. (b) Adibatti, B. A.; Trirugnanasambantham, P.; Kulothungan, C.; Viswanathan, S.; Kameswaran, L.; Balakrishna, K.; Sukumar, E. *Phytochemistry* **1991**, *30*, 2449. (c) Huffman, J. W.; Lu, J.; Hynd, G.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **2001**, *9*, 2863. (d) Parlow, J. J.; South, M. S. *Tetrahedron* **2003**, *59*, 7695. (e) Deady, L. W.; Rodemann, T.; Zhuang, L.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **2003**, *46*, 1049. (f) Martinez, C. A.; Yazbeck, D. R.; Tao, J. *Tetrahedron* **2004**, *60*, 759. (g) Deady, L. W.; Rogers, M. L.; Zhuang, L.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2005**, *13*, 1341. (h) Stead, D.; O'Brien, P.; Sanderson, A. J. *Org. Lett.* **2005**, *7*, 4459. (i) Gray, D.; Gallagher, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2419. (j) Pfefferkorn, J. A.; Lou, J.; Minich, M. L.; Filipski, K. J.; He, M.; Zhou, R.; Ahmed, S.; Benbow, J.; Perez, A.-G.; Tu, M.; Litchfield, J.; Sharma, R.; Metzler, K.; Bourbonais, F.; Huang, C.; Beebe, D. A.; Oates, P. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3247. (k) Huang, X.; Aslanian, R.; Zhou, W.; Zhu, X.; Qin, J.; Greenlee, W.; Zhu, Z.; Zhang, L.; Hyde, L.; Chu, I.; Cohen-williams, M.; Palani, A. *ACS Med. Chem. Lett.* **2010**, *1*, 184.

(2) (a) Sato, T.; Yoshimatsu, K.; Otera, J. *Synlett* **1995**, 845. (b) Liu, H.; Ko, S.-B.; Josien, H.; Curran, D. P. *Tetrahedron Lett.* **1995**, *36*, 8917. (c) Conreaux, D.; Bossharth, E.; Monteiro, N.; Desbordes, P.; Balme, G. *Tetrahedron Lett.* **2005**, *46*, 7917. (d) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757 and references therein.

(3) (a) Ballesteros, P.; Claramunt, R. M.; Elguero, J. *Tetrahedron* **1987**, *43*, 2564. (b) Loupy, A.; Philippon, N.; Pigeon, P.; Galons, H. *Heterocycles* **1991**, *32*, 1947. (c) Cherng, Y.-J. *Tetrahedron* **2002**, *58*, 4931. (d) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923. (e) Yang, J.; Dudley, G. B. *J. Org. Chem.* **2009**, *74*, 7998.

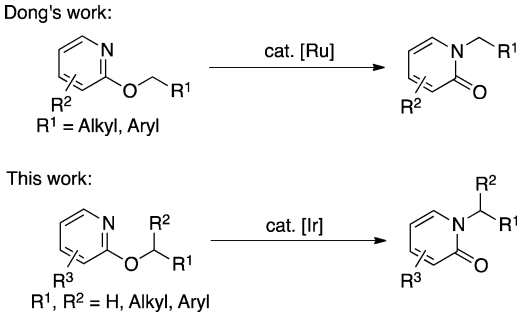
(4) (a) Ikehara, M.; Tanaka, S. *Tetrahedron Lett.* **1974**, *15*, 497. (b) Lanni, E. L.; Bosscher, M. A.; Ooms, B. D.; Shandro, C. A.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.* **2008**, *73*, 6425. (c) Tasker, S. Z.; Bosscher, M. A.; Shandro, C. A.; Lanni, E. L.; Ryu, K. A.; Snapper, G. S.; Utter, J. M.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.* **2012**, *77*, 8220.

(5) (a) Stewart, H. F.; Seibert, R. P. *J. Org. Chem.* **1968**, *33*, 4560. (b) Balavoine, G.; Guibe, F. *Tetrahedron Lett.* **1979**, *41*, 3949.

(6) (a) Reddy, A. C. S.; Narsaiah, B.; Venkataratnam, R. V. *Tetrahedron Lett.* **1996**, *37*, 2829. (b) Itami, K.; Yamazaki, D.; Yoshida, J. *Org. Lett.* **2003**, *5*, 2161. (c) Rodrigues, A.; Lee, E. E.; Batey, R. A. *Org. Lett.* **2010**, *12*, 260. (d) Fontana, G.; Piccionello, A. P. *Tetrahedron Lett.* **2011**, *52*, 884.

10.1021/ol400557z
Published on Web 03/29/2013

Scheme 1. Examples of *O*-to-*N*-Alkyl Migration via C−O Bond Cleavage



catalyst in the presence of a stoichiometric amount of base, which led to efficient *O*-to-*N*-alkyl migration in pyridines and other related heterocycles by sp^3 ethereal C−O bond cleavage.[7]

Here, we disclose *O*-to-*N*-alkyl migration in pyridines by sp^3 C−O bond cleavage using a cationic iridium catalyst. The reaction of 2-alkoxypyridines bearing a secondary *O*-alkyl group could also be achieved to give the corresponding *N*-alkylpyridones (Scheme 1). In contrast, the Ru-catalyzed migration of a 2-alkoxypyridine bearing a secondary *O*-alkyl group did not give the desired *N*-substituted pyridone.[7]

We have focused on the development of cationic iridium-catalyzed reactions initiated by C−H bond activation,[8] and we recently presented the cationic iridium-catalyzed enantioselective activation of the secondary sp^3 C−H bonds adjacent to a nitrogen atom using pyridyl as a directing group.[9] Based on the reported protocol, we studied the cationic iridium-catalyzed activation of sp^3 C−H bond adjacent to an oxygen atom in 2-methoxypyridine under the same conditions (Scheme 2, eq 1). Although the desired C−H alkylated product was not obtained, a trace amount of *N*-methylpyridone was formed by C−O bond cleavage. It is noteworthy that the yield of *N*-methylpyridone was improved in the absence of the phosphine ligand, and the yield reached 95% NMR yield, when tetrakis(3,5-bis-(trifluoromethyl)phenyl)borate (BARF) was used as a counteranion (Scheme 2, eq 2).

O-to-*N*-alkyl migration in pyridines bearing a secondary *O*-alkyl group is more challenging, and we chose 2-(1-phenylethoxy)pyridine (**1a**) as a model substrate for

Scheme 2. Ir-Catalyzed *O*-to-*N*-Alkyl Migration of 2-Methoxypyridine

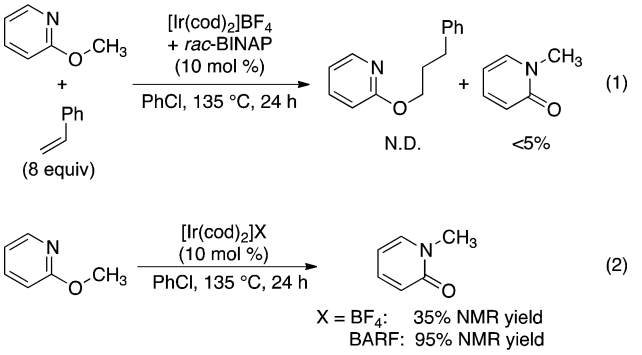
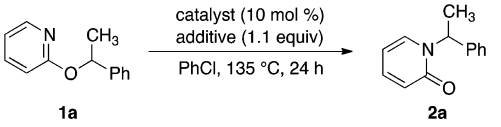


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	additive	yield[b] (%)
1	$[Ir(cod)_2]BARF$	none	23
2	$[Ir(cod)_2]BARF$	pyridine	15
3	$[Ir(cod)_2]BARF$	NEt_3	24
4	$[Ir(cod)_2]BARF$	Li_2CO_3	64
5	$[Ir(cod)_2]BARF$	Na_2CO_3	94
6	$[Ir(cod)_2]BARF$	K_2CO_3	45
7	$[Ir(cod)_2]BARF$	Cs_2CO_3	n.r
8	$[Ir(cod)_2]BARF$	NaOAc	95 (78)
9	$[Ir(cod)_2]BARF$	PivONa	95
10	$[Ir(cod)_2]BF_4$	NaOAc	<5
11	$[Ir(cod)_2]OTf$	NaOAc	41
12	$[Ir(cod)_2]BARF$	NaOAc[c]	81

[a] Conditions: 2-(1-phenylethoxy)pyridine (**1a**) (0.1 mmol), catalyst (0.01 mmol), additive (0.11 mmol), PhCl (0.5 mL), unless otherwise noted. [b] NMR yield. Isolated yield was given in parentheses. [c] NaOAc (20 mol %) was used.

determining the optimal reaction conditions (Table 1). When $[Ir(cod)_2]BARF$ by itself was used as a catalyst in chlorobenzene, alkoxypyridine **1a** was completely consumed, but only a low yield of the desired pyridone **2a** was obtained (entry 1). Next, we examined various organic and inorganic additives for the present reaction (entries 2−9) and found that sodium acetate and pivalate exhibited higher catalytic efficiencies among them (entries 8 and 9). Next, we tuned the counteranion of the iridium complex using NaOAc as an additive, but did not get better results than when BARF was used (entries 10 and 11). A catalytic amount of NaOAc was sufficient to achieve an efficient transformation, but gave a slightly decreased yield (entry 12); thus, we used the entry 8 conditions for further investigations.

A control experiment was conducted to clarify the role of NaOAc (Scheme 3). The reaction of **1a** was examined

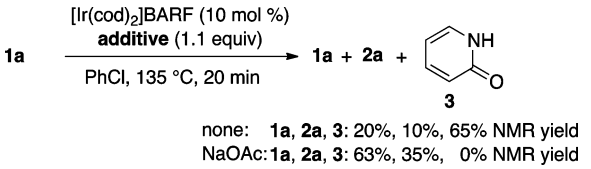
(7) Yeung, C. S.; Hsieh, T. H. H.; Dong, V. M. *Chem. Sci.* **2011**, *2*, 544.

(8) (a) Tsuchikama, K.; Kasagawa, M.; Hashimoto, Y.; Endo, K.; Shibata, T. *J. Organomet. Chem.* **2008**, *693*, 3939. (b) Tsuchikama, K.; Hashimoto, Y.; Endo, K.; Shibata, T. *Adv. Synth. Catal.* **2009**, *351*, 2850. (c) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821. (d) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Synlett* **2010**, 97. (e) Shibata, T.; Hashimoto, Y.; Otsuka, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2075. (f) Shibata, T.; Hirashima, H.; Kasagawa, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2171. (g) Takebayashi, S.; Shibata, T. *Organometallics* **2012**, *31*, 4114. (h) Pan, S.; Ryu, Y.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474.

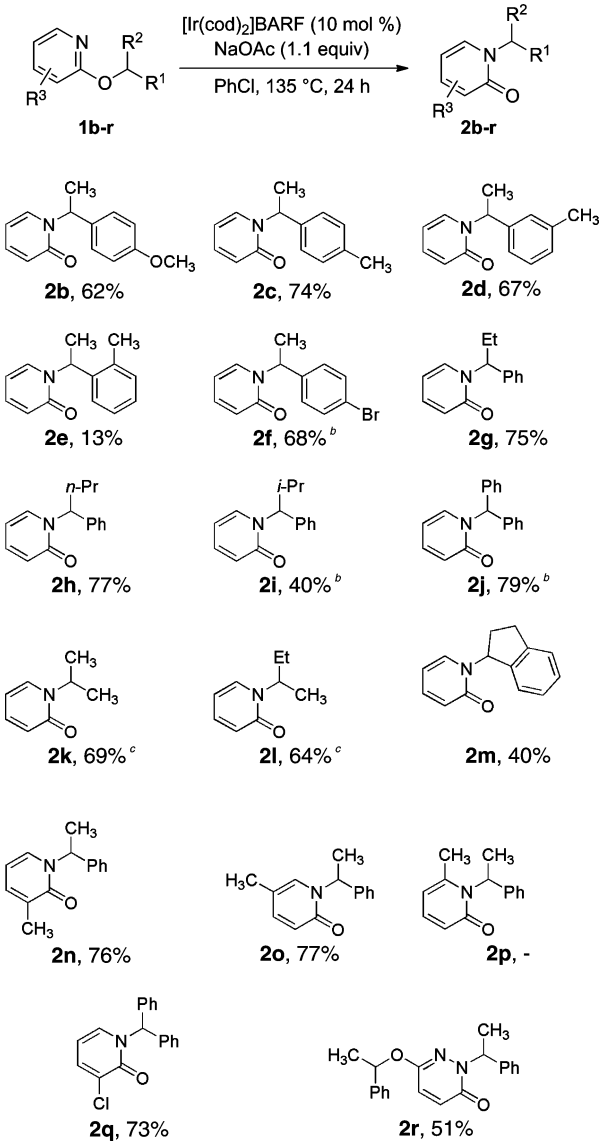
(9) (a) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692. (b) Pan, S.; Matsuo, Y.; Endo, K.; Shibata, T. *Tetrahedron* **2012**, *68*, 9009.

(10) When **2a** was subjected to the same reaction conditions, no H/D exchange was observed.

Scheme 3. Investigation of the Role of NaOAc



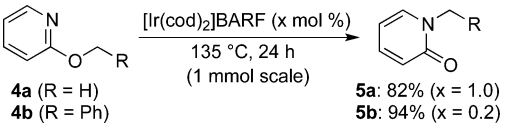
Scheme 4. *O*-to-*N*-Alkyl Migration of 2-Alkoxypyridines with a Secondary Alkyl Group[a]



[a] Conditions: 2-alkoxyheterocycles **1** (0.1 mmol), $[Ir(cod)_2]BARF$ (0.01 mmol), NaOAc (0.11 mmol), PhCl (0.5 mL), 135 °C for 24 h, unless otherwise noted. [b] The reaction time was 48 h. [c] $[Ir(cod)_2]BF_4$ were used in place of $[Ir(cod)_2]BARF$, and the reaction proceeded without NaOAc.

without and with NaOAc, followed by quenching after a short reaction time, and the crude products were analyzed by NMR. Pyridone **3** was generated in the absence of

Scheme 5. *O*-to-*N*-Alkyl Migration of 2-Alkoxypyridines with a Primary Alkyl Group



NaOAc by β-hydrogen elimination after oxidative C–O bond cleavage by the Ir complex. In contrast, the formation of pyridone **3** was not detected in the presence of NaOAc. These results suggest that NaOAc completely suppressed β-hydrogen elimination.

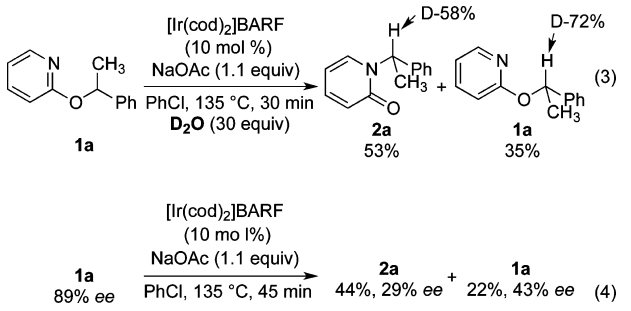
Subsequently, the scope of 2-alkoxypyridines bearing a secondary *O*-alkyl group was examined for the present transformation (Scheme 4). 2-Alkoxypyridines **1b**–**d** with an electron-donating group on the benzene ring gave the desired pyridones **2b**–**d** in moderate to good yields. Significant steric effects on the reactivities were observed from substituents: *o*-methyl substituent on the aromatic moiety deterred the reaction, giving low yield of the corresponding product **2e**. The reaction of 2-alkoxypyridine **1f** with an electron-withdrawing group required a long reaction time. 2-Benzyloxypyridines **1g**–**i** possessing other alkyl groups at the benzylic position could be also transformed into the corresponding *N*-substituted pyridones **2g**–**i**. Not only 1-arylalkyl groups, but also 1-alkylethyl groups, such as isopropyl and *sec*-butyl, could be used as the migrating group, and *N*-alkylpyridones **2k** and **2l** were obtained. Methyl-substituted pyridines **1n**–**p** were also investigated and the yields varied depending on the position of the methyl group. Almost no effect was observed from substitution at 3 and 5 positions, but 6-methyl-2-alkoxypyridine did not give pyridone **2p**. These results indicate that steric bulkiness around the nitrogen atom is important and that the coordination of the metal to the nitrogen atom is crucial. The introduction of an electron-withdrawing group could be possible, and chloropyridone **2q** was obtained in good yield. One of the two alkyl groups migrated to give product **2r** in a moderate yield when 3,6-dialkoxypyridazine **1r** was used as the substrate.

For 2-alkoxypyridines bearing a primary *O*-alkyl group, the migration proceeded efficiently without NaOAc or solvent, and the reaction of 2-methoxypyridine and 2-benzyloxypyridine gave *N*-methylpyridone **5a** and *N*-benzylpyridone **5b**, respectively, in good to excellent yields at low catalyst loadings (Scheme 5). The protocol is a facile way of synthesizing *N*-alkyl pyridones bearing primary alkyl groups.

A series of experiments were carried out as a preliminary mechanistic study (Scheme 6). The reaction of **1a** was examined in the presence of D_2O (30 equiv), followed by quenching within 30 min (Scheme 6, eq 3). H/D exchange at the benzylic position was observed in both of the migrated product **2a** and the recovered **1a**.[10] Next, chiral substrate **1a**

(11) In the absence of NaOAc, the significant decrease of enantiomeric excess was also observed in **1a** and **2a**, which means that the racemization was not due to base.

Scheme 6. Investigation of Mechanism

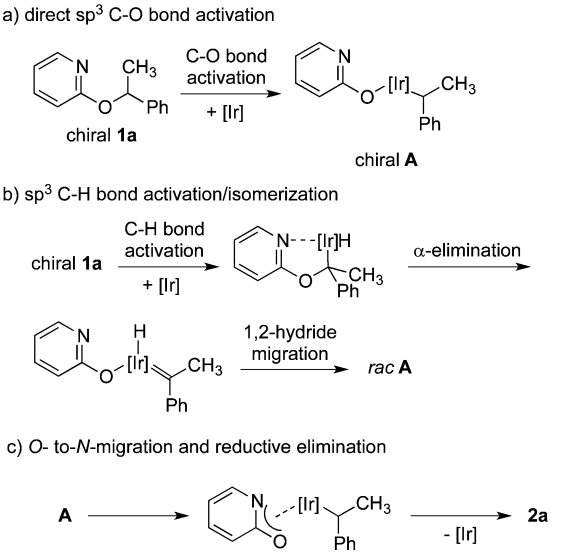


was subjected to the reaction (Scheme 6, eq 4). Interestingly, a significant decrease of the enantiomeric excess was observed in both of the migrated product **2a** and the recovered **1a**.[11]

Based on these results, we speculated the reaction mechanism (Scheme 7). First, two pathways lead to C−O bond cleavage: (a) direct oxidative C−O bond cleavage to give intermediate **A**, which does not induce racemization, and (b) oxidative C−H bond cleavage along with carbene formation and 1,2-hydride migration, which induce racemization.[12] The subsequent intramolecular *O*-to-*N*-alkyl migration and reductive elimination processes do not generate free radicals or ionic intermediates.[13,14]

In summary, we developed a protocol for the cationic Ir(I)-catalyzed *O*-to-*N*-alkyl migration in 2-alkoxypyridines bearing a secondary *O*-alkyl group to afford various *N*-substituted pyridones. In this transformation, the β-hydrogen elimination was completely suppressed by adding NaOAc. Further studies on the scope of the substrate and the precise mechanism are in progress in our laboratory.

Scheme 7. Proposed Mechanism



Acknowledgment. This research was supported by Grant-in-Aid for Scientific Research on Innovative Areas, "Molecular Activation Directed toward Straightforward Synthesis," MEXT, JST, ACT-C, and Grants for Excellent Graduate Schools (Practical Chemical Wisdom), Waseda University, MEXT, Japan.

Supporting Information Available. Experimental procedure and physical property of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) Cleavage of sp^3 C−O bond via oxidative addition of C−H bond with Ir pincer complexes: Choi, J.; Choliy, Y.; Zhang, X.; Emge, T. J.; Krogh-Jespersen, K.; Goldman, A. S. *J. Am. Chem. Soc.* **2009**, *131*, 15627.

(13) We examined a crossover experiment where the 1:1 mixture of **1c** and **1o** was submitted to the same reaction conditions: only trace amounts of the crossover products (< 5%) were observed by GC−MS analysis.

(14) The [1s,4s]-sigmatropic rearrangement can also be a possible mechanism: (a) Schöllkopf, U.; Hoppe, I. *Tetrahedron Lett.* **1970**, 4527. (b) Bowman, W. R.; Bridge, C. F. *Synth. Commun.* **1999**, *29*, 4051 and ref 3d.