Synthesis of *N*-Aryl Pyridin-2-ones via Ligand Coupling Reactions Using Pentavalent Organobismuth Reagents

Kazuhiro Ikegai[†,††] and Teruaki Mukaiyama*[†,††]
[†] *Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI), Toshima, Kita-ku, Tokyo 114-0003*
[††] *Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

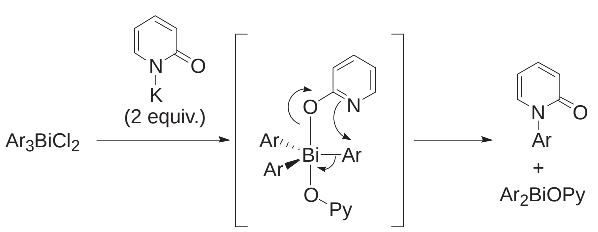
(Received August 1, 2005; CL-050997)

An efficient method for the synthesis of *N*-aryl pyridin-2-ones was established by way of ligand coupling reactions using pentavalent organobismuth reagents such as triarylbismuth dichlorides.

Pyridin-2-ones and the related heterocyclic compounds are important components in many active pharmaceuticals together with their *N*-aryl derivatives that are frequently employed in the investigation of their structure–activity relationships.[1] It is known that the copper-catalyzed Ullman reactions are carried out under drastic reaction conditions and yields of the desired products are moderate.[2] Improved copper-catalyzed reactions for N-arylation of pyridin-2-ones and the related heterocycles by using aryl boronic acids or halides as arylating agents were also reported.[1,3]

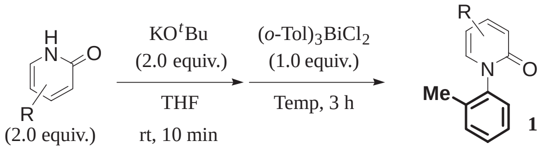
Various tri-, tetra-, and penta-arylbismuth(V) compounds[4] such as Ph_3BiCl_2, Ph_4BiOTs, and Ph_5Bi are well-known reagents for C- or O-arylation of alcohols,[5] phenols,[6] active methylene or methyne compounds,[7] metal-enolates,[8] and enones.[9] Covalently bonded Bi^V–substrate complexes are important intermediates in these arylation reactions. On the other hand, N-arylation of amines and amides with bismuth(V) reagents was reported to proceed smoothly only when copper catalysts were employed.[10,11] Taking the reactions of C-phenylation of phenols and enolates into consideration, however, N-phenylation of heteroaromatic lactams such as pyridin-2-one may proceed smoothly via covalent bismuth(V)–OPy intermediates as shown in Scheme 1. Here, we would like to report a new and efficient method for N-arylation of pyridin-2-ones by using triarylbismuth dichloride and potassium *tert*-buthoxide (*t*-BuOK), which provides various *N*-aryl pyridin-2-ones in good to excellent yields.

A typical experimental procedure is as follows: a solution of 2.0 equimolar amounts of pyridin-2-one and *t*-BuOK in dry THF was stirred at rt for 10 min., followed by the addition of 1.0 equivalent of a triarylbismuth dichloride. Solution thus resulted was allowed to react at the temperatures shown in Tables 1 and 2. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with 1 M HCl, 2 M NaOH, and brine, then dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by preparative TLC on silica gel (hexane/EtOAc) to afford the desired arylated product.

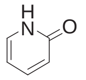
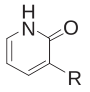
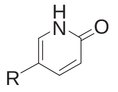
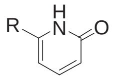
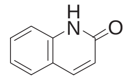
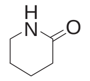
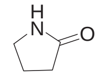


Scheme 1. N-arylation of pyridin-2-one using Ar_3BiCl_2.

Table 1. N-*o*-tolylation of various pyridin-2-ones



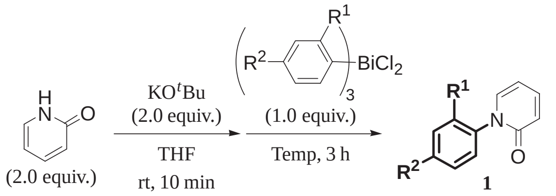
1

Entry	Substrate		Temp/°C	Yield /%	Product
1			rt	95	**1a**
2		R = Me	rt	95	**1b**
3		R = Br	reflux	93	**1c**
4		R = NO_2	reflux	78	**1d**
5		R = Cl	reflux	79	**1e**
6		R = Br	reflux	51	**1f**
7		R = CO_2Et	reflux	86	**1g**
8		R = NO_2	reflux	85	**1h**
9		R = Me	reflux	42	**1i**
10		R = Cl	reflux	ND[a]	**1j**
11			reflux	71	**1k**
12			reflux	37	**1l**
13			reflux	18	**1m**

[a] Not detected.

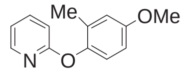
Various 1-(2-methylphenyl)pyridin-2-ones were easily synthesized in good to excellent yields by using tri(*o*-tolyl)bismuth dichloride under mild conditions (Table 1). It should be noted that these *o*-tolylated products are not available by the copper-catalyzed N-arylation reactions between pyridin-2-ones and 2-halotoluene owing to the steric hindrance of *o*-tolyl group.[1] While N-tolylation of simple pyridin-2-one and 3-methylpyridin-2-one proceeded smoothly at room temperature (Entries 1 and 2),[12,13] refluxing conditions were needed when substrates bearing electron-withdrawing functionalities were used (Entries 3–8). Although 6-chloropyridin-2-one did not afford the desired product (Entry 10), 6-methylpyridin-2-one and quinorin-2-one gave the N-tolylated compounds **1i** and **1k** under refluxing conditions (42 and 71% yields, respectively). Aliphatic lactams gave the desired products **1l** and **1m** in poor yields as expected from

Table 2. Substituent effects on bismuth reagents

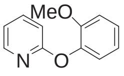


Entry	R^1	R^2	Temp/°C	Yield/%	Product
1	H	H	reflux	71	**1n**
2	Me	H	rt	95	**1a**
3	Me	Cl	rt	91	**1o**
4	Me	OMe	rt	38 (47[a])	**1p** (**2p**)
5	CF_3	H	rt	71	**1q**
6	OMe	H	reflux	47 (9[a])	**1r** (**2r**)

[a] Yields of the corresponding O-arylated products **2**.



2p



2r

Table 3. Effects of organobismuth(V) reagents[a]

Ph_3BiCl_2	Ph_3BiF_2	$[Ph_4Bi^+][BF_4^-]$[b]	$Ph_3Bi(OAc)_2$	Ph_3BiCO_3
71%	73%	51%	0%	0%

[a] N-phenylation of pyridin-2-one was carried out by using bismuth(V) reagents according to the general procedure under refluxing conditions. [b] 1.0 equiv. of pyridin-2-on and *t*-BuOK were used.

Barton's reports[10,11a] (Entries 12 and 13).

Various ortho-substituted phenyl groups as well as simple phenyl one were transferred to the nitrogen atom of pyridin-2-on (Table 2). Importantly, triphenylbismuth dichloride (Ph_3BiCl_2) was less reactive than bulky (*o*-tolyl)$_3$BiCl$_2$ and N-phenylated product **1n** was produced only when the reaction was carried out under refluxing conditions (Entry 1). This is probably due to the steric effects which make C–Bi^V bonds in (*o*-tolyl)$_3$BiCl$_2$ weaker compared with those in Ph_3BiCl_2. Further, the introduction of methoxy groups on the phenyl groups attached to Bi^V atom resulted in the formation of a mixture of N- and O-arylated products (Entries 4 and 6).

A postulated reaction mechanism is depicted in Scheme 1. Two equivalents of potassium pyridin-2-one were substituted at the Bi^V center and the corresponding O-adduct was generated as a key intermediate. The adduct thermally decomposed to afford the N-arylated product together with Bi^{III} byproducts[14] through ligand coupling processes. In order to further verify this mechanism, the use of other organobismuth(V) reagents for Ph_3BiCl_2 was also examined (Table 3). The use of Ph_3BiF_2 or $[Ph_4Bi^+][BF_4^-]$[15] gave **1n** in good yields, whereas triphenylbismuth diacetate or carbonate did not afford *N*-phenylpyridin-2-one under the same conditions. This might suggest that the formation of a covalently bonded Bi^V–pyridin-2-one intermediate is an important step in the present arylation method.

It is noted that an efficient method for N-arylation of pyridin-2-ones using triarylbismuth dichlorides was developed. These reactions proceeded smoothly under mild conditions without any assistance of copper catalysis. Further studies on aryl transfer reactions onto heterocycles by using hypervalent organobismuth reagents are now in progress.

This study was supported in part by the Grant of the 21st Century COE Program from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References and Notes

1 a) C. S. Li and D. D. Dixon, *Tetrahedron Lett.*, **45**, 4257 (2004). b) W. Wawzonek and T. V. Truong, *J. Heterocycl. Chem.*, **25**, 381 (1988), and references therein.

2 For reviews on copper-catalyzed Ullman reactions, see: a) J. Lindley, *Tetrahedron*, **40**, 1433 (1984). b) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, **42**, 5400 (2003).

3 a) W. W. K. R. Mederski, M. Lefort, M. Germann, and D. Kux, *Tetrahedron*, **55**, 12757 (1999). b) P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon, and P. K. Jadhav, *Tetrahedron Lett.*, **42**, 3415 (2001). c) B. Renger, *Synthesis*, **1985**, 856. d) M. Sugahara and T. Ukita, *Chem. Pharm. Bull.*, **45**, 719 (1997).

4 For reviews on organobismuth chemistry, see: a) R. A. Abramovitch, D. H. R. Barton, and J.-P. Finet, *Tetrahedron*, **44**, 3039 (1988). b) J.-P. Finet, *Chem. Rev.*, **89**, 1487 (1989). c) Y. Matano and H. Suzuki, *Bull. Chem. Soc. Jpn.*, **69**, 2673 (1996). d) H. Suzuki, T. Ikegaimi, Y. Matano, *Synthesis*, **1997**, 249. e) N. Komatsu, in "Organobismuth Chemistry," ed. by H. Suzuki and Y. Matano, Elsevier, New York (2001), Chap. 5, p 371. f) G. I. Elliott and J. P. Konopelski, *Tetrahedron*, **57**, 5683 (2001).

5 a) D. H. R. Barton, J.-P. Finet, W. B. Motherwell, and C. Pichon, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 251. b) S. David and A. Thieffry, *J. Org. Chem.*, **48**, 441 (1983).

6 a) D. H. R. Barton, N. Y. Bhatnagar, J.-C. Blazejewski, B. Charpiot, J.-P. Finet, D. J. Lester, W. B. Motherwell, M. T. B. Papoula, and S. P. Stanforth, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2657. b) D. H. R. Barton, N. Y. Bhatnagar, J.-P. Finet, J. Khamsl, W. B. Motherwell, and S. P. Stanforth, *Tetrahedron*, **43**, 323 (1987).

7 a) D. H. R. Barton, J.-C. Blazejewski, B. Charpiot, J.-P. Finet, W. B. Motherwell, M. T. B. Papoula, and S. P. Stanforth, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2667. b) R. S. Fornicola, E. Oblinger, and J. Montgomery, *J. Org. Chem.*, **63**, 3528 (1998). c) K. C. Santhosh and K. K. Balasubramanian, *J. Chem. Soc., Chem. Commun.*, **1992**, 224.

8 a) T. Ooi, R. Goto, and K. Maruoka, *J. Am. Chem. Soc.*, **125**, 10494 (2003). b) T. Arnauld and D. H. R. Barton, *J. Org. Chem.*, **64**, 6915 (1999).

9 P. K. Koech and M. J. Krische, *J. Am. Chem. Soc.*, **126**, 5350 (2004).

10 a) T. Arnauld, D. H. R. Barton, and E. Doris, *Tetrahedron*, **53**, 4137 (1997). b) D. H. R. Barton, J.-P. Finet, and J. Khamsi, *Tetrahedron Lett.*, **30**, 937 (1989). c) D. H. R. Barton, J.-P. Finet, and J. Khamsi, *Tetrahedron Lett.*, **27**, 3615 (1986).

11 A few examples of N-phenylation with organobismuth compounds in the absence of copper catalysts were reported. a) D. H. R. Barton, J.-P. Finet, and C. Pichon, *J. Chem. Soc., Chem. Commun.*, **1986**, 65. b) M. S. Akhtar, W. J. Brouillette, and D. V. Waterhous, *J. Org. Chem.*, **55**, 5222 (1990). See also Ref. 5a.

12 When equimolar amounts of the potassium salt of pyridin-2-one and (*o*-tolyl)$_3$BiCl$_2$ were mixed at room temperature, the product **1a** was formed only in 40% yield.

13 The use of sodium hydride or 1,1,3,3-tertramethylguanidine was less effective compared with that of *t*-BuOK in N-*o*-tolylation of pyridin-2-one (75 or 69% yield, respectively).

14 Unfortunately, our attempt to isolate bismuth(III)-byproducts was unsuccessful owing to their labilities, while small amounts of triarylbismuthines were detected together with N-arylated products.

15 Y. Matano, S. A. Begum, T. Miyamatsu, and H. Suzuki, *Organometallics*, **17**, 4332 (1998).

Published on the web (Advance View) October 1, 2005; DOI 10.1246/cl.2005.1496