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Reductive coupling of aromatic oxims and azines to 1,2-diamines using Zn-MsOH or Zn-$TiCl_4$

Naoki Kise* and Nasuo Ueda

Department of Biotechnology, Faculty of Engineering, Tottori University, Koyama, Tottori 680-8552, Japan

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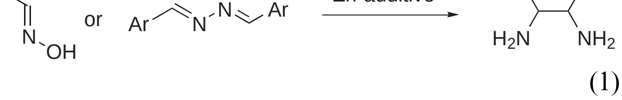
Abstract—The reduction of aromatic aldoxims and azines with Zn in the presence of MsOH or $TiCl_4$ afforded *N*,*N*′-unsubstituted 1,2-diamines in one-step. The reductive coupling with Zn-MsOH gave *meso* 1,2-diamines selectively, whereas *dl* 1,2-diamines were formed selectively by the reduction with Zn-$TiCl_4$. © 2001 Elsevier Science Ltd. All rights reserved.

Since reductive coupling of imines (imino-pinacol coupling) is a useful method for the synthesis of 1,2-diamines, numerous methods have been reported using Zn,[1] low-valent titanium,[2] SmI_2,[3] other metal reducing agents,[4] and electroreduction.[5] These methods, however, afforded *N*,*N*′-disubstituted 1,2-diamines from imines. In order to obtain *N*,*N*′-unsubstituted 1,2-diamines, it was necessary to remove the substituents on the nitrogen atoms. The reductive coupling of silylimines with $NbCl_4(THF)_2$[6] or low-valent titanium[7] and that of dibenzylidine sulfamides with Zn-TMSCl[8] have been reported as alternative methods for easy access to *N*,*N*′-unsubstituted 1,2-diamines. Herein we report that the reductive coupling of aromatic aldoxims and azines was achieved using Zn-MsOH and Zn-$TiCl_4$ (Eq. (1)). These reactions provide a useful method for the one-pot synthesis of *N*,*N*′-unsubstituted 1,2-diamines from readily available aromatic oxims and azines. We also found that the reductions with Zn-MsOH and those with Zn-$TiCl_4$ showed different diastereoselectivities in the resulting 1,2-diamines.



(1)

The results of the reduction of benzaldoxim (**1a**) with a metal (5 equiv.) at room temperature are summarized in Table 1. In the absence of an additive, **1a** was recovered completely (run 1). Therefore, the presence of an additive was crucial for the reductive coupling of **1a**. First, the reactions were carried out with Zn in the presence of an acid (5 equiv.) in acetonitrile (runs 2–4). As an acid, MsOH afforded the best yield (65%, *dl*:*meso*= 25:75) of 1,2-diphenyl-1,2-diaminoethane (**2a**) (run 2). When the reduction with Zn-MsOH in acetonitrile was carried out at −20°C, a similar result was obtained (**2a**: 60%, *dl*:*meso*=27:73). Other acids, TfOH and H_2SO_4, also gave **2a** in moderate yields (runs 3 and 4), whereas TFA and AcOH brought about poor results (**2a**:<5 and 0%, respectively). The reduction of **1a** with Zn-MsOH in THF increased *meso* selectivity in **2a** (*dl*:*meso*= 15:85), although the yield of **2a** was decreased to some extent (run 5). The reduction of **1a** did not occur using Pb, Sn, or Mg in place of Zn under the same conditions as in run 2. Next, the reactions were carried out in the presence of a metal chloride in THF (runs 6–10). The reduction with Zn-$TiCl_4$ afforded **2a** in 81% yield (run 6). Other metals, such as Mg and Li, also gave **2a** in moderate yields (runs 7 and 8). On the other hand, the use of $ZrCl_4$ or $CeCl_3$ as an additive yielded benzylamine (**3a**) as a main product (runs 9 and 10). The reaction with Zn-Me_3SiCl[1d,8,9] was not effective for the reduction of **1a** (**2a**:<5%) and most of **1a** was recovered.

Table 2 shows the results of the reactions of several aromatic aldoxims with Zn-MsOH and with Zn-$TiCl_4$ at ambient temperature. In the reductions with Zn-MsOH, aromatic aldoxims *para*-substituted by an electron-donating group (**1b–d**) afforded 1,2-diaryl-1,2-diamines **2b–d** in good yields, whereas those *para*-substituted by an electron-withdrawing group (**1e**,**f**) brought about amines **3e**,**f** as major products. The reactions of *o*-bromobenzaldoxim (**1h**) and 1-naphthylaldoxim (**1i**) resulted in exclusive formation of amines **3h**,**i**, and only small amounts of 1,2-diamines **2h**,**j** were obtained, probably due to the steric hindrance. On the contrary, the reductions with Zn-$TiCl_4$

Keywords: reductive coupling; oxim; azine; 1,2-diamine.

* Corresponding author. Fax: +81-857-31-5636; e-mail: kise@bio.tottori-u.ac.jp

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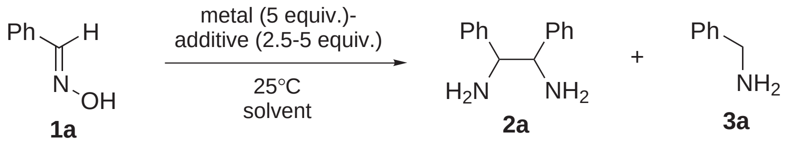
Table 1. Reductive coupling of benzaldoxim

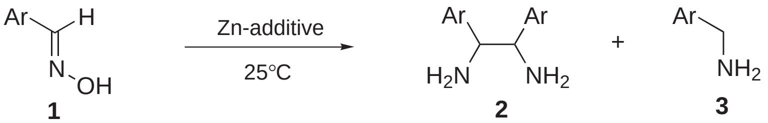


Run	Metal-additive (equiv.)	Solvent	Yield[a] (%)	
			2a (*dl*/*meso*)[b]	**3a**
1	Zn-none	CH_3CN	0	0
2	Zn-MsOH (5)	CH_3CN	65 (25/75)	18
3	Zn-TfOH (5)	CH_3CN	53 (25/75)	21
4	Zn-H_2SO_4 (5)	CH_3CN	42 (35/65)	45
5	Zn-MsOH (5)	THF	56 (15/85)	16
6	Zn-$TiCl_4$ (2.5)	THF	81 (55/45)	3
7	Mg-$TiCl_4$ (2.5)	THF	52 (70/30)	9
8	Li-$TiCl_4$ (2.5)	THF	47 (53/47)	8
9	Zn-$ZrCl_4$ (2.5)	THF	11 (35/65)	51
10	Zn-$CeCl_3$ (2.5)	THF	0	66

[a] Isolated yields.

[b] Determined by ^1H NMR.

Table 2. Reductive coupling of aromatic aldoxims



1	Ar	Yield[a] (%) with Zn-MsOH[b]		Yield[a] (%) with Zn-$TiCl_4$[c]	
		2 (*dl*/*meso*)[d]	**3**	**2** (*dl*/*meso*)[d]	**3**
1b	*p*-MeC_6H_4	67 (23/77)	14	88 (58/42)	<2
1c	*p*-$MeOC_6H_4$	70 (20/80)	17	90 (63/37)	<2
1d	*p*-ClC_6H_4	56 (30/70)	32	79 (55/45)	3
1e	*p*-NCC_6H_4	11 (36/64)	78	68 (62/38)	3
1f	*p*-$Me_2NC_6H_4$	9 (33/67)	86	78 (67/33)	22
1g	1-Furyl	19 (35/65)	50	79 (57/43)	3
1h	*m*-BrC_6H_4	46 (31/69)	41	71 (49/51)	4
1i	*o*-BrC_6H_4	17 (25/75)	42	67 (27/73)	7
1j	1-Naphthyl	19 (20/80)	44	63 (40/60)	5
1k	2-Naphthyl	50 (37/63)	19	60 (45/55)	<2

[a] Isolated yields.

[b] With Zn (5 equiv.) and MsOH (5 equiv.) in acetonitrile.

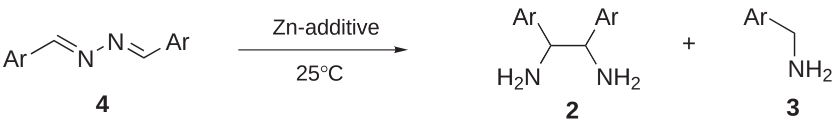
[c] With Zn (5 equiv.) and $TiCl_4$ (2.5 equiv.) in THF.

[d] Determined by ^1H NMR spectra. Ref. 11.

gave 1,2-diamines in moderate to high yields irrespective of the aryl group in **1**. In addition, the reactions of **1** with Zn-$TiCl_4$ generally afforded *dl*-**2** selectively, while those with Zn-MsOH produced *meso*-**2** preferentially.

As exemplified in Table 3, aromatic aldehyde azines **4** could be employed as effective substrates for the reductive coupling to prepare *N*,*N*′-unsubstituted 1,2-diamines **2**. Similarly to the results obtained from aromatic aldoxims (Table 2), the reductions with Zn-MsOH gave *meso*-**2** selectively. The reductions with Zn-$TiCl_4$ brought about better yields and *dl* selectivity in **2**. Since it is generally accepted that a low-valent titanium[2,10] is generated from metal–$TiCl_4$, the substrate is reduced by a low-valent titanium in the reduction with Zn-$TiCl_4$. On the other hand, the reduction with Zn-MsOH proceeds through electron transfer

Table 3. Reductive coupling of aromatic azines



4	Ar	Yield[a] (%) with Zn-MsOH[b]		Yield[a] (%) with Zn-TiCl$_4$[c]	
		2 (*dl*/*meso*)[d]	**3**	**2** (*dl*/*meso*)[d]	**3**
4a	Ph	62 (20/80)	19	73 (72/28)	10
4b	*p*-MeC$_6$H$_4$	41 (30/70)	13	68 (77/23)	6
4c	*p*-MeOC$_6$H$_4$	57 (30/70)	13	58 (78/22)	26
4d	*p*-ClC$_6$H$_4$	26 (36/64)	35	59 (63/37)	13
4e	*p*-NCC$_6$H$_4$	18 (44/56)	65	55 (50/50)	23
4f	*p*-Me$_2$NC$_6$H$_4$	<2	95	58 (82/18)	32
4g	1-Furyl	22 (44/56)	37	61 (74/26)	11
4h	*m*-BrC$_6$H$_4$	17 (37/63)	33	46 (70/30)	5

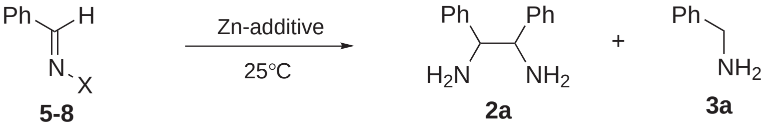
[a] Isolated yields.

[b] With Zn (10 equiv.) and MsOH (10 equiv.) in THF.

[c] With Zn (10 equiv.) and TiCl$_4$ (5 equiv.) in THF.

[d] Determined by ^{1}H NMR spectra. Ref. 11.

Table 4. Reductive coupling of *O*-methyloxim and hydrazones



	X	Yield[a] (%) with Zn-MsOH[b]		Yield[a] (%) with Zn-TiCl$_4$[c]	
		2a (*dl*/*meso*)[d]	**3a**	**2a** (*dl*/*meso*)[d]	**3a**
5	OMe	65 (23/77)	28	76 (60/40)	<2
6	NHPh	50 (25/75)	33	0	46
7	NHTs	47 (28/72)	31	57 (44/56)	18
8	NHCO$_2$Me	49 (28/72)	33	22 (36/64)	54

[a] Isolated yields.

[b] With Zn (5 equiv.) and MsOH (5 equiv.) in acetonitrile.

[c] With Zn (5 equiv.) and TiCl$_4$ (2.5 equiv.) in THF.

[d] Determined by ^{1}H NMR spectra.

from Zn to the substrate activated by MsOH. Therefore, it seems that these methods show different diastereoselectivities.

The reactions of *O*-methylbenzaldoxim **5** and benzaldehyde hydrazones **6**–**8** were attempted using Zn-MsOH or Zn-TiCl$_4$ as shown in Table 4. The results obtained from **5** were similar to those from benzaldoxim (Table 1, runs 2,6). Hydrazones **6**–**8** also gave **2a** in moderate yields, although considerable amounts of **3a** were formed.

In conclusion, aromatic aldoxims and azines readily available from aromatic aldehydes were effectively transformed to the corresponding *N*,*N*′-unsubstituted 1,2-diaryl-1,2-diamines by reductive coupling with Zn in the presence of MsOH or TiCl$_4$. As an additive, the use of MsOH selectively led to meso 1,2-diamines, while that of TiCl$_4$ to *dl* 1,2-diamines.

A typical procedure is as follows (Table 1, run 2): zinc powder (Wako Pure Chemical Industries Ltd) was washed successively with 1 M HCl, water, and ether and dried in vacuo. To a solution of benzaldoxim (0.24 g, 2 mmol) in dry acetonitrile (10 mL) was added freshly distilled MsOH (0.65 mL, 10 mmol) and zinc powder (0.65 g, 10 mmol) at 0°C under an atmosphere of nitrogen, and the mixture was stirred for 8 h at room temperature. The mixture was diluted with 1 M HCl (20 mL), filtered to remove unreacted zinc, and then extracted with dichloromethane twice. The water layer was basified (pH 10) with 3 M NaOH and filtered. The filtrate was extracted with dichloromethane three times and the organic layer was washed with water, dried over magnesium sulfate, and concentrated. After removal of the solvent, 1,2-diphenyl-1,2-diaminoethane (**2a**) was isolated as a diastereomeric mixture (65% yield, *dl*:*meso* = 25:75[10]) by column chromatography on basic alumina (hexane/ethyl acetate). Recrystallization of the mixture from hexane/ethyl acetate (10/1) gave pure *meso*-**2a** in 35% yield.

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11. The diastereomeric ratios of **2** were determined by their ^{1}H NMR spectra. The chemical shifts (δ) of methyn protons adjacent to the nitrogen atom in **2** were as follows: *dl*-**2a** 4.09; *meso*-**2a** 4.01; *dl*-**2b** 4.07; *meso*-**2b** 3.95; *dl*-**2c** 4.01; *meso*-**2c** 3.93; *dl*-**2d** 3.99; *meso*-**2d** 3.97; *dl*-**2e** 4.14; *meso*-**2e** 4.09; *dl*-**2f** 4.01; *meso*-**2f** 3.86; *dl*-**2g** 4.28; *meso*-**2g** 4.22; *dl*-**2h** 4.03; *meso*-**2h** 3.96; *dl*-**2i** 4.67; *meso*-**2i** 4.71; *dl*-**2j** 5.11; *meso*-**2j** 5.23; *dl*-**2k** 4.42; *meso*-**2k** 4.29.