Low Valent Titanium Mediated Imino−Pinacol Coupling: An Improved and Expeditious Route to Vicinal Diamino-Based Ligands

Sanjay Talukdar and Asoke Banerji*

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai (Bombay)-400 085, India

Received September 9, 1997

Vicinal diamines find extensive applications in radiopharmaceuticals[1a−c] and as complexing agents and chiral auxiliaries.[2a,b] In connection with our ongoing program on nuclear medicine, an efficient route to vicinal diamino-based ligands was needed. Recently, we have been exploring the potential of low valent titanium (LVT) induced carbonyl−olefin McMurry coupling reaction in a multitude of synthetic endeavors.[3,4a−f] Although reductive coupling of carbonyls to vicinal diols using different LVT reagents[5a−e] has been extensively studied, analogous reactions involving carbon−nitrogen functions to the corresponding 1,2-diamino compounds are less common.[6]

Although vicinal diamino units occur frequently in natural products and medicinal agents, not many general routes for their preparation are reported. Reductive dimerization of imines offers attractive possibilities for the direct access to vicinal diamines. A variety of reductants[7a−m] including active metals have been developed for this purpose, viz., samarium(II) iodide,[7a−c] indium,[7d] Pb/Al bimetal redox system,[7e] Zn−Cu couple,[7f] niobium,[7g] LVT,[7h] and electrochemical reduction.[7i] In the indirect and multistep protocols, use of substrates such as olefins[8] or 1,2-dicarbonyls[9a,b] or amino acid esters[10] was reported.

Our experience with LVT reagents[3,4a−f] for the reductive coupling of carbonyls prompted us to explore the scope of this reagent toward the reduction of the corresponding nitrogen analogues (imino−pinacol coupling). We envisaged that analogous to carbonyl coupling reaction,[5a−e] the imino−pinacol coupling probably would also proceed through a single electron transfer (SET) mechanism via a radical anion intermediate (**2**, Scheme 1). In principle, the intermediate **2** can undergo dimerization to diamines **3** by bimolecular process (path a) or can be quenched by hydrogen from the medium to give unimolecularly reduced amines **4** (path b). In fact, the serious shortcoming of the earlier report[7h] on the synthesis of vicinal diamines via reductive dimerization of imines using LVT reagent (generated in situ from $TiCl_4$−Mg/Hg−THF, stoichiometrically Ti^{II}) is the low yields due to concomitant formation of amines as a result of competitive[7k] unimolecular reduction of imines, in addition to extended reaction time. In the present investigation, this point has been addressed. The rationale for the present approach is to direct the reaction to follow path a (bimolecular process) in preference to path b (unimolecular process).

Results and Discussion

Transformation of *N*-benzylideneaniline (**1a**) to *N*,*N*′-diphenyl-1,2-diphenyl-1,2-ethanediamine (**3a**) was chosen as a model reaction (Scheme 1). To optimize the reaction conditions, different sources[5a−e] of LVT were tried. Use of $TiCl_3$−Mg−DME (reagent **A)** as the source of LVT species gave **3a** in 52% yield at 25 °C (Table 1, entry 1). When Li was used as the reducing metal instead of Mg as in $TiCl_3$−Li−DME (reagent **B)** (Table 1, entry 2), the yield of **3a** showed slight improvement, though the coupling proceeded slowly (5.5 h). Change of the solvent from DME to THF, i.e., use of $TiCl_3$−Mg−THF (reagent **C)** improved the yield of **3a** to 62%, requiring 3.5 h (Table 1, entry 3). However, best results were obtained using $TiCl_3$−Li−THF (reagent **D**) when **3a** was obtained in 78% yield within only 2.5 h (Table 1, entry 4). Therefore, the reagent **D** was used for subsequent studies. It is important to note that the diamine **3a** was the only product in all the experiments described above. However, when the reaction was carried out at reflux temperature using reagent **D**, a mixture of three different products was obtained. These were characterized as **3a** (26%), *N*-benzylaniline (**4a,** 25%), and bibenzyl (**5,** 30%) (Table 1, entry 5). Formation of **3a**, **4a,** and **5** from **1a** under refluxing conditions is conceivable through the intermediacy of a ketyl-like radical (**2a**). The dimerization of the radical **2a** followed by aqueous workup results in the formation of vicinal diamine **3a**. However, the facile

(1) (a) Jurisson, S.; Berning, D.; Jia, W.; Ma, D. *Chem. Rev.* **1993**, *93*, 1137. (b) Parker, D. *Chem. Britain* **1994,** 818. (c) Schwochau, K. *Angew. Chem., Int. Ed. Engl.* **1994,** *33*, 2258.

(2) (a) Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett.* **1993,** *34*, 6897. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(3) Nayak, S. K.; Kadam, S. M.; Talukdar, S.; Banerji, A. *J. Indian Inst. Sci.* **1994**, *74*, 401.

(4) (a) Balu, N.; Nayak, S. K.; Banerji, A. *J. Am. Chem. Soc.* **1996**, *118*, 5932. (b) Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1991**, *56*, 1940. (c) Banerji, A.; Nayak, S. K. *J. Chem. Soc., Chem. Commun.* **1991**, 1432. (d) Talukdar, S. Ph.D. Thesis, University of Mumbai, **1997**. (e) Talukdar, S.; Nayak, S. K.; Banerji, A. *Full. Sci. Tech*, **1995**, *3*, 327. (f) Banerji, A.; Nayak, S. K. *J. Chem. Soc., Chem. Commun.* **1990**, 150.

(5) (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (b) Dushin, R. G. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol 12, p 1071. (c) Lectka, T. In *Active Metals−Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, 1996; p 85. (d) Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H. Y. *J. Org. Chem.* **1982**, *47*, 248. (e) Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996,** *35*, 2442 and references therein.

(6) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255.

(7) (a) Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun.* **1990,** *20*, 981. (b) Liao, P.; Huang, Y.; Zhang, Y. *Synth. Commun.* **1997**, *27*, 1483 and references therein. (c) Aurrecoechea, J. M.; Fernández-Acebes, A. *Tetrahedron Lett.* **1992**, *33*, 4763. (d) Kalyanam, N.; Venkateswara Rao, G. *Tetrahedron Lett.* **1993**, *34*, 1647. (e) Tanaka, H.; Dhimane, H.; Fujita, H.; Ikemoto, Y.; Torii, S. *Tetrahedron Lett.* **1988**, *29*, 3811. (f) Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609. (g) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152. (h) Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255. (i) Tanaka, H.; Nakahara, T.; Dhimane, H.; Torii, S. *Synlett.* **1989**, 51. (j) von Betschart, C.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 2215. (k) Eisch, J. J.; Kaska, D. D.; Peterson, C. J. *J. Org. Chem.* **1966**, *31*, 453. (l) Jones, D. S.; Srinivasan, A.; Kasina, S.; Fritzberg, A. R.; Wilkening, D. W. *J. Org. Chem.* **1989**, *54*, 1940 and references therein. (m) Smith, J. G.; Ho, I.. *J. Org. Chem.* **1972**, *37*, 653.

(8) Jung, S.-H.; Kohn, H. *J. Am. Chem. Soc.* **1985**, *107*, 2931.

(9) (a) Neumann, W. L.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, *32*, 5865. (b) Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3.

(10) Wey, S.-J.; O'Connor, K. J.; Burrows, C. J. *Tetrahedron Lett.* **1993**, *34*, 1905.

S0022-3263(97)01689-7 CCC: $15.00
Published on Web 04/28/1998

Scheme 1

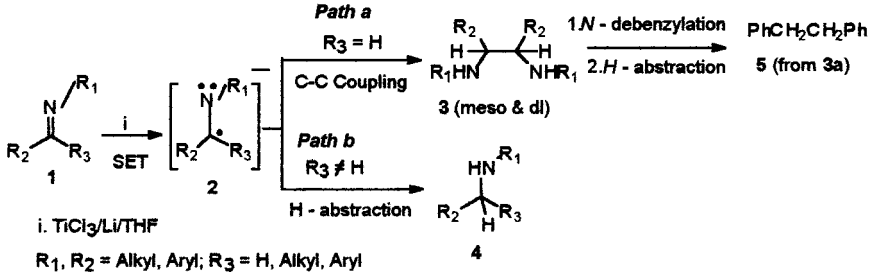

Table 1. Reductive Dimerization of *N*-Benzylideneaniline (1a) Using Different LVT Reagents

entry	reagent	time (h), temp (°C)	product(s) (% yield)
1	$TiCl_3$−Mg−DME (**A**)	3.5, 25	**3a** (52)
2	$TiCl_3$−Li−DME (**B**)	5.5, 25	**3a** (58)
3	$TiCl_3$−Mg−THF (**C**)	3.5, 25	**3a** (62)
4	$TiCl_3$−Li−THF (**D**)	2.5, 25	**3a** (78)
5	$TiCl_3$−Li−THF (**D**)	5, reflux	**3a** (26), **4a** (25), **5** (30)

Table 2. Dimerization of Aldimines (R_3 = H, 1) at 25 °C: Generation of Vicinal Diamines (3)

entry	R_1	R_2	compd	time (h)	% yield[a] (*dl:meso*)[b] of **3**	ref
1	Ph	Ph	**1a**, **3a**	2.5	78 (75:25)	7k
2	2′-ClC_6H_4	Ph	**1b**, **3b**	3	76 (57:43)	7d
3	Ph	2′-$MeOC_6H_4$	**1c**, **3c**	3.5	72 (29:71)	7m
4	Ph	4′-ClC_6H_4	**1d**, **3d**	2.5	65 (60:40)	7m
5	Ph	4′-$Me_2NC_6H_4$	**1e**, **3e**	3	79 (73:27)	7b
6	Ph	4′-MeC_6H_4	**1f**, **3f**	3	83 (70:30)	7m
7	Ph	c-C_6H_{11}	**1g**, **3g**	5	62	7a
8	$PhCH_2$	Ph	**1h**, **3h**	3	72 (67:33)	7a
9	c-C_6H_{11}	Ph	**1i**, **3i**	2.5	70 (27:73)	7a

[a] All yields refer to isolated products (purity > 95%, analyzed by ^{1}H NMR); no significant amounts of other products were detected. The products were fully characterized by IR and ^{1}H NMR. [b] *dl:meso* ratio was obtained from ^{1}H NMR.

delivery of H• radical by THF[5c,11] serves to quench a proportion of the intermediate radical generating the corresponding unimolecularly reduced *N*-benzylaniline (**4a**). Formation of **5** can be explained by the cleavage of the C−N bonds (*N*-debenzylation) of **3a**. This is in accordance with our earlier observation[12a,b] of *N*-benzyl bond cleavage at reflux temperature using $TiCl_3$−Li−THF. The generation of bibenzyl from 1,2-diphenyl-1,2-ethanediamine is in sharp contrast to the fact that olefins (or stilbenes) are formed from the analogous LVT-mediated cleavage of 1,2-diols. The reaction at room temperature did not favor *N*-benzyl bond cleavage or unimolecular reduction. Thus, the reaction could be biased toward the preferential formation of the desirable products by carrying out it at room temperature (25 °C) using judiciously selected reagents.

To explore the scope of the protocol, experiments were carried out using a variety of imines which were prepared according to the literature procedures.[13] Table 2 presents examples which illustrate the generality and selectivity of the transformation. Aldimines obtained from aliphatic, alicyclic, or aromatic amines and aldehydes underwent reactions to give diamines **3** (Table 2, entries 1−9). The method holds good for aldimines where either of the aldehyde or amine component is nonaromatic. Thus, it is applicable to aldimines containing alkyl amines (Table 2, entries 8 and 9) as well as alkyl aldehyde (Table 2, entry 7) residue. As is seen from the Table 2 the electronic factors have little influence on the reactivity of imines. Thus, strongly electron donating (+R) groups, e.g., 2-OMe, 4-Me_2N, and 4-Me (Table 2, entries 3, 5, and 6) do not have significant influence on the reaction time or on the yield. Similarly, the electron-attracting inductive (−I) effect of chlorine (where −I > +R) also have marginal influences (Table 2, entries 2 and 4). The compatibility of methoxy,[4c] chloro,[12c] and *N*-benzyl[12a,b] functionalities (Table 2, entries 2−4 and 8) which remain unaffected under the present experimental condition is noteworthy.

The vicinal diamines (**3a**−**i**) were obtained as diastereomeric (*dl:meso*) mixtures. The stereochemical assignments of the vicinal diamines were made by comparing[7] the resonances of the benzylic (C_1−C_2 methine) protons for the *dl* (upfield signals) and *meso* (downfield signals) isomers (except for the compound **3g**) as reported[7m] by Smith et al. A chromatographically pure diastereomeric mixture was used for the analysis.

The present LVT reagent ($TiCl_3$−Li−THF, mostly in zerovalent state[5d]) offers significant improvements over the earlier method[7h] (generated in situ from $TiCl_4$−Mg/Hg−THF, stoichiometrically bivalent Ti), by reducing the reaction time considerably (2.5−5 h compared to ∼12 h), simplifying the workup procedure, and, above all, augmenting the yield of the desired diamines; the most marked examples are **1a** and **1h**, where the yields of the diamines **3a** and **3h** increased from 41% and 51% to 78% and 72%, respectively. In the earlier case,[7h] the formation of unimolecularly reduced amines **4a** and **4h** (50% and 30% respectively) actually decreases the yields of **3a** and **3h**.

Unlike aldimines, the reactions of ketimines (R_3 = alkyl, aryl, **1j**−**n**) with reagent **D** did not yield the dimer **3** (Table 3, entries 1−5), but amines **4** were obtained. The steric bulk offered by the alkyl/aryl groups in ketimines biased the unimolecular quenching of the intermediate ketyl-like radical **2** by THF in preference to dimerization (path a). The steric effects therefore govern and direct the course of imine reduction. In addition, aldimines react faster (2.5−5 h) compared to ketimines (6−12 h). The C−N double bond can be chemoselectively reduced in the presence of alkyl acid functionality, thus giving access to useful amino acid-based ligands. In fact, when 4-phenyl-4-(phenylimino)butanoic acid (**1m**) was subjected to LVT reagent, smooth reduction of the imino group took place, leading to the formation (62%) of the biochemically important *N*-substituted γ-amino acid

(11) Jung, J. C.; Choi, H. C.; Kim, Y. H. *Tetrahedron Lett.* **1993**, *34*, 3581.
(12) (a) Talukdar, S.; Banerji, A. *Synth. Commun.* **1995**, *25*, 813. (b) Talukdar, S.; Banerji, A. *Synth. Commun.* **1996**, *26*, 1051. (c) Tyrlik, S.; Wolochowicz, I. *J. Chem. Soc., Chem. Commun.* **1975**, 781.
(13) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489 and references therein.

Table 3. Unimolecular Reduction of Ketimines at 25 °C: Generation of Amines (4)

entry	R_1	R_2	R_3	compd	time (h)	% yield[a] of **4**	ref
1	Ph	Ph	Ph	**1j**, **4j**	6	71	14a
2	Ph	2-naphthyl	Me	**1k**, **4k**	8	65	12b
3	Ph	2-(1′-OH-naphthyl)	Et	**1l**, **4l**	12	66	12b
4	Ph	Ph	$(CH_2)_2CO_2H$	**1m**, **4m**	8	62	12b
5	$PhCH_2$	[b]	[b]	**1n**, **4n**	10	58	14b

[a] All yields refer to pure isolated products, fully characterized by IR and ^{1}H NMR. [b] R_2R_3 = c-C_6H_{10}; i.e., ketone component is cyclohexanone.

derivative 4-anilino-4-phenylbutanoic acid (**4m**) (Table 3, entry 4). Imines obtained from cyclic ketones can also be reduced successfully to generate amines. Thus, *N*-benzylcyclohexylamine (**4n**) was obtained in 58% yield from *N*-cyclohexylidinebenzylamine (**1n**) (Table 3, entry 5).

In conclusion, an efficient one-step synthesis of vicinal diamines from easily accessible aldimines has been developed which essentially involves a carbon−carbon bond formation step. The reaction is operationally simple and can be performed chemoselectively in the presence of a number of otherwise easily reducible functionalities and is general for aldimines obtained from both aliphatic and aromatic precursors. The protocol holds considerable promise for the synthesis of nitrogen-containing macrocycles of contemporary interest via reductive intramolecular coupling of dialdimines. Work in this direction leading to the synthesis of medicinally important piperazine derivatives and aza-crown ethers are currently under progress in this laboratory.

Experimental Section

General Methods. General information regarding instruments and techniques used are the same as mentioned in our previous publication.[4a]

Starting Materials. All imines were prepared from the respective carbonyls and amines by known methods.[13] Lithium rods cut into small pieces were used for the reduction of $TiCl_3$.

General Procedure for the Reduction of Imines. A mixture of $TiCl_3$ (964 mg, 6.25 mmol) and lithium (144 mg, 20.6 mmol) was refluxed (3 h, argon) in dry THF (70 mL). To the LVT reagent thus prepared was added an appropriate imine (2.5 mmol, 5 mL THF) and the reaction mixture was stirred at 25 °C for a specified period of time (Table 2, Table 3). After the completion (monitored by TLC), the reaction mixture was diluted with petroleum ether−ethyl acetate mixture (60:40) and passed through Celite; the organic layer was washed with water and brine and dried (Na_2SO_4). Concentration gave the crude product which was purified by preparative TLC (SiO_2) to furnish the desired product. The yields are reported in Tables 2 and 3.

The vicinal diamines (**3a**−**i**) were obtained as diastereomeric (*dl:meso*) mixtures. Assignments were made by comparing[7] the C_1−C_2 methine (benzylic) proton signals for the *dl* and *meso* isomers. The *dl* and *meso* ratio was determined by ^{1}H NMR spectroscopy.

All the vicinal diamines, viz., *N*,*N*′-diphenyl-1,2-diphenyl-1,2-ethanediamine (**3a**), *N*,*N*′-bis(2′-chlorophenyl)-1,2-diphenyl-1,2-ethanediamine (**3b**), *N*,*N*′-diphenyl-1,2-bis(2′-methoxyphenyl)-1,2-ethanediamine (**3c**), *N*,*N*′-diphenyl-1,2-bis(4′-chlorophenyl)-1,2-ethanediamine (**3d**), *N*,*N*′-diphenyl-1,2-bis(4′-*N*,*N*-dimethylaminophenyl)-1,2-ethanediamine (**3e**), *N*,*N*′-diphenyl-1,2-bis(4′-methylphenyl)-1,2-ethanediamine (**3f**), *N*,*N*′-diphenyl-1,2-dicyclohexyl-1,2-ethanediamine (**3g**), *N*,*N*′-dibenzyl-1,2-diphenyl-1,2-ethanediamine (**3h**), and *N*,*N*′-dicyclohexyl-1,2-diphenyl-1,2-ethanediamine (**3i**), and the amines, viz., anilinodiphenylmethane (**4j**), 1-anilino-1-(2′-naphthyl)ethane (**4k**), 1-anilino-1-(1′-hydroxy-2′-naphthyl)propane (**4l**), 4-anilino-4-phenylbutanoic acid (**4m**), and *N*-benzyl cyclohexylamine (**4n**), are known compounds and were characterized by comparison[7,12b,14] (mp, ^{1}H NMR, IR) with authentic samples (Supplementary Information available).

Supporting Information Available: Experimental data for **3a**-**i** and **4j**−**n** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9716892

(14) (a) Periasamy, M.; Devasagayaraj, A.; Satyanarayana, N.; Narayana, C. *Synth. Commun.* **1989**, *19*, 565. (b) Wang, G.-Z.; Bäckvall, Jan-E. *J. Chem. Soc., Chem. Commun.* **1992**, 980.