

A New One-Pot, Four-Component Synthesis of 1,2-Amino Alcohols: $\text{TiCl}_3/t\text{-BuOOH}$ -Mediated Radical Hydroxymethylation of Imines

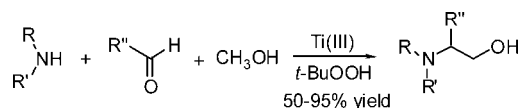
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ABSTRACT



R = Alkyl, Benzyl, Aryl

R' = Alkyl, H

R'' = Aryl, Alkyl, H

An amine, an aldehyde, and methanol can be readily assembled in one pot under very mild conditions through a free-radical multicomponent reaction by using an aqueous acidic $\text{TiCl}_3/t\text{-BuOOH}$ system to afford 1,2-amino alcohols in fair to excellent yields.

The β -amino alcohol motif is a common structure present in a wide range of bioactive natural products.¹ Moreover, 1,2-amino alcohols are suitable intermediates for the synthesis of unnatural amino acids, β -blockers, insecticidal agents, and antibiotics.² In addition, they are successfully employed in asymmetric synthesis as chiral auxiliaries or chiral catalysts.³

For this reason, much effort has been devoted to the development of new effective methods for the enantioselective synthesis of these compounds, and a variety of catalytic procedures has been reported,⁴ including the ring

opening of racemic terminal epoxides,⁵ the nucleophilic addition to sulfinyl imines,⁶ and the use of metallorganic catalysts.⁷

Nevertheless, most of these syntheses often require multistep procedures, expensive reagents, long reaction times, and highly controlled operating conditions.

Nucleophilic radical addition to imines often represents an important alternative to classical ionic procedures for the synthesis of a wide range of derivatives, and in the past decade, many protocols have been reported based on this convenient approach.^{8,9}

[†] Passed away suddenly on May 3, 2008.

(1) Bergemier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576.

(2) (a) Yadav, J. S.; Reddy, A. R.; Narsaiah, A. V.; Reddy, B. V. *S. J. Mol. Catal. A* **2007**, *261*, 207–212. (b) Corey, E. J.; Zhang, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931–1934. (c) Bose, D. S.; Narsaiah, A. V. *Bioorg. Med. Chem.* **2005**, *3*, 627–630.

(3) Ager, D. J.; Prakash, I.; Shaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.

(4) (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451–454. (b) Effenberger, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555–1564. (c) Onkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510–6511. (d) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4241–4244.

(5) (a) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420–7421. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421–431. (c) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973–3975.

(6) (a) Garcia Ruano, J. L.; Aleman, J.; Parra, A. *J. Am. Chem. Soc.* **2005**, *127*, 13048–13054. (b) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948–9957.

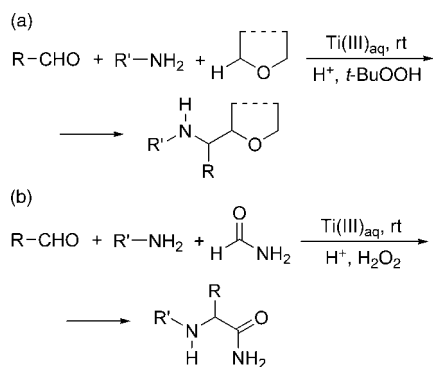
(7) (a) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2007**, *129*, 288–289. (b) Hodgson, D. M.; Štefare, B.; Miles, T. J.; Witherington, J. *Chem. Commun.* **2004**, 2234–2235. (c) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051–2054. (d) Jung, D. Y.; Ko, C. H.; Kim, Y. H. *Synlett* **2004**, *7*, 1315–1317.

Following the radical route to 1,2-amino alcohols, both enantiomers (whose configuration may be easily assigned by NMR)¹⁰ would be obtained in their pure forms by employing one of the several methods reported in the literature.¹¹

Very recently, Tomioka and co-workers reported a new multistep procedure for the synthesis of 1,2-amino alcohols in good yields via nucleophilic radical addition to imines by means of acyloxymethyl radicals, generated from the corresponding iodomethyl esters by action of dimethylzinc or triethylborane.¹² This tin-free methodology operates under very mild conditions (air at room temperature), but it requires long reaction times, the aldimine preformation, the employment of halogenated derivatives, and further hydrolysis of the acyloxy moiety with potassium hydroxide in aqueous methanol.

In the past years, we have outlined a new procedure for the synthesis of polyfunctional derivatives mediated by the TiCl_3 /hydroperoxide system. Employing this methodology a radical version of the Mannich reaction through the aminoalkylation of ethers (Scheme 1, a)¹³ and a radical

Scheme 1. Radical Version of the Mannich Reaction (a) and of the Strecker Synthesis (b)

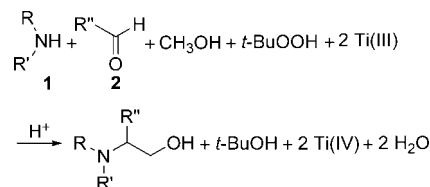


version of the Strecker synthesis by direct carbamoylation of imines (Scheme 1, b)¹⁴ have been developed.

In this paper, we report a new route to obtain 1,2-amino alcohols in one pot in good yields and high selectivity by readily combining three commercial products (an amine **1**, an aldehyde **2**, and methanol) through a radical domino

multicomponent reaction promoted by the aqueous acidic TiCl_3 /*t*-BuOOH (TiCl_3 /TBHP) system (Scheme 2).

Scheme 2. Synthesis of 1,2-Amino Alcohols Mediated by the TiCl_3 /*t*-BuOOH System



To the best of our knowledge, this represents the first example of direct radical hydroxymethylation of imines generated in situ under aqueous conditions.

Tables 1 and 2 report the results obtained in the presence of primary and secondary amines, respectively.

Table 1. Radical Addition of Methanol to In Situ Generated Imines from Primary Amines^a

entry	amine	aldehyde	4: yield ^b (%)	5: yield ^b (%)
1	1a	2a	4a : 30 (37)	5a : 15 (16)
2	1a	2b	4b : 66 (75)	
3	1b	2a	4c : 35 (37)	5b : 14 (15)
4	1b	2b	4d : 62 (67)	
5	1b	2c	4e : 46 (50)	
6 ^c	1b	2d	4f : 82 (89) ^d	
7	1c	2a	4g : 35 (37)	5c : 20 (21)
8	1c	2b	4h : 64 (75)	
9	1d	2a		5d : 18 (19)
10	1d	2b	4i : 60 (65)	

^a Unless otherwise stated, the molar ratio of **1**/2/TBHP/ TiCl_3 was 1:3.75:2.5:4. ^b Yields of isolated products are based on the starting amine; yields based on converted amines were always $\geq 90\%$; yields in parentheses were determined by ^1H NMR with an appropriate internal standard added to the crude reaction mixture. ^c The molar ratio of **1**/2 was 1:0.625. ^d Yield is based on the starting aldehyde.

Both aliphatic and aromatic amines (Figure 1) and aldehydes (Figure 2) were suitable for this protocol, thus confirming the general applicability of the present procedure.

The reactions with primary amines were carried out by adding dropwise TiCl_3 (ca. 8 mmol of a 15% aqueous acidic solution) over 30 min at room temperature to a solution containing **1a–d** (2 mmol), **2** (7.5 mmol), and TBHP (5 mmol) in 10 mL of methanol under N_2 atmosphere until a pale blue color was barely maintained to ensure the complete decomposition of the peroxide. Thus, the procedure looks

(8) For reviews in the field, see: (a) Friestad, G. K. *Tetrahedron* **2001**, 57, 5461–5496. (b) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 7, 1140–1157. (c) Friestad, G. K. *Eur. J. Org. Chem.* **2005**, 3157–3172.

(9) For some leading references, see: (a) Friestad, G. K.; Ji, A. *Org. Lett.* **2008**, 10, 2311–2313. (b) Ueda, M.; Miyabe, H.; Sugino, H.; Naito, T. *Org. Biol. Chem.* **2005**, 3, 1124–1128. (c) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, 8, 87–89. (d) Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.; Tomioka, K. *Org. Lett.* **2006**, 8, 5729–5732.

(10) (a) Leiro, V.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2008**, 10, 2729–2732. (ba) Leiro, V.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2008**, 10, 2733–2736.

(11) Nandhakumar, R.; Guo, Y.-E.; Tang, L.; Nam, W.; Kim, K. M. *Tetrahedron Lett.* **2007**, 48, 6582–6585, and references therein.

(12) Yamada, K.; Nakano, M.; Maekawa, Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, 10, 3805–3808.

(13) Clerici, A.; Cannella, R.; Pastori, N.; Panzeri, W.; Porta, O. *Tetrahedron* **2006**, 62, 5986–5994.

(14) Cannella, R.; Clerici, A.; Panzeri, W.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* **2006**, 128, 5358–5359.

Table 2. Radical Addition of Methanol to In Situ Generated Imines from Secondary Amines^a

$$1\mathbf{e-h} + 2\mathbf{a-d} + \text{CH}_3\text{OH} \xrightarrow[\text{H}^+, \text{rt}]{\text{TBHP/Ti(III)}} \mathbf{6}$$

entry	amine	aldehyde	6 : yield ^b (%)
1	1e	2a	6a : 83 (87)
2	1e	2b	6b : 65 (73)
3	1e	2c	6c : 50 (55)
4 ^c	1e	2d	6d : 30 (33) ^d
5	1f	2a	6e : 95 (95)
6	1f	2b	6f : 17 (22)
7	1g	2a	6g : 80 (82)
8	1g	2b	6h : 23 (22)
9	1h	2a	6i : 30 (36)

^a Unless otherwise stated, the molar ratio of **1**/2/TBHP/TiCl₃ was 1:3.75:1.25:2. ^b See footnotes b–d of Table 1. ^c See footnotes b–d of Table 1. ^d See footnotes b–d of Table 1.

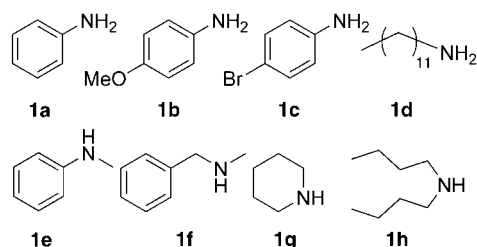


Figure 1. Representative amines **1a–h**.

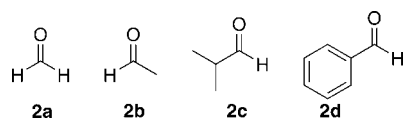


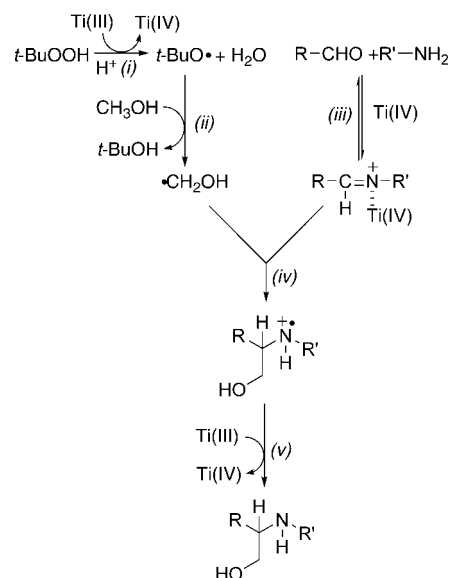
Figure 2. Representative aldehydes **2a–d**.

like a simple titration and occurs under very mild conditions. A similar procedure was followed in the presence of secondary amines **1e–h**, but in this case no benefit was observed by operating with an excess of the TiCl₃/TBHP system. Thus, a lower amount of TiCl₃ (ca. 4 mmol) and of TBHP (2.5 mmol) was sufficient in order to obtain the desired products.

This simple one-pot selective hydroxymethylation would proceed by the sequence (i–v) reported in Scheme 3, where titanium species play a multiple key role.

In the lower (III) oxidation state, titanium acts as a radical initiator inducing the decomposition of TBHP to the corresponding alkoxy radical (path i), which is responsible for the formation of the hydroxymethyl radical by hydrogen abstraction from methanol (path ii); Ti(III) also acts as a radical terminator in the reduction of the final aminium radical intermediate (path v).

Scheme 3. Reaction Mechanism



In the higher (IV) oxidation state, titanium behaves as a strong Lewis acid promoting the formation of the imine in aqueous medium (path iii) and its activation toward the hydroxymethyl radical addition by increasing the electrophilicity of the carbon atom of the C=N bond (path iv).

Steric effects seem to have a crucial role in the process, affecting both the yields and the selectivity in the desired products.

When primary amines (Table 1) were employed in the presence of formaldehyde, a mixture of mono- (**4**) and disubstituted (**5**) β-amino alcohols was obtained (entries 1, 3, 7, and 9) due to the competition between the starting amine **1a–d** and the corresponding product **4** in the imine formation. However, the use of an aldehyde bearing an alkyl or an aryl substituent allowed us obtain monosubstituted products in good yields and with complete selectivity because the enhanced steric hindrance around the C=N bond inhibits the further reaction of **4** to afford **5**. As a representative primary amine we tested *p*-methoxyaniline (PMP-NH₂) **1b** with a wider range of aldehydes, since the protective PMP group can be further removed according to different methodologies.¹⁵

For the same steric reasons, secondary amines, which cannot undergo disubstitution, showed opposite reactivity affording the highest yields in the presence of formaldehyde (Table 2, entries 1, 5, and 7). When crowded aldehydes were employed in place of **2a**, yields decreased because of the concomitant presence of two additional substituents on the C=N bond.

The relatively low yields observed in the presence of **1h** and **2a** (entry 9) may also be ascribed to an enhanced steric

(15) (a) Hasegawa, M.; Tanijama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153–10158. (b) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2006**, *47*, 8109–8113. (c) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Schoemaker, H. E.; Schürmann, M.; van Delft, F. L.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2007**, *349*, 1332–1336.

hindrance due to the long aliphatic chains directly bonded to the nitrogen atom. In fact, no side products were detected, and the starting reagents were quantitatively recovered.

When the reactions were conducted in the presence of **2d**, the side acyl radical addition occurred because hydrogen abstraction from the aldehyde competed with the hydroxymethyl radical formation. However, when an excess of amine was used, it significantly increased the selectivity and avoided side product formation (entry 6 of Table 1 and entry 4 of Table 2).

In conclusion, we have developed a new general and convenient one-pot multicomponent reaction for the synthesis of aliphatic and aromatic 1,2-amino alcohols, utilizing cheap and commercially available starting materials. The reaction does not require either the preformation of the imine or the protection of the amino group and may be easily conducted under aqueous conditions.

Future efforts will focus on the extension of the methodology on a wider range of alcohols, whose behavior, from preliminary results, seems to be quite different from methanol.

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Supporting Information Available: General experimental procedures, characterization data, and spectral data for products **4a–i**, **5a–d**, and **6a–i**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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