



LiClO₄-catalyzed three-component-coupling reactions: a facile synthesis of homoallylic amines

J. S. Yadav,* B. V. S. Reddy, P. S. R. Reddy and M. Shesha Rao

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500007, India

Received 25 March 2002; revised 20 June 2002; accepted 28 June 2002

Abstract—Lithium perchlorate catalyzes efficiently the three-component condensation of aldehydes, amines and allyltributylstannane under mild and neutral reaction conditions to afford the corresponding homoallylic amines in excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

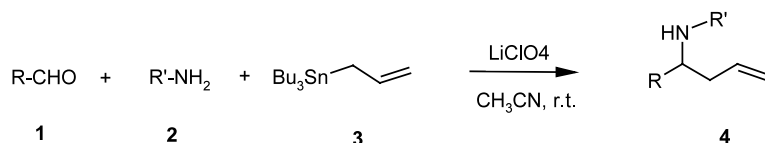
The stereoselective addition of allylmetal reagents to aldehydes and imines is one of the most important carbon–carbon bond forming reactions in organic synthesis.¹ In particular, Lewis acid-catalyzed carbon–carbon bonding forming reactions are of great importance in organic synthesis because of their high reactivity, selectivity and mild reaction conditions.² Generally, homoallylic amines are prepared either by addition of organometallic reagents to imines³ or by nucleophilic addition of allylsilane, allyltin, allylboron or allylgermane reagents to imines in the presence of acid catalysts.⁴ Lewis acids such as TiCl₄, BF₃·OEt₂, and PdCl₂(PPh₃)₂ or PtCl₂(PPh₃)₂ have been employed for this transformation.^{4,5} However, these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine and allyl metal reagent because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids.⁶ In order to circumvent these problems one-pot procedures have been developed for this conversion recently using lanthanide triflates as catalysts.⁷ In fact, these procedures do not require the isolation of the unstable imines prior to the reactions. Metal triflates are strongly acidic and highly expensive, and so the

development of a neutral alternative like lithium perchlorate would extend the scope of this transformation.

In recent years, LiClO₄ in diethyl ether (LPDE) has emerged as a mild Lewis acid imparting high regio-, chemo- and stereoselectivity to various organic transformations.⁸ The LPDE medium provides a convenient procedure to carry out reactions under neutral reaction and work-up conditions. Furthermore, LPDE is found to retain its activity even in the presence of amines and has also been found to activate effectively nitrogen containing compounds such as imines and nitrones.⁹

In continuation of our interest on the catalytic applications of lithium perchlorate for various organic transformations,¹⁰ we herein describe a simple and efficient protocol for the synthesis of homoallylic amines using a catalytic amount of lithium perchlorate under neutral reaction conditions (Scheme 1).

The reaction of benzaldehyde, aniline and allyltributylstannane in the presence of 10 mol% lithium perchlorate¹¹ in acetonitrile at ambient temperature resulted in the formation of the homoallylic amine in



Scheme 1.

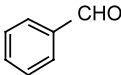
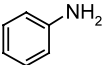
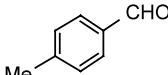
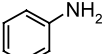
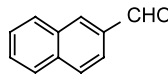
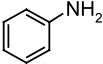
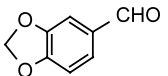
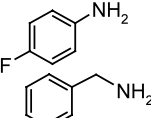
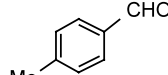
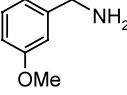
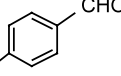
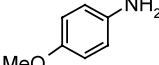
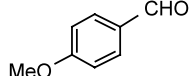
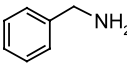
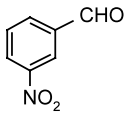
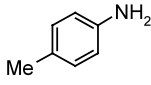
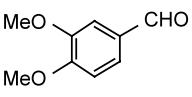
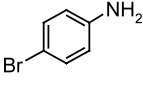
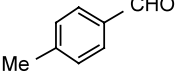
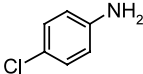
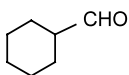
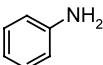
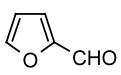
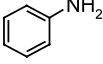
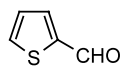
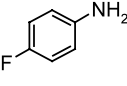
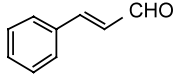
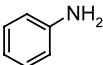
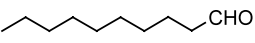
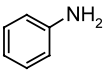
Keywords: lithium perchlorate; allylstannane; coupling reaction; homoallylic amines.

* Corresponding author. Fax: 91-40-7160512; e-mail: yadav@iict.ap.nic.in

90% yield. Similarly various imines (formed in situ from aldehydes and amines) reacted smoothly with the allyl-stannane to afford the corresponding homoallylic amines in high yields.¹² The reactions proceeded smoothly at ambient temperature and were completed

within 2.5–5.5 h. Both aromatic and aliphatic aldehydes afforded excellent yields of products (75–90%) in a short period whereas ketones did not yield any product even after a long reaction times (10–15 h). This method is effective even with aldehydes bearing electron-with-

Table 1. Lithium perchlorate-catalyzed synthesis of homoallylic amines^a

Entry	Aldehyde	Amine	Time(h)	Yield(%) ^b
a			3.0	90
b			2.5	88
c			4.5	85
d			2.0	87
e			5.0	83
f			4.0	90
g			5.0	87
h			5.5	85
i			4.0	89
j			4.0	90
l			5.0	75
m			3.0	85
n			3.5	90
o			4.0	88
p			5.0	83

^a All products were characterized by ¹H NMR, IR and mass spectroscopy

^b Isolated and unoptimized yields

drawing substituents in the aromatic ring. Furthermore, acid-sensitive aldehydes, such as furfuraldehyde and cinnamaldehyde, worked well without any decomposition or polymerization under the reaction conditions. Enolizable aldehydes, such as cyclohexanecarboxaldehyde and decanal, also produced the corresponding homoallylic amines in good yields. In all cases, no homoallylic alcohol (an adduct between the aldehyde and allyltributylstannane) was obtained under these reaction conditions. This is because of the rapid formation and activation of imines in the presence of lithium perchlorate. All the products were characterized by ^1H NMR, IR, and mass spectral analysis. There are several advantages in the use of LiClO_4 as catalyst for this transformation, which include mild reaction conditions, cleaner reaction profiles, high yields of products, greater selectivity and compatibility with acid labile substrates. The scope and generality of this process is illustrated with respect to various amines and aldehydes including aromatic, α,β -unsaturated, heterocyclic, and aliphatic aldehydes and the results are presented in Table 1.

In conclusion, lithium perchlorate is found to be a mild and efficient Lewis acid in promoting three-component-coupling reactions of aldehydes, amines and allyltributylstannane under neutral conditions. In addition to its simplicity, efficiency and mild reaction conditions, this method provides high yields of products in a short period, which makes it a useful and attractive process for the synthesis of homoallylic amines of synthetic importance.

Acknowledgements

B.V.S. and P.S.R. thank the CSIR, New Delhi, for the award of fellowships.

References

- (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207; (b) Marshall, J. A. *CHEMTRACTS* **1992**, *5*, 75.
- Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15.
- (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407; (b) Chan, T. H.; Lu, W. *Tetrahedron Lett.* **1998**, *39*, 8605.
- (a) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146; (b) Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawey, A. A.; Sarhan, A. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 109; (c) Akiyama, T.; Iwai, J. *Synlett* **1998**, 273.
- (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6642; (b) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6642.
- Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.
- (a) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19; (b) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049; (c) Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 323.
- Sankara Raman, S.; Nesakumar, J. E. *Eur. J. Org. Chem.* **2000**, 2003.
- (a) Ipaktschi, J.; Heydari, A. *Chem. Ber.* **1993**, *126*, 1905; (b) Heydari, A.; Larijani, H.; Emami, J.; Karami, B. *Tetrahedron Lett.* **2000**, *41*, 2471.
- (a) Yadav, J. S.; Reddy, B. V. S.; Murthy, Ch. V. S. R.; Kumar, G. M.; Madan, Ch. *Synthesis* **2001**, 783; (b) Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Madhuri, Ch.; Ramalingam, T. *Synlett* **2001**, 240; (c) Yadav, J. S.; Reddy, B. V. S.; Jyothirmai, B.; Murthy, M. S. R. *Synlett* **2002**, 53.
- Caution:** Although, solid lithium perchlorate is stable up to its melting point, solutions in organic solvents should be prepared and handled with the utmost care.
- A mixture of aldehyde (5 mmol), amine (5 mmol), allyltributylstannane (5 mmol) and anhydrous LiClO_4 (10 mol%) in acetonitrile (10 mL) was stirred at ambient temperature for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (2×15 mL). The combined organic layers were washed with water (3×15 mL) and dried over anhydrous Na_2SO_4 , concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure homoallyl amine. The aqueous layer was quenched with saturated sodium bicarbonate solution to destroy lithium perchlorate.

Spectral data for selected products: Compound **4b**: liquid, ^1H NMR (CDCl_3): δ 2.30 (s, 3H), 2.50–2.65 (m, 2H), 4.05 (brs, 1H, NH), 4.38 (t, 1H, $J=6.5$ Hz), 5.10–5.25 (m, 2H), 5.70–5.85 (m, 1H), 6.45 (d, 2H, $J=8.1$ Hz), 6.60 (t, 1H, $J=7.9$ Hz), 7.0–7.18 (m, 4H), 7.25 (d, 2H, $J=8.1$ Hz); EIMS: m/z 237 M^+ , 196, 128, 115, 104, 91, 77, 65, 51.

Compound **4c**: liquid, ^1H NMR (CDCl_3): δ 2.50–2.78 (m, 2H), 4.25 (brs, 1H, NH), 4.38 (t, 1H, $J=6.4$ Hz), 5.18–5.25 (m, 2H), 5.75–5.90 (m, 1H), 6.50 (d, 2H, $J=8.0$ Hz), 6.60 (t, 1H, $J=7.8$ Hz), 7.10 (t, 2H, $J=7.8$ Hz), 7.50–7.60 (m, 3H), 7.80–8.0 (m, 4H); EIMS: m/z 273 M^+ , 232, 165, 127, 104, 77, 51.