Pergamon

Tetrahedron Letters 42 (2001) 2337–2339

TETRAHEDRON LETTERS

A new intramolecular migration of the imino group of *O*-arylketoximes to the aryl group under the Beckmann condition

Yasuo Kikugawa,* Chiho Tsuji, Etsuko Miyazawa and Takeshi Sakamoto

Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan

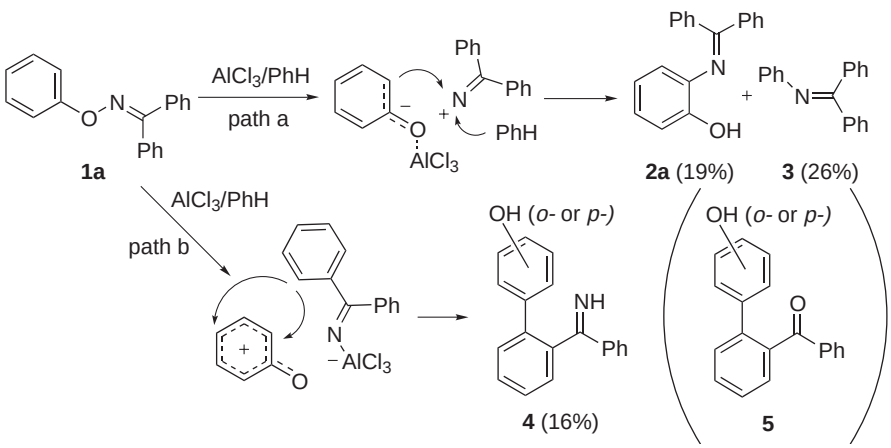
Received 21 December 2000; revised 15 January 2001; accepted 26 January 2001

Abstract—$ZrCl_4$-mediated decomposition of *O*-arylketoximes in benzene leads to regioselective intramolecular migration of the imino group from the oxygen to the *ortho* position of the aryl group via electron-deficient nitrogen intermediates.

The Beckmann rearrangement, the acid-mediated isomerization of oximes to amides, is one of the oldest and most familiar transformations in organic chemistry.[1] Several substrates undergo alternative transformation under conditions of the Beckmann rearrangement. For example, it is well established that *O*-phenylketoximes can be converted to benzofurans under the Beckmann condition via a cyclization analogous to the Fischer indole synthesis.[2,3]

Previously, we reported the $AlCl_3$-mediated heterolytic cleavage of the N–O bond of *N*-phenoxybenzamides that leads to an intramolecular migration of the benzamido group from the oxygen to the *ortho* position of the phenyl ring.[4] In an extension of this work, we have investigated the reaction of *O*-arylketoximes (**1**) with Lewis acids in benzene. We now report that $ZrCl_4$-mediated decomposition of **1** leads to an efficient electrophilic intramolecular migration of the imino group from the oxygen to the *ortho* position of the aryl group[5] (Scheme 1).

We initially used $AlCl_3$ as the Lewis acid. $AlCl_3$ coordinates both with an aryloxy oxygen and an imine nitrogen to produce electron-deficient nitrogen and oxygen, respectively, and gave the rearranged product (**2a**) and



Scheme 1.

Keywords: *O*-aryloxime; $ZrCl_4$; electron-deficient nitrogen; Beckmann condition.
* Corresponding author. Fax: 81-492-71-7984; e-mail: kikugawa@josai.ac.jp

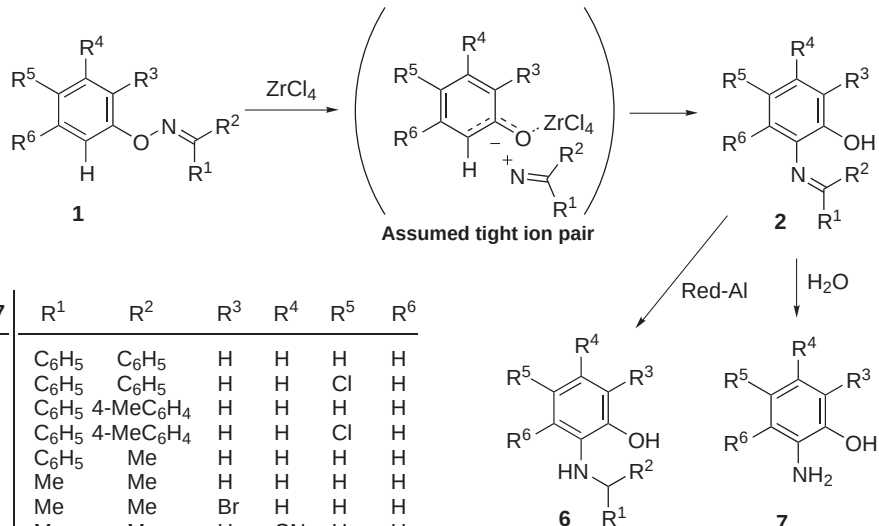
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00181-2

triphenylimine (**3**) via path a and an imino compound, $C_{19}H_{15}ON$ (**4**) via path b. Compound **4** was hydrolyzed to **5**, the structure of which was shown to be (4′-hydroxybiphenyl-2-yl)phenylmethanone by MS and ^1H NMR analyses and by comparison of ^{13}C NMR spectrum with the related compounds in the literature.[6] On the other hand, in the reaction of **1a** with $ZrCl_4$ in benzene, $ZrCl_4$ coordinates exclusively with the aryloxy oxygen and assists in the elimination of the aryloxy group to produce an electron-deficient nitrogen. This migrated exclusively to the *ortho* position of the aryloxy group with no migration to the *para* position. The complete absence of the corresponding *para*-substituted products can be accounted for by assuming an intramolecular mechanism proceeding through a tight ion pair intermediate involving $ZrCl_4$. The formation of this intermediate presumably prevents the Beckmann rearrangement and promotes rearrangement of the imino group to the vicinal *ortho* position of the aryl group. Therefore, oxime stereochemistry is not important in this rearrangement (Scheme 2).

The rearranged products can be reduced without isolation to the corresponding secondary amines with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (**6a**, 77; **6b**, 64; **6c**, 81; **6d**, 78%). Generally they are partially hydrolyzed to primary amines during work up. To obtain primary amines, acetoximes are suitable, because the corresponding rearranged imines are readily hydrolyzed by the usual work-up.

To determine the intramolecular mechanism definitely, a crossover experiment was performed employing **1a** and **1d**. Reaction of almost equimolar concentration of **1a** (100 mg) and **1d** (100 mg) with $ZrCl_4$ (3 mol equiv.) in benzene (10 ml) and subsequent reduction with Red-Al (10 mol equiv.) resulted in a mixture of products (188 mg) after rapid column chromatography. HPLC analysis[7] of the products revealed the exclusive formation of **6a** (85%) and **6d** (88%) along with trace amounts of unidentifiable product (peak area, 1.3%), the retention time (124.9 min) of which is close to that of **6c** (126.2 min), a crossover compound. On the basis of the present result, one can conclude that the reaction proceeds exclusively by an intramolecular mechanism.

A typical experimental procedure is as follows: a mixture of **1g** (162 mg, 0.71 mmol) and $ZrCl_4$ (828 mg, 3.55 mmol) in benzene (5 ml) was refluxed for 1 h. The reaction mixture was quenched with 10% HCl (10 ml) with cooling. The aqueous layer was extracted with AcOEt (25 ml×2) and the combined organic layer was washed with brine (30 ml), dried over Na_2SO_4, and concentrated. The crude product was determined to be 2-bromophenol (16 mg) by TLC. The aqueous layer was basified with 10% Na_2CO_3 (25 ml) and it was extracted with AcOEt (25 ml×2). The combined organic layer was washed with brine (30 ml), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of silica gel with hexane–AcOEt (3:1) as an eluent to afford **7g** (98.0 mg, 73%), mp 86–87°C (methylcyclohexane). IR (KBr) ν: 3400, 3330, 1590, 1490, 1460, 1340, 1230 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.90 (br s, 2H, NH_2), 5.40 (br s, 1H, OH), 6.62–6.68 (m, 2H, Ar-H), 6.82–6.90 (m, 1H, Ar-H). MS (EI) m/z (%): 187 (M^+, 100), 189 (M^++2, 98.1). Anal. calcd for C_6H_6BrNO: C, 38.33; H, 3.22; N, 7.45. Found: C, 38.17; H, 3.13; N, 7.40.



1,2,6,7	R^1	R^2	R^3	R^4	R^5	R^6
a	C_6H_5	C_6H_5	H	H	H	H
b	C_6H_5	C_6H_5	H	H	Cl	H
c	C_6H_5	4-MeC_6H_4	H	H	H	H
d	C_6H_5	4-MeC_6H_4	H	H	Cl	H
e	C_6H_5	Me	H	H	H	H
f	Me	Me	H	H	H	H
g	Me	Me	Br	H	H	H
h	Me	Me	H	CN	H	H
i	Me	Me	H	H	Cl	H
j	Me	Me	H	H	Me	H
k	Me	Me	H	H	CN	H
l	Me	Me	Me	H	H	CN
n	Me	Me	Cl	H	Cl	H
m	Me	Me	Br	H	H	Br
o	Me	Me	Cl	H	Cl	Cl

Scheme 2.

Table 1. Synthesis of *o*-aminophenols from *O*-arylacetoximes with $ZrCl_4$

Starting compds	Reaction time (h)	Product	Yield (%)
1e	2.5	**7e**	70
1f	3.0	**7f**	77
1g	1.0	**7g**	73
1h	3.0	**7h**[a]	29[a]
1i	1.0	**7i**	78
1j	0.3	**7j**	78
1k	9.5	**7k**[b]	21[b]
1l	6.0	**7l**	81
1m	0.3	**7m**	81
1n	0.2	**7n**	76
1o	0.1	**7o**	61

[a] Plus 2-amino-3-cyanophenol (22%) and 3-cyanophenol (42%).
[b] Plus 4-cyanophenol (73%).

The results of similar reactions of several *O*-arylacetoximes with $ZrCl_4$ are presented in Table 1.

Strongly electron-withdrawing substituents such as a cyano group lowered the yield. Five equiv. of $ZrCl_4$ to **1** were needed to obtain high yields of **7**. Use of $AlCl_3$, $CrCl_3$ and $(CF_3SO_3)_2Cu$ gave unsatisfactory results. Solvents such as benzene, toluene, $CHCl_3$ and CH_2Cl_2 are suitable.

As described above, $ZrCl_4$-mediated decomposition of *O*-arylketoximes does not afford benzofuran derivatives under the Beckmann conditions, but leads to regioselective introduction of an amino group to the *ortho* position of the phenolic hydroxyl group. The procedure is notable for its technical simplicity.

References

1. (a) Gawley, R. E. *Org. Reac.* **1988**, *35*, 1; (b) Craig, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, p. 689.
2. Robinson, B. *The Fischer Indole Synthesis*; John Wiley and Sons: New York, 1982.
3. (a) Sheradsky, T. *Tetrahedron Lett.* **1966**, 5225; (b) Mooradian, A.; Dupont, P. E. *Tetrahedron Lett.* **1967**, 2867; (c) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1348; (d) Alemagna, A.; Baldoli, C.; Buttero, P. D.; Licandro, E.; Maiorana, S. *J. Chem. Soc., Chem. Commun.* **1985**, 417.
4. Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 2* **1998**, 7.
5. Recently, several reports in which $ZrCl_4$ was successfully used as a Lewis acid have been published. (a) Akiyama, T.; Yamanaka, M. *Synlett*, **1996**, 1095; (b) Lenaršič, R.; Kočevar, M.; Polanc, S. *J. Org. Chem.* **1999**, *64*, 2558; (c) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett*, **1999**, 321.
6. Alam, N.; Amatore, C.; Combellas, C.; Pinson, J.; Savéant, J.-M.; Thiébault, A.; Verpeaux, J.-N. *J. Org. Chem.* **1988**, *53*, 1496.
7. HPLC conditions: Inertsil ODS-3 column (0.46×25 cm), MeOH–H_2O (75:25); 0.2 ml/min, detected 254 nm. Retention times (min): **6a** (mp 141–142°C), 82.9; **6b** (mp 122–125°C), 131.8; **6c** (mp 114–117°C), 126.2; **6d** (mp 120–122°C), 209.8.