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Reductive amination of aliphatic carbonyls using low–valent titanium reagent: a convenient route to free primary amines

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A simple procedure for reductive amination of aliphatic carbonyls, giving direct access to free primary amines using low–valent titanium (LVT) reagent has been reported.

Keywords: reductive amination, low–valent titanium, regioselective, N–benzyl bonds

Reductive amination[2] of carbonyls offers an attractive possibility for the direct access to a plethora of amines. A variety of reduction processes,[3] including a lexicon of borohydride and other reagents[4-7] have been developed for this purpose. But most of the procedures terminated at the N–alkylation stage. Moreover, the incompatibility of reducible functionalities,[3] use of super-stoichiometric amounts and low solubility of hydride reagents and presence of toxic residual cyanide in the products,[7] limits the utility of some of these methods. Thus, there was an exigency to develop a simple and an alternate protocol for conversion of carbonyls to free primary amines. Herein, we report a simple procedure for reductive amination of aliphatic carbonyls under neutral conditions giving direct access to free amines using low-valent titanium[8-10] (LVT) reagent (Scheme 1). For this purpose, amine derivatives containing both N–benzyl and N–alkyl moieties (Fig. 1, **2a–d**, **5a–c**, **8**) were synthesised via imine formation and their subsequent reduction from aliphatic carbonyls (**1a–d**, **4a–c**, **7**) and benzyl amine. Finally, reaction of the resultant amine with LVT, induces regioselective N-benzyl bond cleavage (resonance-stabilised benzyl radical) in preference over its N-alkyl counterparts, thereby efficiently transferring the amine fragment to the carbonyl residue, ultimately guaranteeing the desired *trans*-amination (Tables 1 and 2).

Table 1 Reductive amination of **1a** to **3a** via **2a** using different LVT reagents

Entry	LVT reagent	Reaction conditions	% yield[a] of **3a**[b]
1	$TiCl_3$-Mg-DME (**A**)	12 h, reflux	38
2	$TiCl_3$-Mg-THF (**B**)	8 h, reflux	44
3	$TiCl_3$-Li-DME (**C**)	12 h, reflux	40
4	$TiCl_3$-Li-THF (**D**)	6.5 h, reflux	49
5	$TiCl_3$-Li-THF-I_2 (**E**)[c]	2.5 h, 25°C	70

[a]Yields were based on phenylacetaldehyde (**1a**). Conversions of **1a** to **2a** were always ~90%. [b]The product **3a** was characterised by IR, ^1H NMR, MS and comparing with authentic samples. [^1H NMR (200 MHz, $CDCl_3$) δ ppm 2.3 (s, 2H, D_2O exchangeable, 2.8 (t, 2H), 3.78 (t, 2H), 7.32 (s, 5H)]. [c]0.25 equiv of iodine with respect to $TiCl_3$ was used.

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Table 2 Reductive amination of carbonyls using $TiCl_3$–Li–THF–I_2[a] reagent

Entry	Carbonyl compound	Benzyl amine	Reaction conditions	Product (% yield[b])
1	**1b**	**2b**	10 h, reflux	**3b** (51)
2	**1c**	**2c**	12 h, reflux	**3c** (65)
3	**1d**[c]	**2d**	8.5 h, reflux	**3d** (68)
4	**4a**	**5a**	5 h, reflux	**6a** (58)
5	**4b**	**5b**	45 min, 25°C	**6b** (62)
6	**4c**	**5c**	4.5 h, 25°C	**6c** (60)
7	**7**	**8**	3.0 h min, 25°C	**9** (55)

[a]0.25 equiv of iodine with respect to $TiCl_3$ was used. [b]Yields were based on starting carbonyls **1a–d**, **4a–c**, **7**. Conversions of **1a–d**, **4a–c**, **7** to **2a–c**, **5a–c**, **8** respectively were always > 85%. The products were characterised by IR, ^1H NMR, MS and comparing with authentic samples. [c]Substrate **1d** was synthesised from 1-pentenyl alcohol, which was initially methylated (Me_2SO_4) and the product obtained was subsequently subjected to ozonolysis (O_3/Na_2S).

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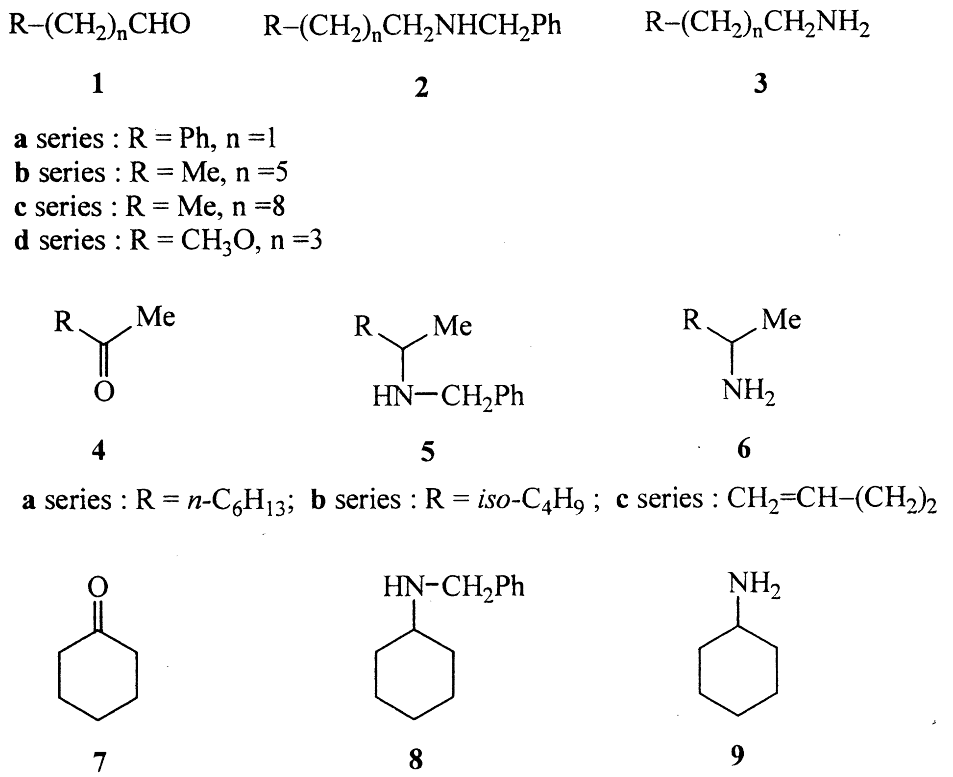
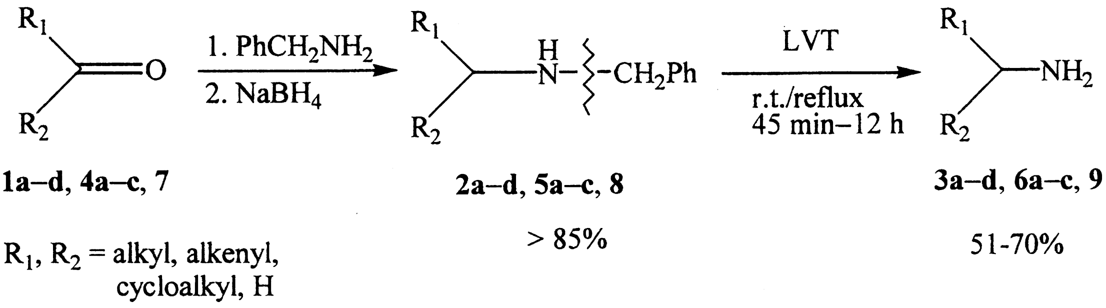


Fig.1



Scheme 1

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