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Reductive coupling of aromatic *N*,*N*-acetals using zinc and chlorotrimethylsilane

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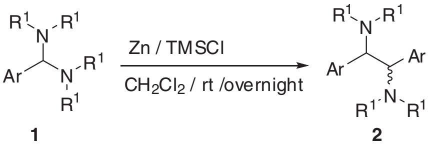
ABSTRACT

The reductive coupling of aromatic *N*,*N*-acetals and *N*,*O*-acetal activated by chlorotrimethylsilane proceeded smoothly in the presence of zinc to give the corresponding diamines in good yields.

Vicinal diamine function is often present in natural products and biologically active molecules. Furthermore, in the field of synthetic chemistry, vicinal diamines are frequently used as synthetic precursors and chiral ligands.[1] A number of synthetic methods have been developed for vicinal diamines. Among them, the reductive coupling of imines is a simple method for the synthesis of vicinal diamines.[2] In our previous report, we described how simple reduction conditions using zinc and chlorotrimethylsilane were effective for the reductive coupling of aromatic *O*,*O*-acetals.[3] Herein, we report that reductive coupling of aromatic *N*,*N*-acetals (**1**), which are analogs of imines, proceeded smoothly in the presence of zinc and chlorotrimethylsilane to give the corresponding diamines (**2**) in good yields (Scheme 1).[4,5]

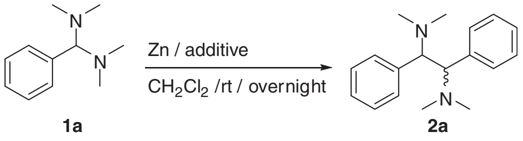
At first, we examined the reductive coupling of **1a** with zinc in the presence or absence of additives (Table 1). Though no reductive coupling took place with zinc alone (entry 1), the addition of 1 equiv of chlorotrimethylsilane (TMSCl) against **1a** led to **2a** in 79% yield (entry 2). The use of 2 equiv of TMSCl successfully improved the product yield, giving **2a** in 83% yield (entry 3).[6,7] These results suggest that TMSCl was employed as an activator of **1a** as well as zinc.[8] In this reductive coupling, the substituent of chlorosilane influenced the yield of **2a**: chlorosilane bearing a bulky alkyl group, such as TESCl and TBSCl, and tetrachlorosilane resulted in low yields of **2a** (entries 4–6). The use of some additives, such as $ZnCl_2$, $AlCl_3$, $TiCl_4$,[9] and $VOCl_3$,[10] also gave **2a** in poor yields (entries 7–10).

This reductive coupling using zinc and chlorotrimethylsilane was useful for other aromatic *N*,*N*-acetals **1** as shown in Table 2. The reductive coupling of *p*-methoxy, *p*-methyl, *p*-chloro, *o*-chloro (**1b**, **1c**, **1d**, and **1e**) derivatives proceeded smoothly to give the corresponding diamines (**2b**, **2c**, **2d**, and **2e**) in moderate to good yields. In the case of *o*-bromo derivative (**1f**), the reductive coupling also took place in moderate yield with moderate *dl*-selectivity. The derivatives bearing an electron-withdrawing group, such as the cyano and trifluoromethyl groups (**1g** and **1h**), also proceeded without difficulty. In 3-pyridyl and 2-thiophenyl *N*,*N*-acetals (**1i** and **1j**), similar treatment led to



Scheme 1.

Table 1
Influence of additives on the reductive coupling of **1a** in the presence of zinc[a]



Entry	Additive	Yield of **2a**[b] (%)	*dl*/meso[c]
1	–	0	–
2	TMSCl[d]	79	54/46
3	TMSCl	83	58/42
4	TESCl	42	54/46
5	TBSCl	26	51/49
6	$SiCl_4$	18	43/57
7	$ZnCl_2$	19	53/47
8	$AlCl_3$	38	47/53
9	$TiCl_4$	18	79/21
10	$VOCl_3$	0	–

[a] Reaction conditions: **1a** (2.0 mmol), Zn (2.0 mmol), additive (4.0 mmol), CH_2Cl_2 (5 mL), rt, overnight, under N_2.
[b] Isolated yield.
[c] Determined by ^1H NMR of crude **2a**.
[d] TMSCl (2.0 mmol) was used.

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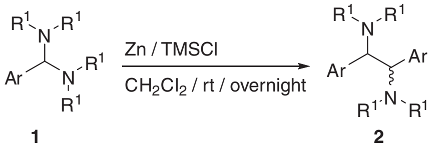
Table 2
Reductive coupling of **1** using zinc and TMSCl[a]

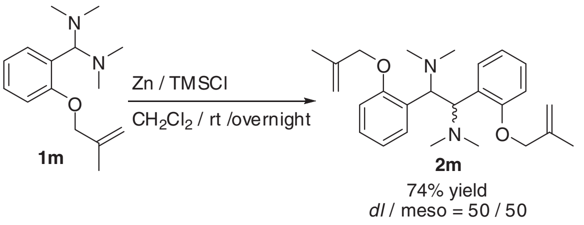


Ar	R^1	1	Yield of **2**[b] (%)	*dl*/meso[c]
p-$MeOC_6H_4$	Me	**1b**	66	47/53
p-MeC_6H_4	Me	**1c**	75	53/47
p-ClC_6H_4	Me	**1d**	97	53/47
o-ClC_6H_4	Me	**1e**	77	57/43
o-BrC_6H_4	Me	**1f**	60	68/32
p-NCC_6H_4	Me	**1g**	99	47/53
p-$CF_3C_6H_4$	Me	**1h**	80	55/45
3-Pyridyl	Me	**1i**	53	53/47
2-Thiophenyl	Me	**1j**	68	49/51
Ph	$-(CH_2)_4-$	**1k**	82	69/31
Ph	$-(CH_2)_5-$	**1l**	79	53/47

[a] Compound **1a** (2.0 mmol), Zn (2.0 mmol), TMSCl (4.0 mmol), CH_2Cl_2 (5 mL), rt, N_2, overnight.
[b] Isolated yield.
[c] Determined by ^1H NMR of crude **2**.

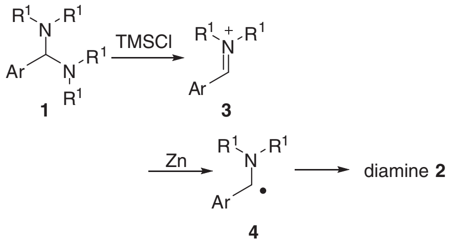
the corresponding coupling products in moderate yields (**2i** and **2j**). The stereoselectivity of this reductive coupling was somewhat affected by the bulkiness of the amino substituent: the derivative from pyrrolidine gave the corresponding coupling product with moderate *dl*-selectivity, as compared to that from piperidine (**2k** and **2l**).

In the case of *N*,*N*-acetal bearing methallyl group (**1m**), the corresponding coupling product (**2m**) was obtained in 74% yield (*dl*/meso = 50/50) without any cyclization product (Scheme 2).

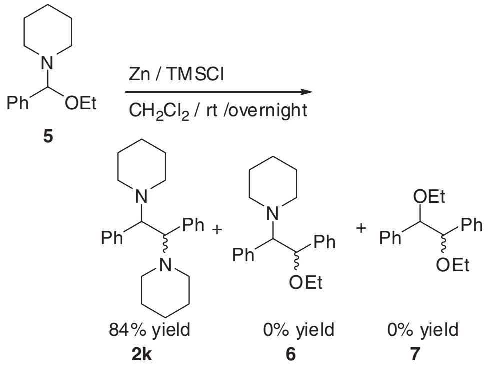


Scheme 2.

It is generally accepted that the reductive coupling of *N*,*N*-acetals proceeds via a radical process as in the case of reductive coupling of carbonyl compounds.[11] Although the detailed pathway is not clear, in the present reductive coupling using zinc and chlorotrimethylsilane, the reductive coupling of **1** seemed to be triggered by the activation of **1** (Scheme 3). Chlorotrimethylsilane serves as an activator of **1**, generating an iminium salt **3**,[12,13] which leads to the corresponding α-aryl-α-amino-radical **4** by one-electron transfer from zinc. Then, the coupling of **4** leads to the corresponding diamine **2**.



Scheme 3.



Scheme 4.

The reductive coupling using zinc and chlorotrimethylsilane was also useful for *N*,*O*-acetal. When *N*,*O*-acetal **5** was treated with zinc and chlorotrimethylsilane, the corresponding 1,2-diamine **2k** was obtained in 84% yield (*dl*/meso = 56/44) without either 2-aminoethanol compound **6** or 1,2-diether **7** (Scheme 4).[14]

In conclusion, the reductive coupling of aromatic *N*,*N*-acetals and *N*,*O*-acetal activated by chlorotrimethylsilane proceeded smoothly in the presence of zinc to give the corresponding diamines in moderate to good yields. Further detailed applications are now in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.104.

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5. Only two references were reported for the reductive coupling of *N*,*N*-acetals using low valent titanium, see: (a) Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999–2021; (b) Betschart, C.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 2215–2231.
6. The general procedure for the reductive coupling of *N*,*N*-acetal **1**: To a suspension of zinc (130.8 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added **1** (2.0 mmol) at room temperature. After cooling in an ice-water bath, chlorotrimethylsilane (508 μL, 4.0 mmol) was added in one portion. The reaction mixture was stirred for 10 min in an ice bath, and then allowed to warm to room temperature. After stirring overnight (ca. 14 h) at room temperature, aqueous NaOH (1 N, 30 mL) was added. The mixture was stirred for additional 30 min, during which zinc hydroxide precipitated. The resulting suspension was filtered in suction, and the filtered solid was washed with CH_2Cl_2 (3 × 10 mL). The organic solution was separated and washed with aqueous NaOH (1 N, 30 mL) and brine (30 mL). After drying over Na_2SO_4, and

subsequent evaporation, the residue was purified using column chromatography on silica gel (30 g; eluent, hexane/Et$_2$O = 100:0, 50:50, 0:100, then, Et$_2$O/Et$_3$N = 99:1, 97:3, 95:5, 100 mL × each). The results are presented in Tables 1 and 2, Schemes 2 and 4. The physical data of diamine **2** are available as Supplementary data.

7. When *N*,*N*-acetal **1** was treated with appropriate alkyl bromide in the presence of zinc and chlorotrimethylsilane, the corresponding alkylation product was obtained instead of diamine **2**, see: Hatano, B.; Nagahashi, K.; Kijima, T. *J. Org. Chem.* **2008**, *73*, 9188–9191.
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14. In reductive coupling of *N*,*O*-acetals in the presence of titanium(IV) iodide and zinc, diamines were obtained, see: Yoshimura, N.; Mukaiyama, T. *Chem. Lett.* **2001**, 1334–1335.