An Efficient Method for the Preparation of Vicinal Tertiary Diamines by Reductive Coupling of Aminoacetals Mediated by Low Valent Titanium Iodide Species

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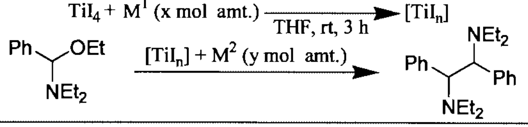
Aminoacetals, easily prepared by condensation of aromatic aldehydes, secondary amines and alcohols, are reductively coupled by using low valent titanium iodide species to afford the corresponding coupling products, vicinal tertiary diamines, in good to high yields under mild reaction conditions.

There are many natural products containing vicinal diamine function and some of which have interesting biological properties and are used synthetic precursors in medicinal chemistry.[1] Further, vicinal diamines are frequently employed in organic synthesis, especially in the field of catalytic asymmetric synthesis. Various synthetic methods were studied intensively for the preparation of vicinal diamines and one of the most popular procedures was the coupling of two nitrogen-containing substrates by carbon–carbon bond forming reaction. Concerning reductive coupling of imines affording the corresponding vicinal secondary diamines, for example, various effective reducing reagents were reported,[1] among which low valent titanium (LVT) compounds proved to be particularly effective.[2] Also, some direct methods for the formation of vicinal tertiary diamines, that is, reductive coupling of iminium salts[3,4] or aminals[4] and deoxygenative coupling of amides[5] and so on were reported. Further, it was reported by Seebach and co-workers[3,4] that reductive coupling of the substrates which were synthetically equivalent to iminium salts by using excess amounts of LVT derived from titanium(IV) chloride ($TiCl_4$) and potassium or magnesium afforded the corresponding vicinal tertiary diamines. In the above reactions, the substrates were prepared by initial formation of adducts from aromatic aldehydes and lithium dialkylamides and the subsequent treatment with $TiCl_4$.

Recently, it was reported from our laboratory that a newly utilized low valent titanium iodide (LVTI) species generated by treating titanium(IV) iodide (TiI_4) with copper or zinc was an effective reducing reagent in coupling reactions of aldehydes and dithioacetals to afford various vicinal diols and vicinal bis(alkylthio) derivatives, respectively, in good to high yields under mild reaction conditions.[6] Therefore, it was expected that treatment of aminoacetals, which were easily prepared from aromatic aldehydes, secondary amines and alcohols,[7] with LVTI would afford vicinal tertiary diamines; the reduction was considered to proceed by selective abstraction of alkoxy group of aminoacetal because titanium has stronger affinity for oxygen and thus the resulted two radical intermediates coupled to give the vicinal tertiary diamine. In this communication, we would like to report an efficient method for the direct preparation of various vicinal tertiary diamines by reductive coupling of aminoacetals with LVTI.

In the first place, α-(diethylamino)benzyl ethyl ether was used as a substrate in reductive coupling by using supernatant solution of LVTI generated by treating with TiI_4 and copper or zinc[8] in tetrahydrofuran (THF) (Table 1). Similar to the case of coupling of dithioacetal,[6b] addition of copper was not effective for the present reaction. On the other hand, desirable reaction was promoted moderately by addition of zinc which afforded the corresponding vicinal tertiary diamine, 1,2-bis(diethylamino)-1,2-diphenylethane, in good yield at the temperatures ranging from room temperature to 55 °C (entries 1–5). When zinc was further added to the supernatant solution of zinc-treated LVTI,[9] the coupling proceeded smoothly to afford the desired vicinal tertiary diamine in excellent yield at the temperatures ranging from 0 °C to room temperature. When the reactions were carried out at lower temperature, this coupling also afforded the diamines after a prolonged reaction time (entries 6 – 9). Concerning the amounts of zinc, double molar amounts of the respective initial and additional zinc to TiI_4 gave a most effective reductant, which promoted the reaction smoothly[10] (entries 7 and 10–17). Incidentally, in the absence of TiI_4, that is, when the reaction was carried out by using only zinc, it did not proceed at all,[11] which indicated that LVTI was essential for this reaction (entry 18).

Table 1. Reductive coupling reaction of α-(diethylamino)benzyl ethyl ether promoted by low valent titanium iodide species

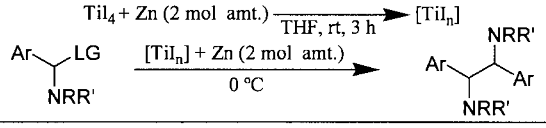


Entry	M^1 (x)	M^2 (y)	Temp / °C	Time / h	Yield[a] / %	[*dl* / *meso*][b]
1	Cu (2.0)	none	55	24	trace	[-]
2	Zn (2.0)	none	55	24	77	[43 / 57]
3	Zn (2.0)	none	rt	24	72	[41 / 59]
4	Zn (2.0)	none	rt	3	47	[42 / 58]
5	Zn (2.0)	none	0	3	35	[47 / 53]
6	Zn (2.0)	Zn (2.0)	rt	3	91	[42 / 58]
7	Zn (2.0)	Zn (2.0)	0	3	95	[45 / 55]
8	Zn (2.0)	Zn (2.0)	–23	9	90	[45 / 55]
9	Zn (2.0)	Zn (2.0)	–45	48	91	[50 / 50]
10	Zn (1.0)	none	0	3	15	[28 / 72]
11	Zn (1.0)	Zn (1.0)	0	3	86	[37 / 63]
12	Zn (1.0)	Zn (2.0)	0	3	80	[35 / 65]
13	Zn (1.0)	Zn (3.0)	0	3	86	[42 / 58]
14	Zn (2.0)	Zn (1.0)	0	3	94	[47 / 53]
15	Zn (3.0)	none	0	3	40	[46 / 54]
16	Zn (3.0)	Zn (1.0)	0	3	84	[44 / 56]
17	Zn (3.0)	Zn (2.0)	0	3	90	[48 / 52]
18[c]	not use Ti	Zn (2.0)	55	48	N. R.	[-]

Reaction conditions: Low valent titanium iodide species ($[TiI_n]$) was prepared by TiI_4 / M^1 = 1.0 / x mmol in THF (0.20 M-Ti). Substrate / $[TiI_n]$ / M^2 = 1.0 / 1.3 / 1.3y mmol in THF (6.5 mL). [a]Isolated yield. [b]Ratios were determined by weight of isolated isomers. [c]Substrate / M^2 = 1.0 / 1.3y mmol in THF (6.5 mL).

Based on the above results, reductive coupling reaction of various other aminoacetals using the above LVTI was next

Table 2. Reductive coupling reaction of various aminoacetals promoted by low valent titanium iodide species



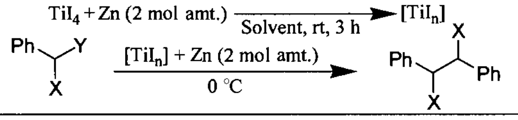
Entry	Ar	R	R'	LG	Time / h	Yield[a] / %	[*dl* / *meso*][b]
1	Ph	Et	Et	EtO	3	95	[45 / 55]
2	Ph	-$(CH_2)_4$-		EtO	5	81	[62 / 38]
3	Ph	-$(CH_2)_5$-		EtO	6	81	[48 / 52]
4	4-Me-Ph	Et	Et	EtO	3	91	[45 / 55]
5	4-CF_3-Ph	Et	Et	EtO	2	98	[48 / 52]
6	4-Br-Ph	Et	Et	EtO	4	84	[44 / 56]
7	4-NC-Ph	Et	Et	EtO	2	94	[56 / 44]
8	2-Furyl	Et	Et	EtO	6	76	[54 / 46]
9	2-Thiophenyl	Et	Et	EtO	6	78	[58 / 42]
10	2-Pyridyl	Et	Et	EtO	6	71	[50 / 50]
11	Ph	Et	Et	MeO	3	94	[47 / 53]
12	Ph	Et	Et	*n*-BuO	3	97	[48 / 52]
13	Ph	Et	Et	EtS	3	90	[48 / 52]

Reaction conditions: Low valent titanium iodide species ($[TiI_n]$) was prepared by TiI_4 / Zn = 1.0 / 2.0 mmol in THF (0.20 M-Ti). Substrate / $[TiI_n]$ / Zn = 1.0 / 1.3 / 2.6 mmol in THF (6.5 ml.). [a]Isolated yield. [b]Ratios were determined by weight of isolated isomers.

examined (Table 2). Concerning the amino group in aminoacetals, both acyclic and cyclic derivatives were applicable (entries 1–3). With regard to the substituents on phenyl groups, various electron-donating and electron-withdrawing substituents gave nearly equal influence on reactivities (entries 4–7). Furthermore, other substrates which had hetero-aromatic ring reacted similarly to give the coupling products in good yields although the yields of these diamines were previously reported[3] to be rather low (entries 8–10). In addition, various alkoxy groups and an alkylthio group behaved nearly the same as leaving group (entries 11–13). Incidentally, diastereoselectivities of this coupling reaction gave nearly the same results in all cases (*dl* / *meso* ~ 1).

This reaction is thought to proceed as follows; that is, reactive LVTI preferentially abstracts an alkoxy (or alkylthio) group over an amino group of an aminoacetal because of the stronger affinity of titanium for oxygen. And the resulted naked α-(dialkylamino)benzyl radical intermediates are not sterically controlled and couple at random conformations to lead to the formation of a mixture of *dl*- and *meso*-diastereomers of vicinal tertiary diamine.

Table 3. Comparison for reactivities of acetal, dithioacetal and aminoacetal in reductive coupling by using low valent titanium iodide species



Entry	X	Y	Solvent	Time / h	Yield[a] / %	[*dl* / *meso*][b]
1	OEt	OEt	CH_2Cl_2–^{t}BuCN	24	88	[50 / 50]
2	SEt	SEt	CH_2Cl_2–^{t}BuCN	1	95	[49 / 51]
3	NEt_2	OEt	CH_2Cl_2–^{t}BuCN	1	complex mixture	[-]
4	OEt	OEt	THF	24	N. R.	[-]
5	SEt	SEt	THF	24	N. R.	[-]
6	NEt_2	OEt	THF	3	95	[45 / 55]

Reaction conditions: Low valent titanium iodide species ($[TiI_n]$) was prepared by TiI_4 / Zn / (^{t}BuCN) = 1.0 / 2.0 / 4.0 mmol in CH_2Cl_2 or THF (0.20 M-Ti). Substrate / $[TiI_n]$ / Zn = 1.0 / 1.3 / 2.6 mmol in solvent (6.5 mL). [a]Isolated yield. [b]Ratios were determined by weight of isolated isomers or ^{1}H NMR analysis.

Then, reactivities of acetal, dithioacetal and aminoacetal in reductive coupling by using LVTI in dichloromethane–pivalonitrile (CH_2Cl_2–^{t}BuCN)[6] or THF were compared (Table 3). In the cases of using CH_2Cl_2–^{t}BuCN as a solvent, dithioacetal smoothly reacted within 1 h and acetal also coupled in a prolonged reaction time while complex mixtures resulted on treating highly reactive aminoacetal (entries 1–3). When THF was used, on the other hand, aminoacetal successfully gave the coupling product while neither acetal nor dithioacetal reacted at all (entries 4–6). These results suggested that THF solvated the LVTI to decrease its reactivity appropriately, and thus the coupling of reactive aminoacetal proceeded smoothly.

Thus, an efficient method for direct preparation of vicinal tertiary diamines by reductive coupling of aminoacetals was established by using reactive LVTI in THF under mild reaction conditions.

References and Notes

1 For a review, see: D. Lucet, T. Le Gall, and C. Mioskowski, *Angew. Chem. Int. Ed.*, **37**, 2580 (1998) and references cited therein.

2 For reviews, see: a) G. M. Robertson, in “Comprehensive Organic Synthesis,” ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 3, p 563. b) T. Wirth, *Angew. Chem., Int. Ed. Engl.*, **35**, 61 (1996). c) A. Fürstner and B Bogdanovic, *Angew. Chem., Int. Ed. Engl.*, **35**, 2442 (1996). Recent reports of preparation of vicinal diamines by reductive coupling of aldimines mediated by LVT, see: d) S. Talukdar and A. Banerji, *J. Org. Chem.*, **63**, 3468 (1998). e) S. Rele, S. Talukdar, A. Banerji, and S. Chattopadhyay, *J. Org. Chem.*, **66**, 2990 (2001).

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7 a) J.-P. Quintard, B. Elissondo, and B. Jousseaume, *Synthesis*, **1984**, 495. b) P. J. Smith and M. Amin, *Can. J. Chem.*, **67**, 1457 (1989).

8 Copper powder was used after drying under vacuum at 100 °C. Zinc powder was activated before use with 1 M aqueous hydrochloric acid and washed with water and ether, then dried under vacuum at 100 °C.

9 A typical reaction procedure for the reductive coupling of α-(diethylamino)benzyl ethyl ether corresponding to Table 1, entry 7: to TiI_4 (1.11 g, 2.0 mmol) and zinc powder (0.26 g, 4.0 mmol) was added THF (10 mL) under argon atmosphere. The color was changed immediately to dark brown and the mixture was further stirred for 3 h at room temperature. Resulted dark brown supernatant solution (6.5 mL, 1.3 mmol Ti) was added to additional zinc powder (0.170 g, 2.6 mmol) and the mixture was stirred for another 30 min. Resulted dark brown suspension was cooled to 0 °C and α-(diethylamino)benzyl ethyl ether (0.207 g, 1.0 mmol) was added. The reaction mixture was further stirred for 3 h, and then saturated aqueous sodium hydrogencarbonate was added. The mixture was filtered and extracted with dichloromethane, and the organic layer was washed with saturated aqueous sodium chloride, dried over sodium sulfate. After filtration and concentration, the crude product was purified by thin layer chromatography to afford the desired vicinal tertiary diamine (*dl*-isomer 0.070 g, 43% yield, *meso*-isomer 0.084 g, 52% yield).

10 When $TiCl_4$ and $TiBr_4$ were employed in place of TiI_4 using double molar amounts of the respective initial and additional zinc, the yields of diamine decreased (72% yield [*dl* / *meso* = 48 / 52] and 69% yield [*dl* / *meso* = 40 / 60], respectively).

11 In the case of reductive coupling of aldimine, it was reported that the reaction was effectively promoted by only zinc in aqueous basic media, see: a) M. P. Dutta, B. Baruah, A. Boruah, D. Prajapati, and J. S. Sandhu, *Synlett*, **1998**, 857. b) T. Tsukinoki, S. Nagashima, Y. Mitoma, and M. Tashiro, *Green Chem.*, **2**, 117 (2000).